Expenditures Associated with Dose Titration At Initiation of Therapy in Patients With Major Depressive Disorder
A Retrospective Analysis of a Large Managed Care Claims Database

Fabian Camacho, MS, MA; Meg C. Kong, PhD; David V. Sheehan, MD, MBA; and Rajesh Balkrishnan, PhD

ABSTRACT

Objective. Although selective serotonin reuptake inhibitors (SSRIs) are considered cost-effective medications for patients with major depressive disorder (MDD), significant dosage adjustments are often necessary when treatment is initiated. Our study was conducted to examine whether dose titration for SSRIs at initiation of therapy was associated with a greater use of health care resources and higher costs.

Study Design. A retrospective database analysis was conducted.

Methods. A nationally representative cohort of individuals with MDD was identified in a large managed care claims database between January 1, 2004, and December 31, 2006. A study-specific titration algorithm was used to identify patients who underwent dose titration, compared with those who did not, within the first eight weeks of initiating SSRI therapy. We calculated propensity scores and identified a 1:1 matched cohort of titration versus non-titration patients. We used univariate and multivariate statistical tests to compare the mean number of therapeutic days, health care service utilization, and expenditures between the two groups during the first eight weeks (56 days) of treatment and six months (180 days) after treatment began.

Results. Over the first eight weeks, the titration cohort had a 32% decrease in the adjusted mean number of therapeutic days (38 vs. 56, respectively; \( P < 0.001 \)), a 50% increase in depression-related outpatient visits (1.8 vs. 1.2; \( P < 0.001 \)), a 38% increase in depression-related outpatient costs ($137 vs. $81; \( P < 0.001 \)), an increase in antidepressant pharmacy costs ($139 vs. $61; \( P < 0.001 \)), and a 64% increase in psychiatric visits (0.69 vs. 0.42; \( P = 0.001 \)), compared with the matched non-titration cohort. These differences were consistent among individual SSRI groups as well as during the six-month period.

Conclusion. Patients undergoing dose titration of SSRIs at the beginning of therapy consumed more medical resources and spent more days receiving a subtherapeutic dose than a comparable control group without dose titration. Differences in the utilization of resources were consistent with increased patient monitoring in the titration group; however, the added benefit of titration could not be assessed with this database.

Key words: dose titration, SSRI, depression, managed care, cost

BACKGROUND

Major depressive disorder (MDD) affects almost 15 million people age 18 or older in the U.S. (approximately 6.7% of the population). By 2005, roughly 12.7% of men and 21.3% of women had depression at some point during their lifetimes. As defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), MDD is commonly treated with a combination of psychotherapy and pharmacotherapy. As diagnosed by health care professionals, it is associated with a significant decrease in patients’ quality of life and is reflected by metrics such as the Quality of Well-Being Scale (QWB) or Self-Form 36-item Survey (SF-36). In addition to the negative impact on quality of life, depression is also costly to the health care system.

The total economic burden of MDD to payers of health care has consistently been significant. Greenberg et al. found that direct medical costs (pharmaceuticals, primary care visits, and psychiatric visits) for depression in the year 2000 were $26.1 billion. MDD patients also incur high indirect costs as a result of lost work hours (absenteeism) and lower on-the-job performance (presenteeism). Goetzler et al. have quantitatively estimated the costs of absenteeism resulting from depression to be $4,741 per year per employee, with an average of 25.6 days of absence per year per employee. Murray and Lopez predicted that by the year 2020, depression will carry the second largest disease burden, as measured by disability-adjusted life years (DALY), because of its high prevalence, high comorbidity with other common ailments, and associated economic burden. Depression is a constant concern for health care providers and a frequent target of disease-management programs.

Effective treatment is essential for the management of depression and its associated economic costs. Schoenbaum

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et al. found that appropriate treatment significantly reduced rates of patients’ self-reported depression (24%) compared with patients not receiving appropriate treatment (70%) after six months in a managed care population.14,15 SSRIs are the most widely prescribed antidepressants and are recommended by several national guidelines as the first line of therapy.16–22

Dose titration is a common practice with antidepressants, including SSRIs. In general, slightly lower therapeutic dosages are used at initiation, followed by a gradual increase until the target dose is achieved. Upward titration is usually performed to minimize tolerability problems by gradual introduction of the drug or as a response to a lack of therapeutic effect so that the optimal dosage can be obtained.23–25 Sometimes treatment algorithms also depend on other factors such as the patient’s profile (e.g., any existing anxiety disorder or previous tolerability problems26), the physician’s practice pattern, the selection of a specific SSRI, and the interrelationships within a complex health care system.27 Although no definitive standards are in place, managed care organizations (MCOs) often make suggested titration schedules publicly available.27 Titrating rates can vary widely among SSRIs, from 2% to almost 45%,9,28–32

Dose titration is often recommended in SSRI therapy and often enhances tolerability and efficacy, but the process can also be associated with negative outcomes.30,31 Specifically, the incidence of relapse or recurrence of MDD has been higher in patients whose doses were titrated,30 probably a result of increases in discontinuation rates associated with titration.31 It has been suggested that such findings are a consequence of patients’ frustration with complicated schedules or delays in achieving the therapeutic dosage.35

Titration has also been linked to increased health care costs.28 Intuitively, the reason might be that patients undergoing titration make more physician visits and need more prescriptions, often leading to greater use of resources and higher costs associated with laboratory monitoring. As a result, dose titration can have both benefits and drawbacks, with implications of complex interactions and mixed conclusions, yet few studies have quantitatively evaluated its role in antidepressant use.

The purpose of our study was to determine whether MDD patients enrolled in a managed care plan whose doses were titrated upward had higher health care resource utilization and associated costs compared with patients whose doses were not titrated. To accomplish this, we used a retrospective database analysis. A quasi-experimental design consisted of a before-and-after comparison between titration and control groups.

**METHODS**

**Data Source**

All prescription claims for SSRIs received between July 1, 2004, and December 31, 2005, were obtained from a large national managed care claims database (PharMetrics, Inc., Watertown, Mass.). This database covered roughly 55 million people, with contributions by more than 85 MCOs throughout the U.S.; 74% of the patients in the database belonged to commercial employer-based insurance plans. Insurance was administered by health maintenance organizations (HMOs, 42%), point-of-service (POS) providers (15%), preferred provider organizations (PPOs, 36%), and other types (19%). Age distribution was representative of the U.S. commercially insured population; 47% of the patients were 0 to 34 years of age, 21% were 35 to 64 years of age, and 17% were 75 to 80 years of age or older.

We followed HIPAA policy in performing all research, using only de-identified data and revealing no personal health information. Our research was exempted from evaluation by the Ohio State University’s institutional review board.

**Inclusion and Exclusion Criteria**

We enrolled patients between 18 and 64 years of age who were continuously eligible 12 months before and 12 months after the start of therapy (Figure 1). Patients had to have a diagnosis of MDD, defined as International Classification of Diseases, 9th revision (ICD-9 296.2x, and 296.3x) or dysthymia (ICD-9 300.4), and they had to have started with only one medication during the study period. We selected patients using the most frequently prescribed SSRI monotherapies: escitalo-
pram oxalate (Lexapro, Forest), sertraline (Zoloft, Pfizer), fluoxetine (Prozac, Eli Lilly), paroxetine (Paxil, GlaxoSmithKline), and citalopram hydrobromide (Celexa, Forest). We excluded the following patients:

- any individuals with evidence of psychosis, as defined by ICD-9 codes 295.x, 296.4, 296.5, 296.6, 296.7, 296.8, and 296.9
- anyone who was using an antipsychotic medication during the study period
- those who were using an antidepressant medication within 12 months before the index date (defined as the start of SSRI monotherapy)
- anyone who had been in a nursing home within 30 days of the index date

**Titration Algorithm**

To identify patients who were undergoing upward dose titration, we developed an algorithm using individual pharmacy claims data during the first eight weeks of the initial fill of the specific SSRI. We created smooth, continuous dosage curves for each subject by fitting extracted dosage data with cubic splines. The algorithm proceeded from the assumption that a steady increase in dosage could be inferred from sequential prescription data and that such an increase indicated that patients were undergoing dose titration under these conditions:

- The slope at each interval point must have been positive and greater than 0.18 mg/day.
- The ultimate difference in estimated dosage from the start to the end of titration must have been greater than 50 mg for sertraline and 10 mg for the other drugs.

Figure 2 illustrates the differences in trends for patients’ doses considered to be titrating, according to the algorithm, compared with those considered to be non-titrating. The criteria we chose ensured that the final dosage would exceed the recommendations in the package insert and that clear false-positive results would be eliminated. We used standard procedures and practices to guide dose titration of SSRIs noted in the literature. We calculated several baseline variables of resource utilization and diagnosis using claims during the year before therapy began. First, using indicators created for each patient in the sample, we measured for the presence of specific ICD-9 codes for depression (300.4x, 296.2x, 296.3x) and whether any patient visits were conducted through an emergency department (ED), laboratory, mental health facility, inpatient, or outpatient setting. We then calculated the costs of health care for each of these settings in addition to depression-related claims and all claims altogether, including prescriptions. These costs were based on managed care plan payments and did not include any patient copays.

Next, we calculated 40 indicators for each patient in the sample to identify the presence or absence of 20 of the most frequently observed ICD-9 code primary diagnoses and the 20 most frequently observed medications during the year prior to initiation.* Finally, an indicator was assigned to record the presence of at least one visit to a psychologist or to a psychiatrist by the patient during this year.

During the first eight weeks (56 days) and six months (180

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**Table 1: Dose–Titration Ranges for Common Selective Serotonin Reuptake Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>25–200</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10–80</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10–20</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10–50</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20–40</td>
</tr>
</tbody>
</table>

Values reproduced from Aetna.27
Costs of Dose Titration in Major Depressive Disorder

Funding Information

Kevin C. Saur, PhD, and the Ohio State University Center for Clinical Research Reliability (Cincinnati, Ohio) for a Quality Improvement Grant in 2006. The Ohio State University Center for Clinical Research Reliability provides research assistance to the investigators. Dr Saur receives support from the National Institute of Mental Health Grant R01 MH071718 and the Ohio State University Research Council. The institutional review board at The Ohio State University approved the study, which is registered with ClinicalTrials.gov (identifier NCT00344809).

Abbreviations

AED = antiepileptic drug
AHA = American Heart Association
AMD = antidepressant
AS = atypical schizophrenia
AV = antiepileptic
BD = bipolar disorder
BMI = body mass index
CMI = Charlson Comorbidity Index
CP = chronic pain
CR = common research
CRKD = chronic renal failure
CT = cardiovascular
d = diabetes mellitus
dm = dyslipidemia
EM = emergency medicine
HIV = human immunodeficiency virus
IRS = inpatient and outpatient resource
KAP = knowledge, attitude, and practice
MDD = major depressive disorder
MS = multiple sclerosis
N = number
NR = not reported
OC = office-based
PC = physician's consultation
PD = Parkinson disease
PM = personal mone
SSRI = selective serotonin reuptake inhibitor
T = titer
V = vomiting
WA = white armor
WBP = World Health Organization
XRP = Xenical
YRD = year-round depression

Statistical Analyses

A graphical description of the study design is shown in Figure 3. We compared health care resource utilization and associated costs during the first 56 days and during the first six months after initiation of therapy among controls and those receiving dose titration.

To correct for sample imbalances during the year prior to initiation, we performed a propensity score analysis,38 followed by pair matching between titration and non-titration groups. Propensity scoring consisted of estimating the predicted probability (propensity) of group selection, given all other baseline characteristics, allowing the control of confounding bias when comparing outcome measures among the two groups. We estimated propensity scores for membership in the titration group by a logistic model, with predictors calculated over the year prior to the initiation of SSRI monotherapy in both groups. Predictors consisted of age, sex, Charlson Comorbidity Index scores, health resource utilization, costs, the 20 most frequently occurring diagnosis codes, and the 20 most frequently prescribed medications over the year.

Using a Mahalanobis metric procedure, we pair-matched all available patients (in a 1:1 ratio) whom we had identified as undergoing titration.39 This procedure was used to match non-titrators to titration patients based on the closest standardized distance between their propensity scores, age, Charlson Index scores, inpatient costs, and number of prescriptions during the year prior to initiation, under the constraint that both matched patients started with the same SSRI antidepressant. We considered this an improvement over conventional propensity score pair matching in this study, because it resulted in more comparable groups at the year before therapy initiation.

After the pair-matching procedure, we compared outcome measures by taking the difference between each pair and testing for the null hypothesis of no difference. Paired Student t tests were used to test for non-zero unadjusted means. To correct for any further imbalance between groups, we included the difference in outcomes in a multivariate regression model as a dependent variable; we regressed this variable using the difference in baseline number and cost of medications as well as inpatient and outpatient baseline costs. We then tested the intercept of the regression model for statistical significance to assess whether predicted change was zero when baseline differences were projected to be zero. We calculated adjusted differences overall and within SSRI monotherapy groups. SAS software (Version 9.1) was used to conduct all analyses (P < 0.05).40

RESULTS

As illustrated in Figure 1, 276,511 patients were initially identified. After applying inclusion and exclusion criteria, we reduced the sample to a total of 15,149 patients. Using the titration algorithm, coupled with individual review to eliminate false-positives, we found that 813 subjects had started new SSRI monotherapy and had undergone dose titration during the first 56 days of the study period.

Using the original matching procedures, we compared baseline characteristics between the titration and matched control groups. We found higher baseline health care utilization and costs as well as a greater average cumulative dosage during the 56-day period for the titration group, thus raising doubts as to the comparability of both groups.

To make the groups more comparable, we modified the Mahalanobis pair-matching procedure to consider matching candidates as only those control patients who had a higher cumulative dosage during the initial 56-day period rather than the titration-case patients who were to be pair-matched. Our modification resulted in a design in which control patients who began with the same maintenance dosage level and continued with the medication were compared with patients undergoing titration to that dose level.

As a result of this modification, only 724 of the 813 patients (89% of the original number) could be matched to a similar counterpart; the remaining 11% had cumulative dosages exceeding those of the available controls. This final group of patients was subdivided into those receiving sertraline (n = 174), fluoxetine (n = 171), escitalopram (n = 173), paroxetine (n = 124), and citalopram (n = 82).

Table 2 shows a statistical comparison of baseline characteristics between the two cohorts after pair matching. We

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* The respective authors can be contacted for further details about the codes and medications used.
observed no statistically significant differences in baseline characteristics. Table 3 presents overall titration outcomes for the combined dose–titration and control groups. During the first 56 days of therapy, the titration group:

- experienced fewer days of therapy (38 days vs. 56 for controls, respectively; t-test, P < 0.001).
- had lower costs for antidepressants ($119 vs. $153, respectively; t-test, P < 0.001).
- made more depression-related outpatient visits (1.8 vs. 1.2, respectively; t-test, P < 0.001).
- had higher outpatient costs ($137 vs. $81, respectively; t-test, P < 0.001).
- made more psychiatric visits (0.69 vs. 0.42, respectively; t-test, P < 0.001).
- had significantly lower non–depression-related pharmacy costs (t-test, P = 0.024).

Non–depression-related outpatient visits also differed significantly (3.5 visits for titration patients vs. 2.8, respectively; t-test, P = 0.002) and psychiatric costs ($22 vs. $10, respectively; t-test, P = 0.043). However, non–depression-related psychologist, inpatient, and ED visits and associated costs did not differ between the two groups. P values resulting from the multivariate analysis agreed with the t-test P values.

Table 4 (page 458) presents the overall outcomes for the combined (dose-titration and control) groups during the first six months since initiation of therapy. Results were as follows:

- lower average antidepressant costs ($263 with titration vs. $341, respectively, t-test, P < 0.001)
- more depression-related outpatient visits (3.5 vs. 2.7, respectively, t-test, P = 0.010)
- higher costs for outpatient visits ($252 vs. $178, respectively; adjusted t-test, P = 0.016)

Statistically significant non–depression-related outcomes were as follows:

- total pharmacy costs ($506 with titration vs. $649 without titration, respectively; t-test, P = .033).
- outpatient visits (9.5 vs. 8.3; t-test, P = 0.030).
- total psychiatrist visits (0.66 vs. 0.33; t-test, P = .02).
- total psychiatric costs ($46 vs. $22, t-test, P = 0.02).

P values resulting from the multivariate analysis also suggested that total pharmacy claims (P = 0.008) and psychiatrist visits (P = 0.042), with adjusted differences, were significantly greater than zero.

Bar charts in Figures 4 and 5 (page 459) show a compari-
# Costs of Dose Titration in Major Depressive Disorder

## Table 3 Depression and Non–Depression-Related Outcomes in Two Patient Groups During the First Eight Weeks of Therapy with Selective Serotonin Reuptake Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Titration Group (N = 724)</th>
<th>Non-Titration Group (N = 724)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t-test*</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td><strong>Depression-Related Outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total days in full therapeutic dose</td>
<td>38 (5.6)</td>
<td>56 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressant costs</td>
<td>$119 (116)</td>
<td>$153 (236)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>1.8 (2.7)</td>
<td>1.2 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$137 (386)</td>
<td>$81 (315)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total psychologist visits</td>
<td>0.79 (2.9)</td>
<td>0.66 (3.4)</td>
<td>0.430</td>
</tr>
<tr>
<td>Total psychologist costs</td>
<td>$27 (140)</td>
<td>$20 (148)</td>
<td>0.340</td>
</tr>
<tr>
<td>Total psychiatrist visits</td>
<td>0.69 (1.8)</td>
<td>0.42 (1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total psychiatrist costs</td>
<td>$52 (180)</td>
<td>$32 (257)</td>
<td>0.0804</td>
</tr>
<tr>
<td>Total emergency visits</td>
<td>0.01 (0.12)</td>
<td>0.00 (0.00)</td>
<td>0.132</td>
</tr>
<tr>
<td>Total emergency costs</td>
<td>$2.1 (43)</td>
<td>$0 (0)</td>
<td>0.182</td>
</tr>
<tr>
<td>Total inpatient visits</td>
<td>0.03 (0.34)</td>
<td>0.011 (0.15)</td>
<td>0.128</td>
</tr>
<tr>
<td>Total inpatient costs</td>
<td>$31.7 (560)</td>
<td>$18 (467)</td>
<td>0.607</td>
</tr>
<tr>
<td><strong>Non–Depression-Related Outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total pharmacy claims</td>
<td>3.5 (4.1)</td>
<td>3.5 (4.0)</td>
<td>0.917</td>
</tr>
<tr>
<td>Total pharmacy costs</td>
<td>$170 (385)</td>
<td>$230 (639)</td>
<td>0.024</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>3.5 (5.1)</td>
<td>2.8 (4.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$383 (1,533)</td>
<td>$284 (690)</td>
<td>0.082</td>
</tr>
<tr>
<td>Total psychologist visits</td>
<td>0.14 (0.84)</td>
<td>0.10 (0.75)</td>
<td>0.394</td>
</tr>
<tr>
<td>Total psychologist costs</td>
<td>$12 (75)</td>
<td>$7 (53)</td>
<td>0.158</td>
</tr>
<tr>
<td>Total psychiatrist visits</td>
<td>0.3 (1.5)</td>
<td>0.2 (1.1)</td>
<td>0.085</td>
</tr>
<tr>
<td>Total psychiatrist costs</td>
<td>$22 (146)</td>
<td>$10 (75)</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>Combined Outcomes at 56 Days:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>5.3 (5.9)</td>
<td>4.0 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$520 (1,585)</td>
<td>$366 (767)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*The P value corresponds to a paired t-test testing for significance in outcome difference.
† Multiple linear regression tests after adjusting for baseline differences in the number and cost of medications as well as inpatient and outpatient baseline costs.
Bold type indicates differences in mean, significant at P < 0.05.
Table 4  Depression-Related and Non–Depression-Related Outcomes in Two Groups of Patients During the First Six Months of Therapy with Selective Serotonin Reuptake Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Titration Group (N = 724)</th>
<th>Non-Titration Group (N = 724)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Median</td>
<td>Mean (SD) Median</td>
<td>t-test*</td>
</tr>
<tr>
<td><strong>Depression-Related Outcomes†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant costs</td>
<td>$263 (257) $222</td>
<td>$341 (441) $256</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>3.5 (6.2) 1</td>
<td>2.7 (6.1) 1</td>
<td>0.010</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$252 (602) $56</td>
<td>$178 (600) $0</td>
<td>0.016</td>
</tr>
<tr>
<td>Total psychologist visits</td>
<td>1.7 (6.5) 0</td>
<td>1.7 (9.7) 0</td>
<td>0.856</td>
</tr>
<tr>
<td>Total psychologist costs</td>
<td>$58 (312) $0</td>
<td>$54 (484) $0</td>
<td>0.883</td>
</tr>
<tr>
<td>Total psychiatrist visits</td>
<td>1.32 (4.0) 0</td>
<td>0.96 (2.7) 0</td>
<td>0.051</td>
</tr>
<tr>
<td>Total psychiatrist costs</td>
<td>$91 (317) $0</td>
<td>$61 (300) $0</td>
<td>0.068</td>
</tr>
<tr>
<td>Total emergency visits</td>
<td>0.01 (0.12) 0</td>
<td>0.00 (0.00) 0</td>
<td>0.132</td>
</tr>
<tr>
<td>Total emergency costs</td>
<td>$2.1 (42.7) $0</td>
<td>$0 (0) $0</td>
<td>0.182</td>
</tr>
<tr>
<td>Total inpatient visits</td>
<td>0.03 (0.34) 0</td>
<td>0.01 (0.20) 0</td>
<td>0.182</td>
</tr>
<tr>
<td>Total inpatient costs</td>
<td>$32 (560) $0</td>
<td>$18 (467) $0</td>
<td>0.604</td>
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<tr>
<td><strong>Non–Depression-Related Outcomes†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total pharmacy claims</td>
<td>9.2 (11.3) 6</td>
<td>10.0 (11.2) 7</td>
<td>0.082</td>
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<tr>
<td>Total pharmacy costs</td>
<td>$506 (1,364) $132</td>
<td>$649 (1,427) $212</td>
<td>0.033</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>9.5 (11.5) 6</td>
<td>8.3 (9.7) 5</td>
<td>0.030</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$1,011 (2,451) $341</td>
<td>$1,355 (11,745) $281</td>
<td>0.435</td>
</tr>
<tr>
<td>Total psychologist visits</td>
<td>0.33 (2.03) 0</td>
<td>0.27 (1.88) 0</td>
<td>0.578</td>
</tr>
<tr>
<td>Total psychologist costs</td>
<td>$25 (151) $0</td>
<td>$18 (131) $0</td>
<td>0.392</td>
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<tr>
<td>Total psychiatrist visits</td>
<td>0.66 (3.0) 0</td>
<td>0.33 (2.2) 0</td>
<td>0.020</td>
</tr>
<tr>
<td>Total psychiatrist costs</td>
<td>$46 (227) $0</td>
<td>$22 (160) $0</td>
<td>0.019</td>
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<tr>
<td><strong>Combined Outcomes at 180 Days†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>13.0 (13.4) 9</td>
<td>11.0 (11.6) 8</td>
<td>0.0020</td>
</tr>
<tr>
<td>Total outpatient costs</td>
<td>$1263 (2544) $572</td>
<td>$1533 (11,760) $416</td>
<td>0.5412</td>
</tr>
</tbody>
</table>

* The P value corresponds to a paired t-test testing for significance in outcome difference.
† Multiple linear regression tests after adjusting for baseline differences in the number and cost of medications as well as inpatient and outpatient baseline costs.
Bold type indicates differences in mean, significant at P < 0.05.
son of depression-related psychiatric and outpatient health care utilization for patients receiving individual SSRI monotherapy. After the Sidak method was used to adjust P values for multiple comparisons, the titration patients had significantly higher total depression-related physician outpatient costs (P < 0.05) and more visits, compared with the escitalopram and sertraline mono-therapy non-titration groups.

Depression-related psychiatric costs and visits were also significantly higher for citalopram (P < 0.05) and almost significantly higher for escitalopram, but not for the other medications. Except for fluoxetine psychiatric costs at 56 days, all differences indicated increased use by the titration patients.

**DISCUSSION**

SSRIs are frequently used to treat depression and other psychiatric illnesses. Although SSRIs are more cost-effective than tricyclic antidepressants, additional costs incurred from dose titration have not been fully explored.

Mitchell et al. reported that upward titration was associated with increasing health care utilization costs in a managed care setting. They cited a study by Thompson et al., who classified MDD patients using SSRIs according to these usage patterns: early discontinuation, switching or augmentation, upward titration, partial compliance, or three-month compliance. In that study, the group experiencing switching or augmentation had the highest medical care costs, whereas upward titration ranked second-lowest in overall costs.

Although Thompson et al. also analyzed managed care claims data to draw their conclusions, they did not specifically target costs differences between titration and non-titration patients at therapy initiation; instead, they compared overall usage patterns of SSRIs and their associated costs. Nevertheless, they also suggested that dose titration was associated with higher costs.

In our study, MDD patients undergoing dose titration with SSRIs incurred higher psychiatric costs (mean, 0.69 vs. 0.42, respectively, during the first eight-week period) and depression-related outpatient costs (mean, 1.8 vs. 1.2 during the first eight-week period) than a comparable control group. Even when we relaxed the assumption that dosage levels for control exceeded dosage levels for the titration case, outpatient cost differences remained statistically significant and greater for the titration group for both eight weeks (56 days) and six months after initiation, indicating that these differences are robust to modifications of the inclusion criteria. This association suggests that the difference might be a result of increased patient monitoring related to titration.

Although dose titration appeared to be the more expensive and resource-intensive treatment in our study, we hesitate to ascribe this difference to a higher cost–benefit ratio for titration because we did not examine the benefit portion. The higher cost and greater resource utilization in titration may reflect better clinical practice and may be in line with guidelines in quality-of-care literature seeking to increase the frequency of follow-up for depression patients during the acute phase of treatment.

The decreased pharmaceutical costs in the titration patients might be explained by the constraint of a higher dosage requirement in the control group. The lower number of therapeutic days, estimated by the algorithm in the titration group, compared with controls, was also expected, because titration doses are initially below therapeutic levels. Although the economic and therapeutic impact differed among the SSRIs selected at therapy initiation, our results suggest that the overall trend holds true, independent of the specific SSRI used. During the first 56 days of therapy, SSRI patients with dose titration had a 32% decrease in the number of therapeutic days and a 50% increase in the number of depression-related outpatient visits. These increases coincided with higher depression-related out-
Costs of Dose Titration in Major Depressive Disorder

In future studies, we would like to evaluate the long-term effects of dose titration. It is important to consider that even though titration patients may be more frequent users of health care initially, they may also become more stabilized with the right dosage, thereby improving medication adherence, reducing the likelihood of relapse, and thus decreasing health care utilization and costs in the future. So far, however, no studies have examined this theory. Clearly, there is a need to further understand the role of dose titration.

Payers of health care, including MCOs, are constantly seeking cost-efficient ways to manage their patient populations. Because depression is one of the most costly diseases, it is frequently targeted by various disease-management programs, with the goal of accurately identifying and applying appropriate, expeditious treatment or interventions to prevent eventual economic and humanistic burdens to payers and patients. With the introduction of innovative agents with improved tolerability profiles and the increased availability of generic forms of current drugs, formulary decision makers at MCOs can make recommendations based not only on efficacy but also on overall effectiveness (i.e., how does the drug work in the real world, and what is its impact on total cost of care?)

Although many studies evaluating the total effectiveness of drugs, or classes of drugs, in treating depression have been published, we believe that ours is the first one to directly assess the incremental burden of dosing schedules—specifically upward titration—from the perspective of both patients and payers. Future economic assessments of antidepressants need to incorporate such calculations, which are often missed but can have a significant economic as well as humanistic burden.

STUDY LIMITATIONS

Like most studies derived from administrative databases, our results are limited by the accuracy of the information captured on claim forms. Potential errors in MDD diagnoses may exist in claims databases. Although we used propensity-scoring techniques to ensure an equal distribution of covariates between titration and non-titration groups of patients, the technique does not fully ensure equal distribution of clinical burden because of a lack of clinical data in the database. Our ability to generalize the study’s findings is limited to patients who had health insurance and who did not seek treatments not covered by their health insurance, because this information was not captured. Only direct costs (e.g., for prescriptions and office visits) were included in the study; we did not include indirect costs, such as decreased work productivity and absenteeism. Therefore, our findings may reflect lower actual expenditures in patient characteristics preceding therapy initiation might have affected the validity of our conclusions.

Despite these limitations, our findings may have significant applications in improving costs and health outcomes of SSRIs for depressed patients. Future research is needed to examine dose titration over a longer period of time and to evaluate the extent to which higher initial expenditures might lead to improved regimen adherence, disease stabilization, and cost savings.

CONCLUSION

Patients with MDD undergoing dose titration with SSRI therapies at the start of therapy used more health care resources and had fewer days at the optimal therapeutic dose than a comparable non-titration control group.

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REFERENCES

Dose Titration in Major Depression

continued from page 460