Impact of Antidepressant Drug Adherence on Comorbid Medication Use and Resource Utilization

Wayne Katon, MD; Christopher Ron Cantrell, PhD; Michael C. Sokol, MD, MS; Evelyn Chiao, PharmD; Joette M. Gdovin, PhD, MPA

Background: Patients with depression are often non-adherent to therapy for depression and chronic comorbid conditions.

Methods: To determine whether improved antidepressant medication adherence is associated with an increased likelihood of chronic comorbid disease medication adherence and reduced medical costs, we conducted a retrospective study of patients initiating antidepressant drug therapy with evidence of dyslipidemia, coronary artery disease (CAD), or both; diabetes mellitus (DM); or CAD/dyslipidemia and DM identified from a claims database. Measures included antidepressant medication adherence, measured by medication possession ratio during 180 days without a 15-day gap before 90 days of therapy; comorbid medication adherence, measured by medication possession ratio during 1 year; and the association between improved antidepressant drug adherence and disease-specific and total medical costs.

Results: Of 8040 patients meeting the study criteria, those adherent to antidepressant medication were more likely to be adherent to comorbid therapy vs those non-adherent to antidepressant drug therapy (CAD/dyslipidemia: odds ratio [OR], 2.13; DM: OR, 1.82; and CAD/dyslipidemia/DM: OR, 1.45; P < .001 for all). Patients adherent to antidepressant drug therapy also had significantly lower disease-specific charges vs nonadherent patients (17% lower in CAD/dyslipidemia, P = .02; 8% lower in DM, P = .39; and 14% lower in CAD/dyslipidemia/DM, P = .38). These patients also incurred lower total medical charges (6.4% lower in CAD/dyslipidemia, P = .048; 11.8% lower in DM, P = .04; and 19.8% lower in CAD/dyslipidemia/DM, P = .03).

Conclusions: Antidepressant drug adherence was associated with increased comorbid disease medication adherence and reduced total medical costs for CAD/dyslipidemia, DM, and CAD/dyslipidemia/DM. Future studies should investigate the relationship between increased adherence and costs beyond 1 year.

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Depression affects 32.6 million to 35.1 million adults in the United States each year and has a lifetime prevalence of 16.2%, but it still often goes undiagnosed, with documented gaps in the quality of care provided by primary care and other nonpsychiatric practitioners.1,2 As a result, the economic burden of depression is high, estimated to be $81.5 billion annually, fueled primarily by losses in work productivity and high relapse rates.3

Although proper diagnosis is essential to the management of depression, the increased burden of depression may also be due to inadequate length of therapy with antidepressant agents. Contrary to clinical practice guidelines for the treatment of depression, which recommend at least 6 to 9 months of continuous therapy, it has been shown that 28% of patients discontinue antidepressant treatment within the first month of therapy, and more than 40% of patients discontinue this therapy by 3 months.4 In addition to poor treatment outcomes, early discontinuation may be associated with excess resource utilization, estimated to be $800 to $3000 per year for each patient who discontinues therapy early.5,6

Patients with depression are more likely than nondepressed patients to have chronic comorbid medical conditions, and they are also up to 3 times more likely to be nonadherent to prescribed medications for these other conditions.7,8 In congestive heart failure and coronary artery disease (CAD) studies, for example, patients with depression were less likely to adhere to prescribed medication regi-
patients with such chronic illnesses.14,15 The association of depression with poor adherence to chronic disease treatment regimens may explain why depression is associated with significantly higher costs in patients with such chronic illnesses.14,15

Although these studies provide valuable information regarding the effect of depression on concurrent chronic disease medication adherence and clinical outcomes, it remains to be determined whether patients with better adherence to antidepressant drug therapy would also have improved adherence to medications for comorbid conditions compared with patients with poor antidepressant drug adherence. Determining how such improvements in adherence would affect overall resource utilization and medical costs in these disease states is also important.7 This study was designed to answer 2 primary research questions in patients with depression and comorbid medical illness: (1) Is improved adherence to antidepressant medication associated with an increased likelihood of being adherent to chronic comorbid disease medications? (2) Is improved adherence to antidepressant medication associated with a decrease in total and comorbid disease-specific medical costs? The comorbid diseases of interest in this study are DM, CAD, and dyslipidemia (a risk factor for CAD), chosen because of their high prevalence and the significant role each has in increased patient morbidity and mortality: each disease affects more than 6% of the US population.16 These comorbid diseases were also chosen because of the high use of oral medication as a primary treatment approach. Because CAD and DM often overlap in patients and, as such, are closely intertwined in clinical outcomes, patients with both CAD and DM were of interest.17,18

**TABLE 1. Antidepressant Medications Used by Participants**

<table>
<thead>
<tr>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion hydrochloride</td>
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<tr>
<td>Bupropion hydrochloride sustained-release</td>
</tr>
<tr>
<td>Citalopram hydrobromide</td>
</tr>
<tr>
<td>Escitalopram oxalate</td>
</tr>
<tr>
<td>Fluoxetine hydrochloride</td>
</tr>
<tr>
<td>Mirtazapine</td>
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<tr>
<td>Nefazodone hydrochloride</td>
</tr>
<tr>
<td>Paroxetine hydrochloride</td>
</tr>
<tr>
<td>Paroxetine hydrochloride controlled release</td>
</tr>
<tr>
<td>Sertraline hydrochloride</td>
</tr>
<tr>
<td>Venlafaxine hydrochloride</td>
</tr>
<tr>
<td>Venlafaxine hydrochloride extended-release</td>
</tr>
</tbody>
</table>

**METHODS**

**DATA SOURCE**

Medical and pharmacy claims data were extracted from the National Managed Care Benchmark Database (IHCIS, Waltham, Mass), a nationally representative sample with data from 30 health plans covering more than 25 million lives in the United States.

**SAMPLE SELECTION**

**Antidepressant Use Criteria**

All patients receiving at least 1 prescription for an antidepressant medication listed in Table 1 between July 1, 2001, and December 31, 2002, were identified in the database. The index date for each patient was the date of their first antidepressant drug prescription within this period. Patients were required to be at least 18 years of age, continuously eligible for 6 months before and 12 months after their index date, and without evidence of antidepressant drug therapy for 6 months before their index date. Persons with a diagnosis of schizophrenia or bipolar disorder and patients who received an antipsychotic medication 6 months before or 1 year after their index date were excluded from the study.

**Identification of Patients With Comorbid Disease Conditions**

Patients who met the antidepressant drug use criteria were then assessed for the presence of CAD/dyslipidemia, DM, or CAD/dyslipidemia/DM. Patients with CAD and dyslipidemia were combined because dyslipidemia is an important risk factor for CAD. The criteria for identification of comorbid diseases were adapted from the HEDIS (Health Plan and Employer Data and Information Set) guidelines when available (Table 2).17 Eligible patients were further required to have received at least 1 prescription for the comorbid disease medication of interest before and after initiation of antidepressant drug therapy. Patients meeting all the selection criteria were then followed up for 12 months after their index date to assess 6-month antidepressant adherence, 12-month comorbid disease medication adherence, and 12-month total medical and comorbid disease-specific medical costs.

**ADHERENCE METRIC**

Medication adherence was measured by calculating a medication possession ratio (MPR) using the continuous multiple interval medications available method.20 The MPR is calculated as the sum of each day's supply of all prescriptions in a specific period divided by the total number of days during the specific period and ranges from 0%, indicating no adherence, to 100%, indicating perfect adherence. Therefore, a patient with a 50% MPR during a 180-day period had 90 days of medication (180 days × 50% = 90 days). Patients were assumed to have consumed all medication acquired.

Eligible patients were deemed adherent or nonadherent with their comorbid disease-specific medication based on an MPR threshold of 80%.21,22 Patients with CAD/dyslipidemia/DM were required to meet the 80% criteria for both CAD/dyslipidemia and DM medications. To determine the threshold for evaluating compliance for antidepressant drugs, 2 separate metrics (traditional MPR and early discontinuation) were used. Because HEDIS performance measures indicate that patients should continue antidepressant drug therapy acutely for a minimum of 90 days and continuously for 180 days during a 231-day period (a traditional MPR of 78%), and previous studies have measured discontinuation based on evidence of a gap of more than 15 days between prescriptions before 90 days (early discontinuation metric), patients were deemed not adherent to antidepressant agents if their MPR was less than 80% or if they had evidence of a 15-day gap in prescriptions before 90 days of con-
international classification of diseases, ninth revision, clinical modification

The association between 6-month antidepressant medication adherence and 12-month comorbid disease–specific and total health care costs was determined using log-linear multivariate regression modeling, controlling for the same covariates plus charges for the 6 months before the index date and 12-month comorbid disease–specific adherence. Medical health care costs included the total amount charged for physician visits, inpatient hospitalizations, outpatient hospital care, emergency department visits, and other services, including mental health specialty care. Pharmacy costs were not captured. Comorbid disease–specific charges for health care costs were determined by the primary international classification of diseases, ninth revision, clinical modification field on the medical claim (Table 2). Charge data were log transformed owing to the skewness of the data. The level of significance was preset at α = .05.

**COMORBIDITY ASSESSMENT**

Comorbidity was assessed by means of (1) the Charlson comorbidity index, with the Dartmouth-Manitoba and Deyo modification; (2) a count of unique medical illnesses beyond those in the Charlson index; (3) a count of the total number of prescriptions received; and (4) a count of unique prescription drug categories received in the 6 months before each patient’s index date.27,28 Charlson index scores for this study were derived by evaluating the presence of various international classification of diseases, ninth revision, clinical modification codes, with higher scores indicating a higher burden of comorbidity. All the previously described methods of capturing comorbidity have been associated with a positive predictive value for the number of hospitalizations, medical costs, and patient mortality.29

**ANALYSIS OF OUTCOMES**

Inferential analyses were performed to assess the impact of 6-month antidepressant drug adherence on 12-month comorbid medication adherence. This association was determined using a logistic regression model controlling for the following covariates: age, sex, insurance plan type (independent, other, point of service, preferred provider organization, and health maintenance organization), utilization of psychiatric specialty care, the presence of an indicator for a 90-day continuous therapy.3,19 Patients not having a 15-day gap before 90 days and remaining 80% adherent to antidepressant drug therapy during the entire 180-day period were deemed adherent.

**STUDY POPULATION**

A total of 8040 patients met the study inclusion and exclusion criteria. Approximately 48% of the sample was female, with an average age of 55.6 years. Although all of the patients initiated antidepressant drug therapy, only 40% had a coded diagnosis of anxiety or depression. The demographic characteristics of each comorbid cohort (CAD/dyslipidemia, DM, and CAD/dyslipidemia/DM) are given in Table 3.
During the 6-month period before the index date, 74% of CAD/dyslipidemia, 77% of DM, and 72% of CAD/dyslipidemia/DM patients were adherent to their comorbid disease medication. After starting antidepressant drug therapy, most patients seemed to remain adherent to their comorbid disease medications in the year after initiating antidepressant medication, although adherence rates were lower (CAD/dyslipidemia/DM, 52.6%; CAD/dyslipidemia, 60.0%; and DM, 64.4%). Overall, patients were less adherent to their antidepressant medication than to their comorbid disease medication based on achieving an 80% MPR during 180 days with no evidence of gaps in therapy (CAD/dyslipidemia/DM, 42.6% adherent to antidepressant drug therapy; CAD/dyslipidemia, 38.7% adherent; and DM, 36.3% adherent). This is represented in Figure 1, with the average rates of adherence weighted by the number of patients in each comorbid diagnosis cohort.

Results of logistic regression controlling for the level of comorbid disease medication adherence in the 6-month period before the index date and other background covariates show that patients who were adherent to antidepressant medication in the 180-day period after the index date were significantly more likely to be adherent to comorbid disease therapy during 1 year compared with patients who were not adherent to their antidepressant medication (Figure 2). This effect was consistent across disease cohorts.

### DISEASE-SPECIFIC CHARGES

Patients with CAD/dyslipidemia/DM incurred the greatest comorbid disease–specific medical charges ($1138), followed by those with DM ($481) and CAD/dyslipidemia ($419). The largest portion of charges was for outpatient care ($871, $411, and $303, respectively). As depicted in Figure 3, patients with CAD/dyslipidemia/DM had higher total medical charges ($6155) than did patients with DM or CAD/dyslipidemia alone.

After adjusting for background covariates, CAD/dyslipidemia patients adherent to antidepressant drug therapy incurred 17% lower disease-specific charges than did nonadherent patients (P = .02) (Table 4). In the DM and CAD/dyslipidemia/DM cohorts, antidepressant drug–adherent patients incurred 8% to 14% lower disease-specific charges than did nonadherent patients ($P < .001 for all).
specific charges than did nonadherent patients, but the differences were not statistically significant. When we evaluated total medical charges, CAD/dyslipidemia and DM patients who were adherent to antidepressant drug therapy incurred statistically significantly lower medical charges (6.4% and 11.8% lower, respectively) than did patients who were nonadherent, and antidepressant drug–adherent CAD/dyslipidemia/DM patients incurred almost 20% lower medical charges. Post hoc analyses were conducted to determine which specific charge category was reduced as adherence increased. Using log-linear multivariate regression models controlling for the same covariates as the a priori analysis for total medical costs, it was found that much of the medical savings were from reductions in inpatient and outpatient medical charges, although the significance of the inpatient and outpatient models varied (Table 4).

**COMMENT**

The purpose of this study was to evaluate the effect of antidepressant drug adherence on comorbid disease medication adherence and on total and comorbid disease–specific medical costs. The results of this study indicate that in patients treated with antidepressant agents, improved antidepressant drug adherence is associated with an almost 2-fold improvement in comorbid disease medication adherence. Although previous studies3,6 have demonstrated that patients with depression often have high rates of antidepressant medication nonadherence and a greater likelihood of comorbid disease medication nonadherence, this is the first study to evaluate their association. Because adherence to antidepressant medication guidelines was the hypothesized driver of comorbid medication adherence, we used a more stringent definition of adherence to antidepressant drug therapy compared with adherence to comorbid disease medications. This finding is important because studies by Thompson,3 Melfi,30 Eaddy31 and Katon and colleagues33 have shown that improved adherence to clinical practice guidelines for depression was associated with lower rates of disease relapse and a reduction in medical resource utilization. Of concern is that only approximately 40% of the patients were adherent to antidepressant drug therapy. Although not evaluated in this study, the cause of poor antidepressant drug adherence in primary care has been linked to the lack of adequate patient education on treatment expectations and infrequent follow-up visits by primary care physicians and the high incidence of medication-related adverse events.5,32 Based on this evidence, there is a need to improve the quality of depression care and to provide physicians and patients with therapeutic options that are effective and well tolerated. Lin et al13 and Katon and colleagues33 also recently showed that patients with depression and DM were more likely to have lapses in relevant medication refills, had greater disease symptom burden, and had higher functional impairment than patients with DM alone. Comorbid depression after myocardial infarction has also been associated with less adherence to medication, diet, and exercise regimens that modify cardiac risk.10 Taken together, these studies suggest that improving the quality of depression care based on adherence to antidepressant medications may be associated with improved outcomes in patients with chronic comorbid conditions and with savings in total medical costs. In this study, patients with CAD/dyslipidemia/DM who are nonadherent to antidepressant drug therapy would incur almost 20% lower total medical charges per year, or approximately $1230 annually, if antidepressant medication adherence were improved.

Owing to the potential for residual confounding, it cannot be definitively determined whether the reduction in medical costs was due to increased antidepressant drug adherence; however, all statistical models controlled for the level of comorbid medication adherence before and after initiating therapy. Previous studies evaluating the economic benefits of antidepressant drug therapy adherence did not account for this, and thus their results may have included effects of improved comorbid medication adherence, making the results of this study seem modest in comparison. However, by including comorbid medication adherence during the period after the index date as a covariate in the statistical models, the effect seen in this study is thought to be primarily attributable to improved antidepressant drug adherence, in the absence of residual confounding. A conclusion that can be drawn from this is that the benefit of improved antidepressant drug therapy observed may be incremental to the benefits expected with improved adherence to comorbid medication.

The 6% to 20% reduction in total medical costs seen across the comorbid disease cohorts for patients adherent to antidepressant drug therapy vs those not adherent may be greater if follow-up was extended. This study assessed only 1-year comorbid disease and total medical costs, thus the benefits of improved antidepressant medication adherence and improved adherence to comorbid disease medication may not be fully realized in such a short time. Studies have shown decreased ambulatory costs for 2 years after an intervention to improve antidepressant drug adherence, suggesting that the reduction in costs in this study would remain during a length-
ened follow-up period. Additional studies with longer follow-up would also validate the impact on comorbid disease morbidity and mortality.

Although this study provides strong evidence regarding the associations among improved antidepressant drug adherence, comorbid disease medication adherence, and resource utilization, there are limitations that must be identified. First, the retrospective cross-sectional study design restricts the ability to draw direct causal inferences related to medication adherence. In an attempt to isolate the effect of antidepressant medication adherence from adherence to medications for other medical conditions, this study adjusted for a wide range of confounders, as described earlier. Because this is the first study to potentially isolate this effect, this may partially explain the moderate effect size seen. In addition, the use of claims data may not allow for accurate representation of the incidence of depression and comorbid anxiety in this population. More than 50% of the patients in this study did not have a coded diagnosis of depression or anxiety, and it is possible that some of these patients received antidepressant agents for the treatment of conditions other than depression or anxiety. Depression and anxiety are often undercoded in administrative databases; previous studies have shown that primary care physicians frequently miscode depression diagnoses as physical symptoms to maximize reimbursement and to avoid stigmatizing the patient. In this study, the presence of a diagnosis was included as a covariate in the regression models to attempt to minimize any potential effects. The use of medical charges, rather than costs, is also a limitation because charges reflect inflated medical costs.

Finally, the claims data provide information on prescription patterns only rather than on actual medication use. Pharmacy records tend to overestimate adherence compared with gold standard monitoring systems. However, it is not likely that these issues would affect the outcome of the study because variations in medication adherence between claims data and medication use are expected to be consistent among patient types. Despite these limitations, the results of this study provide essential information for health care decision makers about the importance of antidepressant drug therapy adherence and the association with comorbid disease medication adherence and health care costs. Future studies should examine similar relationships in other disease areas and should expand the period of analysis beyond 1 year to potentially capture additional benefits from improved antidepressant drug adherence.

In this study, as adherence to antidepressant drug therapy improved, total medical charges decreased significantly across all comorbid disease cohorts. Although the reduction in disease-specific charges was not always statistically significant, the trend showed economic advantages for improving antidepressant drug adherence. Although this study did not capture prescription expenditures, it is expected that pharmacy costs would increase owing to improved adherence to comorbid disease therapy, offsetting somewhat the reduction in medical costs.

In conclusion, the results of this study indicate that adherence to antidepressant drug therapy is generally worse than adherence to comorbid disease medication in CAD/dyslipidemia, DM, and CAD/dyslipidemia/DM. After controlling for levels of medication adherence for comorbid medical conditions before the index date, increased antidepressant drug adherence was associated with increased adherence to comorbid disease medication and a reduction in comorbid disease-specific and total medical costs. Future studies should investigate whether such associations among antidepressant medication adherence, comorbid medication adherence, and resource utilization exist in disease states other than CAD/dyslipidemia, DM, and CAD/dyslipidemia/DM while also expanding the period of analysis beyond 1 year.

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Correspondence: Evelyn Chiao, PharmD, Applied Health Outcomes, 4114 Woodlands Pkwy, Suite 500, Palm Harbor, FL 34685 (echiao@applied-outcomes.com).

Table 4. Difference in Adjusted Disease-Specific and Total Medical Charges for Antidepressant Drug Adherent vs Nonadherent Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Comorbid Disease</th>
<th>Point Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-specific medical charges</td>
<td>CAD/dyslipidemia</td>
<td>-0.17 (-0.32 to -0.03)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>-0.08 (-0.27 to 0.10)</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>CAD/dyslipidemia/DM</td>
<td>-0.14 (-0.45 to 0.17)</td>
<td>.38</td>
</tr>
<tr>
<td>Inpatient charges*</td>
<td>CAD/dyslipidemia</td>
<td>-0.14 (-0.29 to 0.01)</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>-0.45 (-0.72 to -0.19)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>CAD/dyslipidemia/DM</td>
<td>-0.23 (-0.69 to 0.23)</td>
<td>.33</td>
</tr>
<tr>
<td>Outpatient charges*</td>
<td>CAD/dyslipidemia</td>
<td>-0.06 (-0.12 to 0.002)</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>-0.10 (-0.21 to 0.02)</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>CAD/dyslipidemia/DM</td>
<td>-0.22 (-0.40 to -0.05)</td>
<td>.01</td>
</tr>
<tr>
<td>Other ancillary charges*</td>
<td>CAD/dyslipidemia</td>
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<td>.59</td>
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<tr>
<td></td>
<td>DM</td>
<td>-0.03 (-0.26 to 0.20)</td>
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<tr>
<td></td>
<td>CAD/dyslipidemia/DM</td>
<td>0.20 (-0.21 to 0.60)</td>
<td>.34</td>
</tr>
<tr>
<td>Total medical charges</td>
<td>CAD/dyslipidemia</td>
<td>-0.06 (-0.13 to -0.001)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>-0.12 (-0.23 to -0.005)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>CAD/dyslipidemia/DM</td>
<td>-0.20 (-0.38 to -0.02)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus. *Conducted as post hoc analyses.
Author Contributions: Dr Drovin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: Drs Cantrell and Sokol are employees of GlaxoSmithKline. Dr Katon is an Anxiety Advisory Board member for GlaxoSmithKline, and he has been paid a fee by Applied Health Outcomes for his participation in the preparation of this study.

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REFERENCES


