ORIGINAL RESEARCH

Relationship of Total Health Care Charges to Selective Serotonin Reuptake Inhibitor Utilization Patterns Including the Length of Antidepressant Therapy—Results From a Managed Care Administrative Claims Database

MICHAEL T. EADDY, PharmD, PhD; BENJAMIN G. DRUSS, MD, MPH; MATTHEW W. SARNES, PharmD; TIMOTHY S. REGAN, RPh, CPh; and LAURA E. FRANKUM, PharmD

ABSTRACT

OBJECTIVE: Administrative claims data analysis performed in the early 1990s found lower total medical costs for patients with depression who remained on antidepressant therapy with selective serotonin reuptake inhibitors (SSRIs) for at least 90 days compared with patients who discontinued therapy prior to 60 days. Over the past decade, many changes in the health care system have occurred that might impact the reproducibility of these findings. The purpose of this study was to investigate the association between SSRI utilization patterns and the use of health care services in the managed care environment.

METHODS: A large managed care claims database was used to identify patients receiving 2 or more SSRI prescriptions between June 2001 and December 2002. In order to ensure that patients were newly started on SSRI therapy, patients were required to have 6 months of enrollment data prior to their index date, without evidence of antidepressant therapy. Continuous enrollment for 12 months following their index prescription was also required. Patients with schizophrenia, bipolar disorder, or who received antipsychotic medications were excluded from this analysis. Patients were placed into 1 of 5 mutually exclusive antidepressant utilization cohorts: (1) <90 days, (2) ≥90 days, (3) titration, (4) partial compliance, and (5) therapy change. Total medical costs, with and without pharmacy costs, were then compared between antidepressant utilization cohorts for 12 months of claims data.

RESULTS: There were 65,753 patients included in the study. Medical charges without pharmacy charges were lowest in the ≥90-day cohort ($5,143) compared with the partial compliance ($5,909, $P<0.05$), <90-day ($6,289, $P<0.001$), titration ($6,375, $P<0.001$), and therapy change ($7,858, $P<0.001$) cohorts. Differences in total medical charges—without pharmacy charges—were primarily influenced by inpatient charges. The addition of pharmacy charges, including the charges for antidepressants, resulted in total medical charges that were not statistically different for the ≥90-day cohort compared with the <90-day cohort, $7,454 and $7,829, respectively, $P=0.606$.

CONCLUSION: Medical charges—without pharmacy charges—were lower for patients remaining on antidepressant drug therapy for at least 90 continuous days compared with patients who used antidepressants for less than 90 continuous days, but total health care charges, including pharmacy charges, were not different between the 2 groups.

KEYWORDS: Selective serotonin reuptake inhibitors, Depression, Length of therapy, Compliance, Economic burden, Duration of therapy

J Manag Care Pharm. 2005;11(2):145-50

Note: *An editorial on the subject of this article, "Evidence-Based Medicine: Are SSRIs More Effective Than Placebo and What Length of Therapy Is Enough?" appears on pages 172-76 of this issue.*

Depression affects between 32.6 and 35.1 million adults in the United States each year, with a lifetime prevalence of 16.2%.[1] The economic burden of depression is estimated at $81.5 billion annually, primarily fueled by losses in productivity and excessive depression relapse rates.[2] An important factor in controlling the clinical and economic manifestations of depression is to promote the effective use of antidepressant therapy.

Clinical practice guidelines stress the importance of adherence to antidepressant therapy for a minimum length of time.[3,4] In general, these guidelines recommend acute treatment of first-episode depression patients for at least 3 months, followed by continuation of treatment for 6 to 9 months after symptoms have remitted and maintenance treatment for a minimum of 9 months after symptom resolution.[3-7] Despite treatment recommendations, approximately 28% of patients reportedly discontinue antidepressant therapy within 30 days of initiating treatment.[8,9] Only 60% of patients remain on therapy for longer than 90 days, and fewer than 50% remain on therapy for 6 or more months.[8,9]

The clinical benefits associated with antidepressant therapy for a duration specified by treatment guidelines have been documented.[10,11] These clinical benefits may also result in substantial savings in health care costs. Using data from 1991 to 1993 for 2 selective serotonin reuptake inhibitors (SSRIs), fluoxetine and sertraline, Thompson et al. demonstrated that various patterns of antidepressant use were associated with

Authors

MICHAEL T. EADDY, PharmD, PhD, is senior consultant; MATTHEW W. SARNES, PharmD, is senior manager; TIMOTHY S. REGAN, RPh, CPh, is associate director; and LAURA E. FRANKUM, PharmD, is a consultant, Applied Health Outcomes, Palm Harbor, Florida. BENJAMIN G. DRUSS, MD, MPH, is Rosalynn Carter Chair in Mental Health and associate professor of health policy and management, Rollins School of Public Health, Emory University, Atlanta, Georgia.

AUTHOR CORRESPONDENCE: Michael T. Eaddy, PharmD, PhD, Senior Consultant, Applied Health Outcomes, 3488 East Lake Rd., Suite 201, Palm Harbor, FL 34685. Tel: (727) 771-4100; Fax: (727) 771-4145; E-mail: meaddy@applied-outcomes.com

TABLE 1 ICD-9-CM Codes

Inclusion Diagnoses		
Depression	Major depressive disorder, single episode	296.2
	Major depressive disorder, recurrent episode	296.3
	Neurotic depression	300.4
	Depressive disorder, not elsewhere classified	311
Exclusion Diagnoses		
Schizophrenia	Schizophrenic disorders	295.xx
Bipolar disorder	Manic disorder, single episode	296.0x
	Bipolar affective disorder, manic	296.4x
	Bipolar affective disorder, mixed	296.6x
	Bipolar affective disorder depressed	296.5x
	Bipolar affective disorder, unspecified	296.7
	Manic-depressive psychosis, other	296.89
	Affective personality disorder, cyclothymic disorder	301.13
	Manic-depressive psychosis, unspecified	296.80
	Organic affective syndrome	293.83
	Unspecified affective psychosis	296.90

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.
Note: *An "x" indicates that all subcodes were included.*

significant differences in the cost of medical care.[12] The highest costs were found in patients who switched, had augmented therapy, or who discontinued treatment early (i.e., received no more than 60 days of antidepressant therapy during the 12-month follow-up period), while patients who remained on SSRI therapy for ≥90 days had the lowest costs of the 4 groups.[12] Only 10.2% of the 1,200 patients in the study by Thompson et al. continued SSRI therapy for ≥90 days.

It is important to investigate how the length of depression treatment impacts cost within the context of today's environment. Throughout the last 10 years, major changes in the antidepressant, mental health, and broader health care environments have occurred. Specifically, increased awareness of depression as a treatable disease, the introduction of newer SSRIs, and the growth of managed health care all have potentially impacted pharmaceutical treatment patterns and costs of care.

This study examines the association between length of antidepressant therapy and overall health care costs in a large, commercial managed care population. We seek to understand how length of antidepressant therapy and therapy changes are linked with service use in the current health care environment.

Methods

Data Source

Medical and pharmacy administrative claims data were extracted from the Pharmetrics Integrated Outcomes Database (Watertown, MA). At the time of data extraction, the Pharmetrics Database contained more than 1.9 billion claims from approximately 64 managed care organizations with 38 million members distributed throughout the United States.

Sample Selection

Patients who were at least 18 years of age and who had 2 or more pharmacy claims for an SSRI (citalopram, fluoxetine, immediate-release paroxetine, controlled-release paroxetine, or sertraline; note that escitalopram was not available until August 2002) between June 2001 and June 2002 were identified from the database. The index date, defined as the date of the first prescription for an SSRI during this time frame, was ascertained for each eligible patient. There were 3 periods defined for each patient: (1) preindex prescription period—the 6-month period prior to the index date, (2) postindex follow-up period—the 1-year period after the index date, and (3) study period. Based on the preindex and postindex periods, the effective study period for the patients was between January 2001 and June 2003.

In order to ensure that patients were newly started on the current course of SSRI therapy, patients could not have received an antidepressant drug in the preindex period. Patients with schizophrenia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 295.xx) or bipolar disorder (ICD-9-CM codes 296.0x, 296.4x, 296.6x, 296.5x, 296.7, 296.89, 301.13, 296.80, 293.83, and 296.90), or patients who received an antipsychotic medication during the preindex or postindex period were excluded from this analysis. Patients were also required to be 18 years of age and have a diagnosis of depression (ICD-9-CM codes 296.2, 296.3, 300.4, or 311). Claims data for patients meeting all selection criteria were extracted for 12 months after the index date (postindex period) and placed into cohorts based upon the antidepressant utilization patterns. (See Table 1.)

Cohort Classification

Patients were placed into 1 of 5 mutually exclusive cohorts determined by antidepressant utilization patterns within 12 months of initiating antidepressant therapy. Initially, patient-level overlapping prescriptions were collapsed into 1 prescription, based on the national drug code of that prescription. Collapsing prescriptions ensures that similar medications prescribed over the same period are not counted twice. Any overlap was added to the end of the collapsed prescription to give a conservative estimate of treatment duration. After this initial collapse of drug claims, the claims were again collapsed across all drug types (tricyclic antidepressant, SSRIs, and bupropion or venlafaxine) to determine days of continuous therapy. Utilization cohorts were chosen based on earlier efforts in this area and are consistent with published guidelines for acute-phase depression care.[3,4,6,12] The cohorts are defined in Table 2.

Comorbidity Assessment

To assess comorbidities across the cohorts, the Charlson Comorbidity Index, with Dartmouth-Manitoba and Deyo modification, was utilized.[13,14] This index contains 19 categories of comorbidities, primarily defined by ICD-9-CM diagnosis codes. Higher scores represent a higher burden of comorbidity. Charlson index scores for this study were derived by evaluating the presence of various ICD-9-CM codes in the 6-month period before each patient's index date.

Analysis and Measurement of Outcomes

Once patients were placed into cohorts, health care charges within the 12-month period following their index date were evaluated. Health care expenditures were defined as the total provider submitted charges for (1) physician visits, (2) inpatient hospitalizations, (3) outpatient hospital encounters, (4) emergency department visits, (5) antidepressant prescription medications (6) all prescription medications, and (7) other services (laboratory, radiological, and similar ancillary services). Statistical differences in charges across the patient cohorts were determined by utilizing an analysis of covariance model, controlling for differences in age, gender, presence of anxiety, mental health specialty care, preperiod charges (e.g., care provided by a psychiatrist or mental health professional), and the Charlson Comorbidity Index. Differences in the demographic characteristics across cohorts were assessed by chi-square tests for categorical variables and *t* tests for continuous variables. The alpha level of statistical significance was preset at 0.05.

Results

Baseline Characteristics

There were 65,753 patients who met all inclusion criteria and were subsequently analyzed for antidepressant utilization patterns. The distribution of patients receiving pharmacy claims for SSRIs included in the analysis was as follows: citalopram 24% (n = 15,771), fluoxetine 23% (n = 15,175), immediate-release paroxetine 24% (n = 16,012), sertraline 29% (n = 18,768), and controlled-release paroxetine <1% (n = 24). As shown in Figure 1, the highest percentage of patients discontinued therapy within 90 days of initiating treatment (36%). Only 16% of patients remained on therapy for >90 days without evidence of a therapy change, titration in dose, or being partially compliant.

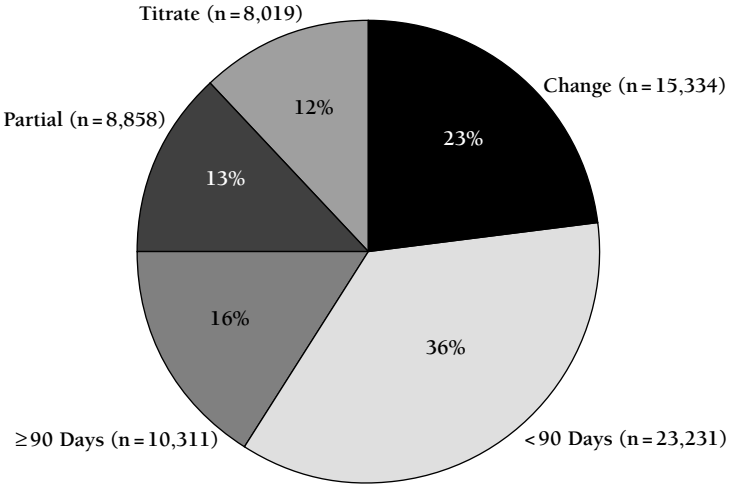
Table 3 shows the demographic characteristics of the SSRI cohorts. Patients remaining on SSRI therapy for ≥ 90 days had lower illness severity by the 3 proxy measures (diagnosis for comorbid anxiety disorder [defined as panic disorder, social anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, or generalized anxiety disorder], use of mental health specialty care, and the Charlson comorbidty score) compared with the >90-day group. Patients discontinuing therapy within 90 days of treatment tended to be younger than patients in the remaining cohorts, all of whom remained on

TABLE 2 Study Cohorts

Cohort	Definition
<90 days	Patients not having at least 90 days of continuous therapy after their index date. Patients with more than a 15-day treatment gap between subsequent prescriptions were assumed to have discontinued therapy at the ending date of the prescription prior to the 15-day treatment gap. It was permissible for patients in this group to have dose adjustments or switch antidepressant agents.
≥90 days	Patients having 90 days or more of continuous therapy. These patients were required to have no gaps in treatment greater than 15 days, no claims for antidepressants other than their index study agent, and no evidence of a titration in SSRI dose.
Partial compliance	Patients having at least 90 days of continuous therapy, with evidence of one or more 15-day gaps in therapy after 90 days. These patients were also required to have no claims for an antidepressant other than their index study agent and no evidence of a titration in SSRI dose.
Upward titration	Patients having at least 90 days of continuous therapy, with evidence of an increase in dosage at some point after starting antidepressant treatment. These patients were also required to have had no claims for antidepressants other than their study index agent and no gaps in treatment greater than 15 days.
Therapy change	Patients having at least 90 days of continuous therapy, with evidence of receiving another antidepressant (switch or augmentation) during the study period. These patients were required to have had no gaps in treatment greater than 15 days.

SSRI = selective serotonin reuptake inhibitor.
Note: *The index drugs were SSRIs (citalopram, fluoxetine, immediate-release paroxetine, controlled-release paroxetine, or sertraline), but the follow-up observation period included assessment of all antidepressant drug therapy.*

FIGURE 1 Distribution of Antidepressant Patients by Compliance Category*



** N = 65,753 (See Table 4 for complete data.)*

TABLE 3 Patient Characteristics and Use of SSRI Drug Therapy

	<90 Days (n=23,231)	≥90 Days (n=10,311)	Partial (n=8,858)	Titration (n=8,019)	Change (n=15,334)
% female	76.0%*	72.8%	74.9%†	76.3%*	78.0%*
Mean age (years ± SD)	42.1* ± 12.7	45.5 ± 11.3	44.6* ± 11.8	43.8* ± 11.6	44.0* ± 11.1
Comorbid anxiety disorder	24.3%*	19.0%	19.3%	25.3%*	28.4%*
Mental health specialty care‡	28.9%*	24.1%	24.4%	30.5%*	37.3%*
Mean Charlson comorbidity score	0.96†	0.89	0.90	0.96†	1.10*
Preperiod medical charges	$2,342	$2,261	$2,068	$2,548	$2,803

** P<0.001 when compared with the ≥90-day cohort.*
† P<0.05 when compared with the ≥90-day cohort.
‡ Mental health specialty care is defined as care provided by a psychiatrist or mental health professional.
SSRI=selective serotonin reuptake inhibitor.

TABLE 4 Annual Average-per-Patient Hospital, Medical, and Pharmacy Charges ($)*

	<90 Days (n=23,231)	≥90 Days (n=10,311)	Partial (n=8,858)	Titration (n=8,019)	Change (n=15,334)
Inpatient	2,094	1,446	2,040	1,996	2,386
Outpatient	1,427	1,302	1,319	1,499	1,868
Emergency department	309	159	177	238	302
Physician	1,434	1,290	1,334	1,584	2,007
Other†	1,025	947	1,038	1,058	1,296
All medical charges	6,289‡	5,143	5,909§	6,375‡	7,858‡
SSRI therapy charges	508	886	802	1,066	1,172
Medical + SSRI charges	6,797‡	6,029	6,711‡	7,441‡	9,030‡
Other pharmacy charges	1,032	1,424	1,236	1,503	1,939
Total charges	7,829	7,453	7,947§	8,944§	10,969§

** These are provider submitted charges for services rendered within 1 year of initiating treatment; e.g., 1-year costs for patients who initiated treatment in June 2001 would consist of all costs incurred from June 2001 through May 2002.*
† "Other" includes laboratory, radiological, and similar ancillary services.
‡ P<0.001 when compared with the ≥90-day cohort.
§ P<0.05 when compared with the ≥90-day cohort.
SSRI=selective serotonin reuptake inhibitor.

therapy for at least 90 continuous days. Patients experiencing a change in therapy and patients in the titration group both appeared to have higher illness severity as measured by the 3 proxies (the Charlson Comorbidity Index, the percentage of patients having comorbid anxiety, and use of mental health specialty care) compared with the >90-day group.

Total Medical Charges

Total medical charges for 12 months were highest in patients having a change in therapy ($7,858) during the study period, while patients in the ≥90-day cohort had the lowest total medical charges ($5,143) (Table 4). Differences in total medical costs between the < 90-day ($P < 0.001$), titration ($P < 0.001$), partial compliance ($P < 0.05$), and therapy change ($P < 0.001$) cohorts were statistically significant compared with the ≥90-day cohort. Differences in total medical charges were primarily driven by inpatient charges, which were highest in the therapy change ($2,386) and <90-day ($2,094) cohorts, and lowest in the ≥90-day ($1,446) cohort. Charges for physician services followed a similar trend, being lowest in the ≥ 90-day cohort. When patients remaining on therapy for 180 days or more (n=8,548, 82.9% of the ≥90-day cohort) were separated from the ≥90-day cohort and compared with the <90-day cohort, medical charges were ($1,089) lower for the >180-day group ($P<0.001$).

Medical, Antidepressant, and Total Pharmacy Charges

When total medical charges were combined with antidepressant-related pharmacy charges (Table 4), patients having a change in therapy experienced the highest costs ($9,030), while patients in the ≥ 90-day cohort experienced the lowest costs ($6,029). The costs for medical and antidepressant pharmacy charges for the ≥ 90-day cohort were lower than the costs for the other utilization cohorts. When all pharmacy charges, including antidepressant drug therapy, were added to total medical charges, the total charges were not different between the <90-day cohort ($7,829) and the ≥90-day cohort ($7,545), $P = 0.606$.

Discussion

The purpose of this analysis was to evaluate differences in resource utilization resulting from various patterns of antidepressant use and longer length of drug therapy. Results of this study provide some support for the earlier findings that patients remaining on therapy for at least 90 days without drug therapy changes incur lower health care charges (absent pharmacy charges), and patients requiring a therapy change incur higher health care charges.[12]

The data presented here also provide some support for earlier findings that patients adhering to antidepressant therapy for at least 90 days achieve improved outcomes.[10,11,15,16] Studies of Medicaid[11] and privately insured populations[10] have found that patients treated for the recommended duration of antidepressant therapy (a minimum of 90 days for acute treatment) had a lower likelihood of depression relapse than individuals remaining on therapy for less than the minimum duration. Assuming that increased resource utilization may in part reflect relapse, the current study is consistent with these earlier findings.

Medication selection is an important factor in increasing adherence to antidepressants and decreasing therapy change since 43% of patients who discontinue antidepressant therapy within 30-days cite adverse events from the medication as the primary cause of early discontinuation.[17] Selecting therapies that have demonstrated a lower incidence of side effects may lessen the need for changing therapies, enhance patient medication compliance, and reduce overall health care costs. This is especially true for patients with a comorbid anxiety disorder, such as panic disorder, in that these patients appear to be particularly sensitive to the side effects of antidepressants.[18,19] The current study found that patients who needed some type of therapy change, either an augmentation or switch in treatment, were significantly more likely to have a comorbid anxiety disorder.

Also of interest is the finding that non-depression-related pharmacy charges were higher in patients who received continuous antidepressant drug therapy for ≥ 90 days. Given previous work documenting a link between depression and poor compliance,[20] it is plausible that improved depression treatment may lead to better compliance with other medications. It is also possible that certain individuals are more adherent to, or higher utilizers of, a range of chronic medications. Future analyses should evaluate the effect of improved antidepressant treatment patterns on non-depression-related medication compliance and associated health care costs.

Limitations

The ability to draw causal relationships between adherence to therapy and cost of care is not possible with the cross-sectional study design. We were also unable to adjust for all potentially confounding variables. While we attempted to measure severity of illness and health status with 3 proxy measures, it is possible that unmeasured patient characteristics led both to medication discontinuation, therapy change, titration, and the increased likelihood of use of health care service uses. Our study adjusted for a wide range of confounders, but caution should always be exercised when making inferences of causality from retrospective analysis of medical claims data.

Since economic and resource utilization data were obtained from retrospective claims, the reason(s) for patient discontinuation, therapy change, titration, or partial compliance could not be determined and may be related to factors other than efficacy or tolerability. Patient-specific data, such as chart review data, are critical for better understanding these reasons and developing interventions to improve adherence to therapy.[17] While it is plausible that resource utilization could be used as a proxy measure of effectiveness, we did not directly assess the effectiveness of antidepressant treatment patterns in reducing the clinical signs and symptoms of depression. It may be inappropriate to use resource utilization in this manner if the true effectiveness of these agents is not reflected in medical charges within a 1-year period of initiating treatment. Readers should also note that we reported per-patient-per-year medical and pharmacy costs since all patients were continuously eligible over a 1-year period; all reported charges can be divided by 12 to determine the values expressed in resource utilization per patient per month. We excluded patients who received only 1 antidepressant pharmacy claim, and discontinuation of therapy after filling 1 prescription has been reported to be as high as 30% of patients initiating SSRI treatment.

Finally, the claims data only provided information on patterns of drug therapy derived from dispensed prescriptions rather than actual use of medications by patients. Pharmacy records tend to overestimate compliance as compared with gold-standard electronic compliance monitoring systems.[21] Additionally, the use of drug samples could not be accounted for with our methodology. We have no reason to believe that drug sampling would differentially affect patients in the various cohorts; however, if the use of drug samples is substantial, it is likely to be a source of patient misclassification in our method. Misclassification could also occur if a physician recommended a decrease in the frequency or dose of a prescription after the prescription was filled.

Despite the limitations of this study, this research provides current data on the relationship between SSRI antidepressant drug use and total health care resource consumption. It is not possible to conclude from these data that titrating or changing therapy are inappropriate treatment patterns. However, selecting the right medication for the right person in initial therapy may decrease the need for titration or therapy change. Future research should seek to better explain the many patient, provider, and treatment-related factors that may affect the relationship between medical care that is concordant with treatment guidelines and patient outcomes, including the total cost of care.

DISCLOSURES

Funding for this study was provided by GlaxoSmithKline (GSK) and was obtained by authors Michael T. Eaddy, Matthew W. Sarnes, and Timothy S. Regan. Eaddy, Sarnes, Regan, and author Laura E. Frankum are employed by Applied Health Outcomes, which serves as a consultant firm for GSK. Author Benjamin G. Druss received an honorarium from GSK for his participation in this article. Eaddy and Regan disclose that they participate in speakers bureaus for GSK, presenting various aspects of their research.

Eaddy served as principal author of the study. Study concept and design were contributed primarily by Eaddy. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Frankum, and its critical revision was the work of Eaddy, Druss, and Regan. Statistical expertise and administrative, technical, and/or material support were provided by Eaddy.

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003;289(23):3095-3105.

2. Greenberg PE, Kessler R, Corey-Lisle P, Birnbaum HG, Leong S, Lowe S. The economic burden of depression in 2000 [poster abstract]. *Value Health.* 2003;6(3):356.

3. *Health Plan Employer Data & Information Set.* Vol. 2. Washington, DC: National Committee for Quality Assurance; 2004.

4. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry.* 2000;157 (suppl 4):1-45.

5. Glassman R, Farnan L, Gharib S, Erb J. *Depression. A Guide to Diagnosis and Treatment.* Boston, MA: Brigham and Women's Hospital; 2001.

6. Trangle M, Anderson C, Lucas S. *Major Depression in Adults in Primary Care.* 8th ed. Bloomington, MN: Institute for Clinical Systems Improvement (ISCI); 2003.

7. Snow V, Lascher S, Mottur-Pilson C, et al. Pharmacologic treatment of acute major depression and dysthymia. *Ann Intern Med.* 2000;132(9):738-42.

8. Eaddy M, Bramley T, Regan T. Time to antidepressant discontinuation: a comparison of controlled-release paroxetine and immediate-release selective serotonin-reuptake inhibitors. *Manag Care Interface.* 2003;16(12):22-27.

9. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care.* 1995;33:67-74.

10. Sood N, Treglia M, Obenchain RL, Dulisse B, Melfi CA, Croghan TW. Determinants of antidepressant treatment outcomes. *Am J Manag Care.* 2000; 6(12):1327-36.

11. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry*. 1998;55:1128-32.

12. Thompson D, Buesching D, Gregor KJ, Oster G. Patterns of antidepressant use and their relation to costs of care. *Am J Manag Care.* 1996;2:1239-46.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83.

14. Deyo R, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-19.

15. Maj M, Veltro F, Pirozzi R, Labrace S, Magliano L. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. *Am J Psychiatry*. 1992;149:795-800.

16. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. *Am J Psychiatry.* 1998;155:1247-53.

17. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother.* 2002;36:578-84.

18. Moller HJ. Anxiety associated with comorbid depression. *J Clin Psychiatry.* 2002;63(suppl 14):22-26.

19. Salchner P, Singewald N. Neuroanatomical substrates involved in the anxiogenic-like effect of acute fluoxetine treatment. *Neuropharm.* 2002;43:1238-48.

20. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160(14):2101-07.

21. Paes AH, Bakker A, Soe-Agnie CJ. Measurement of patient compliance. *Pharm World Sci.* 1998;20(2):73-77.