ORIGINAL ARTICLE

The Effects of Adherence to Antidepressant Treatment Guidelines on Relapse and Recurrence of Depression

Catherine A. Melfi, PhD; Anita J. Chawla, PhD; Thomas W. Croghan, MD; Mark P. Hanna, MS; Sean Kennedy, BS; Kate Sredl, BA

Background: Depression is associated with high rates of relapse and recurrence during a patient's lifetime. Current guidelines regarding treatment recommend 4 to 9 months of continuation antidepressant therapy following remission of acute symptoms to allow more complete resolution of the episode. In this article, we test whether adherence to these recommendations reduces the likelihood of relapse or recurrence in a Medicaid population.

Methods: We used a Medicaid database covering 1989 through 1994. The sample consists of the 4052 adult patients who filled an antidepressant prescription at the time of an initial diagnosis of depression. These patients were followed up for up to 2 years. Timing and counts of antidepressant prescription claims are used to construct a proxy measure for adherence to guidelines. Relapse or recurrence is defined by evidence of a new episode requiring antidepressant treatment, hospital admission for depression, electroconvulsive therapy, emergency department visit for mental health, or attempted suicide. We used survival analysis to predict relapse or recurrence for each patient and to examine the effect of following treatment guidelines on relapse and recurrence.

Results: Approximately one fourth of the patients had a relapse or recurrence during their follow-up period. Factors that affect relapse and recurrence include comorbidities, race, and guideline adherence. Those who continued therapy with their initial antidepressant were least likely to experience relapse or recurrence; those who discontinued their antidepressant early were most likely to experience relapse or recurrence.

Conclusion: Adherence to depression treatment guidelines with an antidepressant that is likely to have continuous use by patients reduces the probability of relapse or recurrence.

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From the Health Outcomes Evaluation Group, Eli Lilly & Co, Indianapolis, Ind (Drs Melfi and Croghan); Department of Medicine, Indiana University School of Medicine, Indianapolis (Drs Melfi and Croghan and Mr Hanna); the MEDSTAT Group Inc, Washington, DC (Dr Chawla); and the MEDSTAT Group Inc, Santa Barbara, Calif (Mr Kennedy and Ms Sredl).

THERE HAVE BEEN major advances in the treatment of depressive illnesses during the past decade. Adequate pharmacological or psychotherapeutic treatments are accessible to increasing numbers of patients. However, depressive disorders are still associated with high rates of relapse and recurrence during a patient's lifetime. The National Institute of Mental Health Consensus Development Conference on relapse and recurrence of depression found that 50% to 85% of people who have an episode of depression will suffer a recurrent episode during their lifetime. Of these, 50% will experience recurrence within 2 years of the initial episode.[1]

Treatment of an episode of depression has 3 phases.[2] The goal of the acute treatment phase is relief of symptoms, and its length may vary depending on responsiveness to treatment and the need to find an optimal regimen. Following the acute phase, continuation therapy for a period of 4 to 9 months is recommended to allow more complete resolution of the episode, and to prevent the relapse or reemergence of the existing episode.[2-5] The need for the third phase, the long-term maintenance phase, depends on the number of prior episodes[6-8] and other risk factors such as associated anxiety,[8,9] and is recommended to prevent recurrence or the emergence of a new episode of depression.

Most studies of effects of medication treatment on relapse and recurrence have focused on maintenance phase treatment for patients at high risk.[10-13] The effectiveness of maintenance treatment in these patients is clear, but important gaps in our understanding remain. Many patients are not considered at high risk for relapse or recurrence and therefore do not meet criteria for maintenance treatment. Furthermore, most patients do not currently receive the recommended length of continuation treatment.[14-16] These issues suggest the need to look more closely at the effects of completing the continuation phase of treatment on relapse or recurrence of depression.

To our knowledge, only 1 study has examined the effects of continuation treatment on long-term relapse and recurrence.[17] In that study, patients who received continuing treatment with an antidepressant and/or lithium

SUBJECTS AND METHODS

Claims records from a state Medicaid population covering 1989 to 1994 were searched to identify patients who had a diagnosis of depression (identified by *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* codes 296.2x, 296.3x, 300.4x, 309.0x, and 311.xx) and coincident filling of prescription for an antidepressant. Diagnoses included major depressive disorder, single episode; major depressive disorder, recurrent episode; neurotic depression; brief depressive reaction; prolonged depressive reaction; and depression not elsewhere classified. We included only the tricyclic antidepressants (TCAs) amitryptiline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine, and the SSRIs fluoxetine, paroxetine, and sertraline. We are not able to identify the particular state from which the data come because of a confidentiality agreement with that state.

EPISODE CONSTRUCTION

Consistent with but extending current methods on claims-based episode construction,[16,18,19] we constructed 30-month episodes of depression care. Each episode was identified by a paid claim for an antidepressant prescription and a depression diagnosis within 30 days of the prescription date. We defined a 6-month *pretreatment period* prior to this index prescription during which there was neither evidence of depression nor an indicator of mental health care. These exclusions were based on prescription claims for antidepressants or other psychotropic drugs and on *Current Procedural Terminology* and *ICD-9-CM* codes for mental health services such as psychotherapy. These exclusions increase the probability that the included episodes represent new depression treatment occurrences, critical to our subsequent measurement of antidepressant treatment.

The second 6-month period during each 30-month episode comprises the *treatment period*. To characterize this portion of the episode, we defined treatment characteristics that would serve as a proxy for adherence to antidepressant treatment recommendations published by the Agency for Health Care Policy and Research.[2] These guidelines suggest an acute treatment period of 6 to 8 weeks, followed by 4 to 9 months of continuation treatment once depressive symptoms have resolved. Those who do not respond adequately during the acute phase often require switching to or adding a second antidepressant. Although a 6-month treatment period is somewhat arbitrary, it was chosen because it allows 8 weeks for the acute treatment period and the minimum 4 months for continuation treatment so we can address the question of minimum adherence to guidelines.

The final 18 months of the episode define the *follow-up period*, during which we looked for indicators of the consequences of adherence to recommended care during the treatment period. Specifically, we identified relapse or recurrence of depression by reinitiation of antidepressant treatment after a gap of at least 6 months following the previous antidepressant prescription, or by evidence of a suicide attempt, psychiatric hospitalization, mental health–related emergency department visit, or receipt of electroconvulsive therapy indicated in the patient's medical or pharmacy claims during the follow-up period. Because these measures are claims-based and are not clinical assessments, we did not distinguish between relapse and recurrence. Thus, we refer to our outcome measure as "relapse/recurrence."

DEFINING PATIENT TREATMENT COHORTS

Using the treatment guidelines as a reference framework, we identified 3 cohorts of patients based on antidepressant claims. We first identified those who filled fewer than 4 prescriptions for any antidepressant during the treatment period, or who filled their final antidepressant prescription of the treatment period during the 75 days following their index prescription. These patients clearly do not meet the antidepressant treatment guidelines; thus we refer to them as the *discontinued early* cohort.

We next identified patients who switched to or added a second antidepressant to their initial antidepressant (the *switch/augment* cohort). Switching or augmenting is often an indication that the initial antidepressant failed to achieve the desired response, either because of adverse effects or failure to resolve symptoms. Because of our selection hierarchy, patients in this cohort received at least 4 antidepressant prescriptions during the treatment period.

The final cohort includes those who filled at least 4 prescriptions for the initial antidepressant during the treatment period, identified as the *continuous use* cohort. The 4-prescription minimum serves as a proxy indicator for those who, at least minimally, met medication treatment recom-

experienced significantly fewer recurrent episodes during the ensuing 2 to 5 years. While this provides a strong rationale for continuation treatment, further questions remain. First, that study was conducted when many current treatments, including the selective serotonin reuptake inhibitors (SSRIs) and new psychotherapy techniques, were not available or were not in widespread use and these were not included in the study. Second, the study was conducted at a specialized university center in southern Italy, where the most severe cases of depression are likely to be seen. Finally, current recommendations were not available so the study design could not explicitly test the effect of following those recommendations.

In this study, we test the hypothesis that adherence to current recommendations regarding continuation treatment will reduce the likelihood of relapse or recurrence. In doing so, we extend the current literature by including all identifiable patients and not just those at high risk or those who achieve full symptom relief. Perhaps most importantly, we include those who might discontinue treatment because of spontaneous remission.

RESULTS

DESCRIPTIVE STATISTICS

Patient characteristics are presented in **Table 1**. This group of patients was preponderantly female (93.1%) and ranged in age from 18 to 83 years (mean age, 34.7 years). The proportions of African American and white patients were similar (46.7% and 46.9%, respectively) and race was unknown for 5.9% of the group. Sixty-three per-

mendations. While 4 prescriptions in 6 months may seem to represent reasonably poor adherence with guidelines, our early work on this project suggests variability in prescription fill dates, making precise measurement of actual use difficult. Furthermore, on average, those who filled 3 or more prescriptions received an average of 8 prescriptions (data not shown), suggesting that our proxy indicator could function as a surrogate for medication guideline compliance. Finally, alternative specifications of our definition of continuous use did not alter the conclusions of this work.

For inclusion in the sample, we required patients to have continuous enrollment during the pretreatment period and for at least 12 months following the index event, which includes the treatment period, and at least 6 months during the follow-up period. We excluded from the sample patients who had evidence of psychosis or bipolar affective disorder based on *ICD-9-CM* codes or prescription claims for antipsychotics at any time during the (up to) 30-month episode.

MODEL SPECIFICATION AND ESTIMATION STRATEGY

To examine the effects of adherence to treatment guidelines on relapse/recurrence, we used survival analysis and estimated a Cox proportional hazards model with the treatment cohorts and other variables as the covariates. Variables included in the final model were established based on univariate analyses, as well as comparison of the predictive ability of alternative specifications of the model. The full model is described here.

Because comorbidities may affect depressive episodes, we included variables to control for comorbid conditions. For a general comorbidity adjustment, we considered various indexes that can be constructed from claims data. Our data were categorized into 25 standard major diagnostic categories (MDCs) based on the mapping defined by the Health Care Financing Administration's diagnostic related groups. These include categories such as musculoskeletal disorders, digestive system disorders, and others. We conducted univariate analysis with each MDC to see if any were independently predictive of relapse/recurrence. The only one that was independently predictive was the one representing substance abuse disorders, so this was included as an indicator variable. As a general comorbidity adjustment, an integer variable was created representing the number of MDCs other than substance abuse for each patient. As a measure of recent health issues, we also included a variable to indicate whether the patient was hospitalized for any medical reason during the 6-month pretreatment period. Finally, because anxiety with depression may be associated with an increased risk of relapse or recurrence, we included an indicator for a prescription for a benzodiazapine as a proxy for an anxiety disorder.

Severity of depression is difficult to measure in a claims database. We considered using the 6 categories associated with the *ICD-9-CM* codes recorded on the claims as a measure of depression severity. Those were not predictive, most likely because so many patients have the code for "depressive disorder not elsewhere classified." Variables included in the model to proxy for severity were (1) an indicator for whether the patient was seen by a mental health specialist (psychiatrist, neurologist, or service provided at a mental health facility) at initial diagnosis; and (2) an indicator for whether the patient received psychotherapy in addition to an antidepressant during the treatment period.

We included the demographic variables of age, sex, and race. Previous work indicates that men are less likely than women to have a relapse or recurrence of depression.[6] The race categories used were white, black, and other or unknown. Medicaid eligibility categories were collapsed into 2 groups: (1) aged, blind, disabled; and (2) Aid to Families With Dependent Children (AFDC), poverty related, and unknown. These categories represent Medicaid recipients whose eligibility is based on medical conditions and those whose eligibility is based on income, thus providing an indicator of relative socioeconomic status within the Medicaid population.

Depression care changed substantially from 1989 to 1994, especially with regard to antidepressant medications, the introduction of managed behavioral health care, and general awareness of depression and mental illness. To account for these and other changes, we included an integer variable that captures time trend, based on year of index event.

Finally, we included variables that indicate which of the 3 antidepressant treatment cohorts each patient was in. The groups are discontinued early, switch/augment, and continuous use, as defined previously.

The Cox proportional hazards model was estimated using the PHREG procedure in the SAS statistical software (SAS Institute, Cary, NC). The α level of significance used was .05.

cent of the patients were in the AFDC eligibility category for Medicaid, and most of the remaining patients were in the blind/disabled category. This patient population also had a significant number of comorbid conditions, the distribution of which is presented in Table 1. There were 210 patients (5.2%) with diagnoses for substance abuse–related conditions.

Table 1 also presents the distribution of antidepressant treatment cohorts. All 4052 patients received a prescription for an antidepressant within 30 days of their diagnosis, and 2849 (70.3%) filled fewer than 4 prescriptions for antidepressants during the treatment period or filled their final prescription during the 75 days following their first prescription. There were 760 patients (18.8%) in the continuous use cohort and 443 (10.9%) in the switch/augment cohort. A TCA was prescribed as the first antidepressant for 47.6% of the patients, and an SSRI was prescribed for 52.4% of the patients at the time of their diagnosis of depression. Finally, 742 patients (18.3%) received psychotherapy during the 6-month treatment period, and 1614 (39.8%) were seen by a mental health specialist at the time of diagnosis.

Lengths of the follow-up period varied between 6 and 18 months, with about half the patients having 18 months of continuous enrollment during the follow-up period. Overall, 24% of the patients experienced a relapse/recurrence. The survival curves for the 3 treatment cohorts are presented.

SURVIVAL CURVES

The **Figure** shows the Kaplan-Meier survival curves for relapse/recurrence according to treatment cohorts. The label on the horizontal axis refers to days following the

Table 1. Descriptive Statistics (N = 4052)*

Variable	No. (%)
Sex	
F	3771 (93.1)
M	281 (6.9)
Race	
White	1891 (46.7)
African American	1902 (46.9)
Other	19 (0.5)
Unknown	240 (5.9)
Medicaid eligibility category	
AFDC	2536 (62.6)
Poverty related	43 (1.1)
Aged	22 (0.5)
Blind/disabled	1395 (34.4)
Unknown	56 (1.4)
Comorbid conditions	
Substance abuse	210 (5.2)
Benzodiazepine use	403 (9.9)
Mean No. of other comorbid conditions (range)	6.09 (0-16)
Treatment cohort	
Continuous use (patient filled at least 4 prescriptions for the same AD in first 6 mo)	760 (18.8)
Switch/augment (patient switched or augmented AD in first 6 mo and filled at least 4 AD prescriptions)	443 (10.9)
Discontinued early (patient filled fewer than 4 AD prescriptions in first 6 mo)	2849 (70.3)
Antidepressant type	
TCA	1982 (47.6)
SSRI	2124 (52.4)
Saw a mental health professional	1614 (39.8)
Received psychotherapy	742 (18.3)

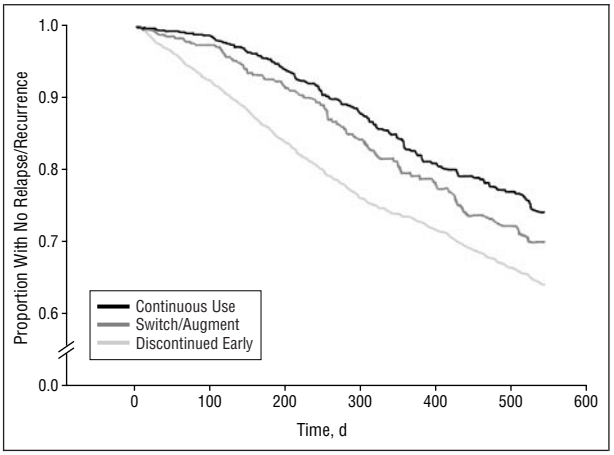
**AFDC indicates Aid to Families With Dependent Children; AD, antidepressant; TCA, tricyclic antidepressant; and SSRI, selective serotonin reuptake inhibitor.*

end of the treatment period. The group most likely to experience a relapse/recurrence is the discontinued early cohort, while patients with more than 4 prescriptions for 1 antidepressant (continuous use) were least likely to experience a relapse/recurrence.

PREDICTORS OF RELAPSE/RECURRENCE

We report the results of the Cox proportional hazards model in **Table 2**. In general, significant variables in the model include race, comorbidities, time trend, and treatment cohort. Specifically, we found that benzodiazapine use increases the risk of relapse/recurrence (risk ratio = 1.22; $P = .04$) while African Americans (compared with white patients) were at reduced risk of relapse/recurrence as we measure it (risk ratio = 0.86; $P = .03$). Comorbid substance abuse increases the risk of relapse/recurrence (risk ratio = 1.60; $P<.01$), as do additional comorbidities (risk ratio = 1.10; $P<.01$). Furthermore, a hospitalization in the prior period is predictive of relapse/recurrence (risk ratio = 1.31; $P<.01$).

Antidepressant treatment cohorts are also predictive of the risk of relapse/recurrence. Compared with the continuous use cohort, those who discontinued antidepressant treatment early had a significantly increased risk of a relapse/recurrence (risk ratio = 1.77; $P<.01$). Membership in the switched/augmented cohort was not significantly associated with increased risk for relapse/recurrence as we measure it (risk ratio = 1.06; $P = .67$).



Proportion of patients with no relapse/recurrence following 6-month treatment period, according to antidepressant treatment cohort.

COMMENT

The main objective of this research was to test the hypothesis that following medication treatment recommendations under naturalistic conditions would prevent or delay relapse and recurrence of depression. The results provide further evidence that appropriate medication use can improve the overall effectiveness of depression treatment. In this Medicaid system, premature discontinuation of antidepressant treatment was associated with a 77% increase in the risk of relapse/recurrence (risk ratio = 1.77).

There are limitations to the inferences that can be drawn from this study. Because data are from a single state's Medicaid plan, generalization of the results must be made carefully. Also, women are substantially overrepresented in our data. Finally, the fact that our indicator of relapse/recurrence is based on paid Medicaid claims may mean that some patients who had a relapse or recurrence will not be counted as such. Many mentally ill patients who have received medical care for past episodes do not seek or receive care for subsequent episodes.[20] Thus, we believe that our study may significantly underestimate the actual number of second episodes or relapses of depression. Use of a resource-based indicator could be responsible for the significant association between the number of comorbid conditions and the risk of relapse/recurrence as measured by our indicator. A larger number of comorbid conditions may be a proxy for care-seeking behavior, in general, on the part of depression sufferers, whether due to other medical needs, patient preference, or other factors.

Despite these limitations, there are several aspects of this study that are important for policymakers to consider carefully. Perhaps most important, fewer than 30% of the antidepressant users in this study received treatment even minimally consistent with current guidelines. Although these guidelines were published toward the end of the study period, the information on which the guidelines are based had been available for some time.[13] The high

Table 2. Cox Proportional Hazards Model Results (Dependent Variable = Time to Relapse/Recurrence)

Variable	Coefficient (SE)	*P*	Risk Ratio (95% Confidence Interval)
Age	0.002 (0.003)	.58	1.002 (0.995-1.008)
African American*	−0.153 (0.069)	.03	0.858 (0.750-0.981)
Other/unknown race*	0.196 (0.123)	.11	1.217 (0.956-1.550)
Aged/blind/disabled†	0.041 (0.081)	.61	1.042 (0.889-1.222)
Male	−0.048 (0.142)	.74	0.953 (0.722-1.259)
Psychotherapy	0.153 (0.090)	.09	1.166 (0.977-1.391)
Mental health professional	−0.083 (0.070)	.24	0.920 (0.802-1.056)
Year = 1990‡	0.079 (0.133)	.55	1.082 (0.833-1.405)
Year = 1991‡	0.089 (0.132)	.50	1.093 (0.844-1.415)
Year = 1992‡	0.258 (0.136)	.06	1.294 (0.992-1.688)
Year = 1993‡	0.192 (0.136)	.16	1.212 (0.929-1.581)
Year = 1994‡	0.459 (0.199)	.02	1.582 (1.072-2.335)
Discontinued early§	0.572 (0.095)	<.01	1.772 (1.470-2.137)
Switch/augment§	0.060 (0.140)	.67	1.062 (0.807-1.398)
Benzodiazapine use	0.199 (0.097)	.04	1.220 (1.010-1.475)
Substance abuse	0.472 (0.116)	<.01	1.603 (1.277-2.012)
Hospitalization in the prior period	0.272 (0.083)	<.01	1.313 (1.116-1.543)
No. of major diagnostic category comorbidities (excluding substance abuse)	0.091 (0.011)	<.01	1.095 (1.071-1.120)

**Omitted race category is white.*
†Omitted eligibility category is Aid to Families With Dependent Children/poverty/unknown.
‡Omitted year variable is 1989.
§Omitted treatment cohort is continuous use.

rate of those who discontinue medication early suggests that perhaps prescribing physicians need to provide patients with information about the amount of time they should expect to continue receiving their medication. In this study, we also presented further evidence to support adherence to antidepressant guidelines, especially in terms of the prevention of relapse or recurrence.

We had hypothesized that those who required switching to or augmenting with a second antidepressant might be at a higher risk for relapse or recurrence. The switch/augment cohort, however, did not separate statistically from the continuous use group after controlling for other factors, including some severity measures. It may be the case that patients in this cohort never stabilized with a single medication, perhaps due to dissatisfaction with their medication regimen. If these patients continued to try different medications during the follow-up period, they would most likely not experience any of the markers of relapse/recurrence.

Finally, we have presented an easily measured method for calculating an important indicator of antidepressant treatment. Duration of treatment is a National Committee for Quality Assurance Health Plan Employer Data and Information Set (HEDIS) 3.0 performance test measure for depression treatment. These measures are used for accreditation of health plans. The results of our study suggest that our method is clinically meaningful, and the information is available to most health plans through pharmacy benefit managers.

In summary, even after adjusting for variables that take into account severity of illness and comorbidities, we find that continuous use of a single antidepressant from the start of a depressive episode is related to the greatest reduction in the probability of relapse or recurrence. Our work provides further evidence that adherence to current medication recommendations could substantially reduce the likelihood of relapse and recurrence of depression.

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Reprints: Catherine A. Melfi, PhD, Health Outcomes Evaluation Group, Lilly Corporate Center (DC 1850), Eli Lilly & Co, Indianapolis, IN 46285 (e-mail: melfi@lilly.com).

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