

Determinants of Antidepressant Treatment Outcome

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Abstract

Objective: To understand the determinants of the outcome of an episode of major depression, including factors that affect receipt of guideline-consistent care and their subsequent effect on treatment outcomes, particularly relapse or recurrence. Results of previous studies are generalized to a population typical of depressed individuals in the United States, ie, a cohort of antidepressant users with employer-provided health benefits.

Study Design: A quasi-experimental design was used to assess the determinants of the outcome of an episode of major depression. Healthcare utilization-based measures of treatment characteristics and outcomes were used.

Patients and Methods: The final analytical file for this study contained data on 2917 patients who had an antidepressant prescription associated with an indicator of a depressive disorder. We identified relapse or recurrence of depression by (1) a new

episode of antidepressant therapy, (2) suicide attempt, (3) psychiatric hospitalization, (4) mental health-related emergency department visits, or (5) electroconvulsive therapy. Antidepressant use patterns were used to construct a measure for adherence to treatment guidelines. Multivariate Cox proportional hazard and logit regression models were used to predict relapse/recurrence and adherence with treatment guidelines, respectively, for each patient.

Results: Factors that affect relapse/recurrence include comorbidities, demographics, and adherence to treatment guidelines. Factors that affect adherence to treatment guidelines include choice of initial antidepressant drug, comorbidities, psychotherapy, and frequency of physician visits.

Conclusions: Adherence to treatment guidelines was associated with a significant reduction in the likelihood of relapse or recurrence of depression. Choice of initial antidepressant drug affects adherence to treatment guidelines.

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Despite significant advances in depression therapy, considerable variability remains in treatment outcomes. For instance, depressive disorders are associated with high rates of relapse and recurrence during a patient's lifetime. The National Institute of Mental Health consensus conference on relapse and recurrence of depression found that 50% to 85% of people who have an episode of major depression experience a recurrent episode during their lifetime. Of these, 50% will experience recurrence within 2 years of the initial episode.¹

These findings highlight the need to understand and implement strategies to prevent or delay the onset of second and subsequent episodes.

Treatment of an episode of major depression is divided into 3 phases. The first is a 6- to 8-week *acute phase* with the goal of obtaining relief of symptoms. Once symptom relief has been achieved, current recommendations call for a *continuation phase* of 4 to 9 months to achieve more complete restoration of normal functioning and to prevent relapse. The third phase of treatment, known as the *maintenance phase*, is recommended for those at high risk of recurrent depressive episodes. Studies of recurrence prevention during maintenance phase treatment have focused on patients at high risk^{2,3} or the elderly⁴ treated in mental health specialty settings. Many depressed persons treated in primary care settings also meet criteria for maintenance treatment,⁵ but most do not even receive the recommended length of continuation phase treatment.⁶⁻⁸ Hence, the applicability of the results of maintenance phase randomized clinical trials to patients in primary care is not clear.

Results of 3 previous studies suggest that adhering to recommendations for the length of continuation phase treatment can prevent or delay relapse and recurrence. In a study conducted before introduction of selective serotonin reuptake inhibitors (SSRIs), Maj et al⁹ showed that patients who received continuing treatment with an antidepressant and/or lithium experienced significantly fewer recurrent episodes during the ensuing 2 to 5 years. More recently, Reimherr et al¹⁰ found that 38 weeks of continuous treatment with fluoxetine effectively prevented relapse, thus extending the previous result to at least one SSRI. Melfi et al¹¹ provided external validity to evidence from these randomized clinical trials by explicitly testing the treatment guidelines and found that minimal adherence to the guidelines was associated with a 77% reduction in the likelihood of relapse/recurrence. Although a significant contribution, the study by Melfi et al was conducted in a single state Medicaid program in which only half of the antidepressant drug recipients received an SSRI and less than 30% had courses of antidepressant drug treatment consistent with the guidelines.

The purpose of this study is to confirm and extend the results of the study by Melfi et al¹¹ in several important ways. First, we seek to understand the determinants of the outcome of an episode of major depression in more detail, including factors that affect receipt of guideline-consistent care and

the subsequent effect on relapse/recurrence. Second, we want to further generalize the results of the previous studies to a typical population of depressed individuals in the United States, ie, a cohort of antidepressant drug users with employer-provided healthcare benefits. Finally, this study is unique in that it simultaneously analyzes the outcome (relapse/recurrence) of not meeting treatment guidelines for depression and the factors affecting treatment compliance using a single dataset.

... METHODS ...

Patients and Data

The analytical file used in this study was constructed from the 1992-1996 panels of the MarketScan™ database (the MEDSTAT Group, Ann Arbor, MI). MarketScan™ is composed of a system of comprehensive and standardized medical and prescription claims for approximately 7 million enrollees from 20 large employers in the United States with fee-for-service and managed care health insurance plans. All individuals with a diagnostic indicator for a depressive disorder and treatment with an antidepressant drug were included in the master file. Indicators of depressive disorders were based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes on an insurance claim at any time during the study period. The codes used to identify patients included 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, and 311.xx. These indicators correspond to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnoses of major depressive disorder, single episode; major depressive disorder, recurrent episode; dysthymia; brief depressive reaction; prolonged depressive reaction; and depression not elsewhere classified, respectively. We included only the tricyclic antidepressants (TCAs) amitriptyline hydrochloride, amoxapine, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, nortriptyline hydrochloride, protriptyline hydrochloride, and trimipramine malleate and the SSRIs fluoxetine, paroxetine, and sertraline hydrochloride. Individuals with indicators of comorbid psychosis, including psychotic depression and bipolar affective disorder, were excluded from the analysis.

Episode Construction

Thirty-month episodes of depression care were constructed. Each episode began the day the initial

antidepressant drug was dispensed. This “index” prescription was linked to an indicator of a depressive disorder within 30 days of that prescription. The first 6 months of each episode occurred before the index prescription and defined the *pretreatment period*. To study new episodes of antidepressant drug treatment, we excluded from further analysis any individual who filled a prescription for an antidepressant drug during this period.

The 6 months immediately after the index prescription was defined as the *treatment period*. This portion of the episode was used to identify patient cohorts based on initial antidepressant drug (fluoxetine, paroxetine, sertraline, and TCAs) and antidepressant drug use pattern. Use patterns were based on current depression treatment guidelines.^{12,13} Patients filling fewer than 4 antidepressant drug prescriptions in the treatment period defined the *discontinued early* cohort. These patients did not meet even minimal medication guidelines. We next identified a *switched/augmented* cohort. Patients in this cohort either switched antidepressant drugs or added a second antidepressant drug to their index prescription but filled 4 or more antidepressant prescriptions during the treatment period. The remaining patients filled 4 or more prescriptions of the index drug during the treatment period and are referred to as the *continuous use* cohort. These use pattern definitions are identical to those used in previous studies.^{11,14} Although observing claims for prescriptions may not yield a precise measure of duration of therapy, these definitions seem to provide meaningful surrogates for at least minimal adherence to treatment guidelines.

The *follow-up period* consisted of the final 20 months of the episode, during which relapse or recurrence of depression was identified when 1 or more of the following indicators appeared on the insurance claim: (1) a new episode of antidepressant drug therapy after a gap of 6 or more months after the previous antidepressant drug prescription, (2) a suicide attempt, (3) a psychiatric hospitalization, (4) a mental health–related emergency department visit, or (5) receipt of electroconvulsive therapy. We recognize the imperfection of using claims-based measures of a clinical event. Relapse and recurrence are defined by the return of symptoms after their resolution. Our claims-based definition recognizes the clinical situation by allowing 4 or more months for symptom resolution to occur before examining the data for evidence of events that are likely to occur if an individual returns for care when symptoms reappear.

Of 641 persons who met our criteria for relapse/recurrence, 499 (78%) met the criteria because of a new episode of antidepressant drug treatment. This high frequency presents a special problem for the analysis because it artificially delays by 6 months any measurement of an underlying relapse/recurrence for part of the cohort. Analytically, this shifts the distribution of eligibility for relapse/recurrence. However, the definitions and the main analyses presented seem to us to be more faithful to reality. Specifically, this requirement assured new episodes of depression treatment, an occurrence consistent with a recurrent episode of depression and less consistent with continued severe symptoms or relapse. The final analytical file for this study contained data on 2917 patients who were continuously enrolled during the 30-month episode.

... MODEL SPECIFICATION AND
STATISTICAL METHODS ...

Determinants of Relapse or Recurrence of Depression

A Cox proportional hazards model was used to estimate the effect of adherence to treatment guidelines on the likelihood of relapse/recurrence. The censoring variable for this model was the occurrence of relapse/recurrence, and the time variable was the number of days to relapse/recurrence from the date of the initial antidepressant drug prescription. Initial covariates for the analysis included patient demographics; indicators of medical and psychiatric comorbidity and severity; and treatment variables, including the use pattern cohort. However, statistical tests based on weighted Schoenfeld residuals¹⁵ revealed that the use pattern cohorts did not satisfy the proportional hazards assumption. Moreover, in preliminary analysis, there was no significant difference between the survival functions for the continuous use and switched/augmented cohorts, although these groups might represent patients with different clinical characteristics and responses to medication treatment. Consistent with the results of Melfi et al,¹¹ these 2 cohorts were combined into a single guideline-adherent cohort and contrasted with the discontinued early cohort. The latter cohort was then used as a stratification factor rather than as a covariate. This modification allowed for nonproportional hazards to exist between the 2 cohorts. The log-rank test was used to test the statistical significance of the association between relapse/recurrence and the stratification factor.

The final model specification and variable definitions were chosen based on previous research, simplicity of interpretation, and predictive ability of alternative specifications. Moreover, the final model specification satisfied the assumptions of the Cox proportional hazards model. Results of alternative model specifications based on stepwise regression (forward or backward selection) and other model selection procedures are consistent with the main conclusions of this study.

The demographic variables indicating age and sex of the patient were included in the model. Indicators of health status and severity included any hospitalization during the pretreatment period, the number of comorbid conditions recorded in the insurance record during the treatment and follow-up periods, and use of anxiolytic medications. Comorbid conditions were aggregated at the level of the Major

Diagnostic Categories, a scheme based on body system or disease-related groupings of clinical conditions defined by the Health Care Financing Administration.¹⁶ Univariate analysis revealed that most conditions were poor predictors of relapse or recurrence. In the final model, the sum of unique Major Diagnostic Categories reported for each patient during the treatment and follow-up period was included as a measure of comorbid conditions. Because anxiety disorders frequently complicate depressive disorders and may be associated with poorer outcome, an indicator of whether a patient received an anxiolytic drug prescription during the treatment or follow-up period was included. Finally, an indicator for hospitalization in the pretreatment period was included in the final model specification to control for health status in the pretreatment period.

Treatment variables in the model included an indicator of the type of provider who listed a depressive disorder on the medical claim that was temporally associated with the index antidepressant drug prescription; an indicator of psychotherapy during the treatment period; the year in which the index prescription was filled; and the antidepressant drug use pattern. The provider indicator reflected a mental health specialist if a psychiatrist or psychologist filed the medical claim or if it was from a mental health facility. Use of psychotherapy was determined by the presence of 1 or more *Current Procedural Terminology* codes 90841 through 90857. We included dummy variables for the year of the index prescription because access to and awareness of alternative antidepressant drug treatments changed during the 5-year span of the dataset.

Determinants of Adherence to Treatment Guidelines

To identify factors that affect adherence to treatment guidelines, a logit model was estimated in which the binary dependent variable was 1 for patients who discontinued early and 0 for all others. In other words, a course of treatment was considered to be consistent with guideline care if the patient filled 4 or more prescriptions for any antidepressant medication during the treatment period. As in the relapse/recurrence models, the covariates for this analysis included general categories for patient

Table 1. Descriptive Statistics

Variable	Patients, No. (%)
Sex	
Male	898 (30.8)
Female	2017 (69.2)
Unknown	2
Comorbid conditions	
Anxiolytic prescription	1286 (44.1)
Comorbid conditions, mean (range), No.	7.48 (0-18)
Previous hospitalization	216 (7.4)
Previous nonpsychiatric hospitalization	123 (4.2)
Previous psychiatric hospitalization	93 (3.2)
Treatment cohort	
Discontinued early	738 (25.3)
Switched/augmented	739 (25.3)
Continuous use	1440 (49.4)
Initial antidepressant drug type	
Fluoxetine	1087 (37.3)
Paroxetine	352 (12.1)
Sertraline	939 (32.2)
Tricyclic antidepressant	539 (18.5)
Saw a mental health professional	1125 (38.6)
Received psychotherapy	1814 (62.2)
Year of initial antidepressant drug prescription	
1992	482 (16.5)
1993	1049 (36.0)
1994	1384 (47.5)

demographics, indicators of medical and psychiatric comorbidity and severity, and treatment variables. Final model specification and variable definitions were chosen based on the predictive ability of the model and univariate analysis.

The variables representing patient demographics, treatment and provider characteristics, and comorbid conditions were the same as those in the relapse/recurrence models. However, splitting the pretreatment period hospitalization variable into indicators of psychiatric hospitalization and general medical hospitalization based on the primary discharge diagnosis improved the predictive ability of the guideline-adherence models. The model also included indicator variables for an initial antidepressant drug prescription of sertraline, paroxetine, or a TCA. Initial fluoxetine use was the reference category for this analysis.

... RESULTS ...

Descriptive Statistics

Descriptive statistics of the patients in this study are presented in Table 1. Most patients were women, and the mean age of patients was 43 years (data not shown). Nearly three quarters of the patients met the definition for care that was consistent with antidepressant drug guidelines. Of these, about one quarter switched or augmented their initial antidepressant therapy. A mental health specialist saw 38.6% of the patients at the time of initial diagnosis, and 62.2% received psychotherapy during the treatment period.

Predictors of Relapse/Recurrence

Typical results from the Cox proportional hazards models are presented in Table 2. Significant variables associated with relapse/recurrence were the number of Major Diagnostic Category comorbidities, anxiolytic medication use, year of index prescription, psychotherapy, and demographic characteristics. Older

individuals and women were less likely to experience relapse/recurrence in this study. Receiving psychotherapy was associated with significantly increased risk of relapse/recurrence. Individuals whose index prescription was in 1992 or 1993 had a significantly increased risk of relapse compared with those with an index prescription occurring in 1994. Use of anxiolytic medications was also associated with significantly increased risk of relapse/recurrence. Each unit increase in the number of comorbid conditions also increased the likelihood of relapse. Initiating antidepressant medication care with a mental health specialist and having been hospitalized in the pretreatment period were not associated with relapse/recurrence.

The results from the Cox model were used to adjust the survival plots of those who did and did not adhere to our definitions of antidepressant drug treatment guidelines (Figure 1). Although the survival plots are not proportional, the log-rank test showed that adherence to medication guidelines was

Table 2. Cox Proportional Hazards Model*

Variable	Parameter Estimate (SE)	P	Hazard Ratio (95% Confidence Interval)
Age	-0.011 (0.004)	<.01	0.989 (0.982-0.997)
Female	-0.184 (0.089)	.04	0.832 (0.699-0.992)
Received psychotherapy	0.233 (0.090)	<.01	1.262 (1.058-1.506)
Saw a mental health professional	-0.126 (0.087)	.15	0.881 (0.744-1.044)
Year of initial antidepressant drug prescription [†]			
1992	0.332 (0.109)	<.01	1.394 (1.126-1.726)
1993	0.182 (0.089)	.04	1.199 (1.007-1.428)
Anxiolytic prescription	0.342 (0.083)	<.01	1.409 (1.200-1.655)
Hospitalization in the pretreatment period	0.090 (0.138)	.51	1.094 (0.835-1.434)
No. of Major Diagnostic Category comorbidities	0.046 (0.013)	<.01	1.047 (1.019-1.075)

*The time variable is days to relapse, the censor variable is relapse, and the stratification factor is discontinued early.

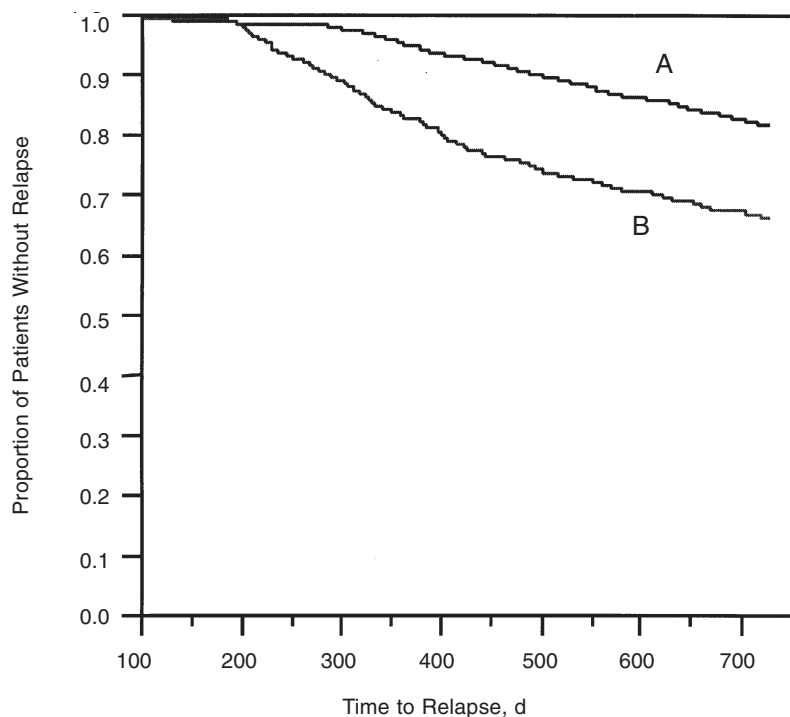
[†]Reference year is 1994.

associated with a significant reduction in the likelihood of relapse/recurrence ($P < .01$) in this study population. The shape of the survival plots is instructive. For the first 200 days after the index prescription, the survival functions are close to each other, suggesting nearly equal rates of relapse/recurrence for the 2 cohorts. Around day 200, the survival functions separate, showing progressively higher rates of relapse/recurrence for the nonadherent cohort. At day 330, the ratio of the proportion of patients who experienced relapse/recurrence in the nonadherent cohort to the proportion of patients who experienced relapse/recurrence in the adherent cohort is approximately 5.1. At this point in time, the likelihood of surviving without relapse/recurrence was 0.977 (95% confidence interval [CI], 0.970-0.984) for patients who met treatment guidelines and 0.890 (95% CI, 0.862-0.918) for those who did not. At day 530, this ratio was reduced to 2.6

(0.915 [95% CI, 0.895-0.935] vs 0.784 [95% CI, 0.740-0.830]). At day 730, this ratio was 1.96 (0.859 [95% CI, 0.829-0.889] vs 0.728 [95% CI, 0.677-0.782]). For many, adherence to treatment guidelines seems to prevent recurrence for at least 2 years after initiation of treatment, whereas for others the effect is to delay the onset.

The models presented here address a specific question regarding relapse/recurrence from the time antidepressant drug treatment is initiated. However, there are elements of the study design that could lead to biased conclusions. To mitigate these potential flaws in design, we carried out several alternative analyses, including survival models only for those whose relapse/recurrence was defined by resumption of antidepressant drug treatment, using the date of the last filled antidepressant drug prescription as the index date for measuring time to relapse/recurrence (Figure 2) and finally using the day of the last filled antidepressant drug prescription plus 6 months as the index date (Figure 3). These analyses were associated with slightly higher rates of relapse/recurrence for the guideline-adherent cohort compared with the rates shown in Figure 1. However, in each case the log-rank test suggested that the differences in the survival functions for the continuous use cohort and discontinued early cohort were highly significant ($P < .0001$).

Figure 1. Adjusted Survival Curves



Curve A denotes patients who met treatment guidelines.
Curve B denotes patients who discontinued early.

Predictors of Adherence with Medication Guidelines

The results of the guideline-adherence model are presented in Table 3. Significant variables in the model included age, sex, receiving psychotherapy during the treatment period, and choice of initial antidepressant drug. Older patients and women have a lower probability of early discontinuation. Patients who received psychotherapy during the treatment period were less likely to discontinue early.

The results confirmed the hypothesis that initial antidepressant drug choice is an important predictor of adherence to treatment guidelines. Patients initially treated

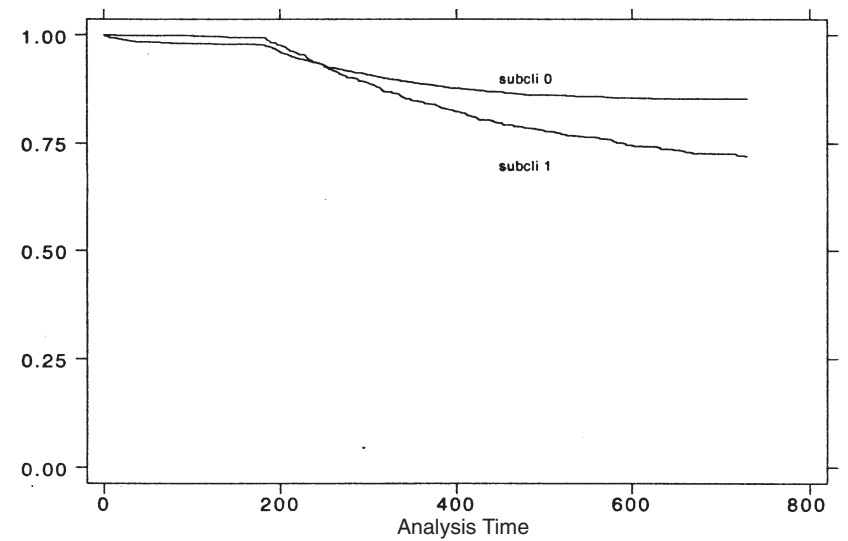
with TCAs or sertraline were more likely to prematurely discontinue antidepressant drug treatment than those initially treated with fluoxetine. Initiation of treatment with paroxetine was not associated with significant differences in the probability of adherence to treatment guidelines compared with fluoxetine.

... DISCUSSION ...

The main finding of this study is that antidepressant medication users who failed to meet the definition of adherence to medication guidelines are much more likely to return to care for relapse or recurrence of a depressive disorder. Our results confirm those of Melfi et al¹¹ in a population with employer-provided insurance benefits, the most common source of medical insurance in the United States. This association emphasizes the importance of achieving an adequate course of medication treatment for all antidepressant drug recipients.

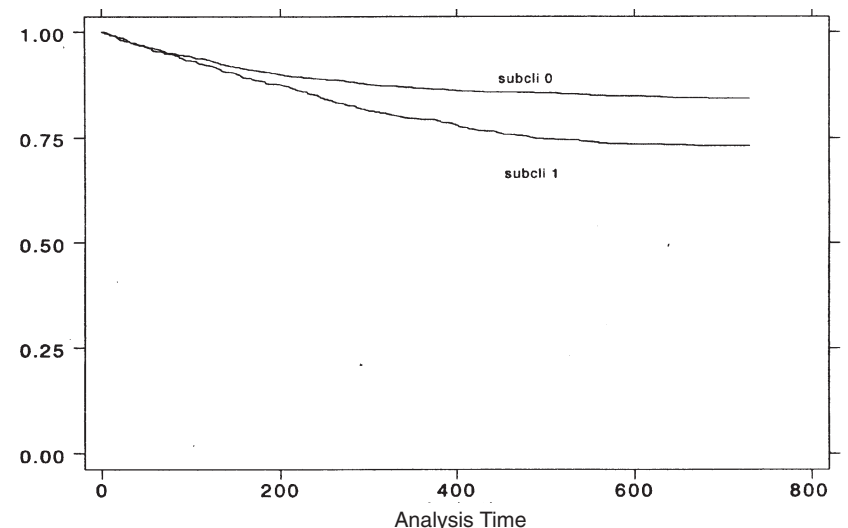
The results of our analyses also significantly extend our understanding regarding the complexities and usefulness of pharmaco-economic analysis of antidepressant drug treatments. Although there is a great deal of variability in the long-term treatment response of depressed persons, this analysis indicates that drug selection and treatment adherence are important factors in determining the eventual outcome of treatment. Compared with fluoxetine users, TCA and sertraline users were less likely to meet the definition of guideline-consistent care.

Figure 2. Time to Relapse When Days Are Counted From the Time of the Last Filled Prescription



Survivor functions by subcli adjusted for age.

Figure 3. Time to Relapse When Days Are Counted From the Date of the Last Filled Prescription + 180 Days



Survivor functions (log-rank test $P < .0001$). Wilcoxon (Breslow) test shows $P < .0001$ towards left-hand ends.

This result is consistent with recent research by Russell et al,¹⁷ who reported that patients initially treated with fluoxetine receive longer length of therapy (192.6 days) than patients initially treated with sertraline (166.9 days).

Several other results of the analysis deserve comment. The significant effect of psychotherapy on the probability of meeting medications guidelines is consistent with previous research.¹⁸ It is also clear from clinical studies that psychotherapy alone or in combination with medication therapy can prevent

or delay relapse and recurrence of depressive disorders.^{3,4} In the study presented here, psychotherapy was associated with increased rates of relapse or recurrence. We believe that this finding is related to our use of claims-based indicators of relapse/recurrence that rely in part on recognition of the return of clinical symptoms. Depressed persons who are currently receiving or have received psychotherapy may be more willing to return for care, to be recognized as depressed, and to accept more intense treatment. It is also possible that use of psychotherapy during

acute treatment may be an indicator of more severe disorder. Each of these factors suggests reverse causation as the explanation for the association of psychotherapy with relapse/recurrence, ie, that relapse/recurrence in our models predicts use of psychotherapy in the treatment period and not the other way around.

The design of the present study has limitations that are similar to those of many claims-based analyses. We previously outlined the difficulties of identifying clinical events from insurance claims. The nonrandom choice of initial antidepressant drug that occurs in clinical practice might introduce selection bias into the adherence to treatment guidelines model. The selection of a particular medication for a specific patient depends on a variety of factors, including likelihood of adherence to medication treatment and other clinical factors.¹² Unobserved factors may also introduce selection bias into the interpretation of findings regarding the effect of adherence to treatment guidelines on relapse/recurrence. For example, individuals willing to complete treatment may be more willing to return for

Table 3. Logit Model: Discontinued Antidepressant Treatment Early

Variable	Parameter Estimate (SE)	P	Odds Ratio (95% Confidence Interval)
Intercept	-0.327 (0.222)	.14	
Age	-0.012 (0.004)	<.01	0.988 (0.980-0.996)
Female	-0.364 (0.096)	<.01	0.694 (0.575-0.839)
Received psychotherapy	-0.450 (0.096)	<.01	0.637 (0.528-0.770)
Anxiolytic prescription	-0.026 (0.091)	.77	0.974 (0.815-1.165)
Initial tricyclic antidepressant user*	0.572 (0.122)	<.01	1.771 (1.395-2.248)
Initial sertraline user*	0.354 (0.106)	<.01	1.425 (1.159-1.753)
Initial paroxetine user*	0.021 (0.155)	.89	1.021 (0.760-1.372)
Psychiatric hospitalization in pretreatment period	0.387 (0.232)	.09	1.474 (0.935-2.323)
Nonpsychiatric hospitalization in pretreatment period	0.199 (0.206)	.34	1.220 (0.814-1.827)
No. of Major Diagnostic Category comorbidities	0.006 (0.015)	.71	1.006 (0.976-1.035)
Saw a mental health professional	0.047 (0.097)	.49	1.048 (0.867-1.267)
Year of initial antidepressant drug prescription [†]			
1993	-0.036 (0.096)	.70	0.964 (0.798-1.164)
1992	-0.229 (0.130)	.078	0.794 (0.615-1.026)

*Reference initial antidepressant drug is fluoxetine.

[†]Reference year is 1994.

treatment when symptoms return, making identification of relapse/recurrence more likely. However, if adherent persons return for care before expiration of the 6-month interepisode period we used for the medication indicator, then we could have missed cases of depression relapse. Although we could not control for these factors in the current analysis, we believe that our definitions generally underestimate differences in the likelihood of relapse. As many as 50% of previously treated persons with current depression do not seek care for a current episode.¹⁹ In addition, previous research^{14,20,21} using instrumental variable techniques has not revealed evidence of selection bias in either treatment adherence or relapse/recurrence models.

We also note that we carried out extensive sensitivity testing to produce parsimonious models that were highly predictive and faithful to the data. Although this sensitivity testing provides confidence in the robustness of our findings, using multiple statistical tests also introduces the possibility of a significant finding due to chance. However, this degree of sensitivity testing was necessary to produce understandable results. For example, psychotherapy might have shared influence on treatment adherence through correlation with care from a mental health professional at the time of diagnosis. The correlation between these variables was 0.355 in this population, with most individuals who received psychotherapy initiating treatment with a mental health specialist. During sensitivity testing, we consistently found that psychotherapy was an important predictor of outcome, independent of the specialty of the provider who made the initial diagnosis. Analysis of time to relapse stratified by the mental health professional variable alone did not yield a significant result. Including mental health provider and psychotherapy variables (and the interaction between the 2) yielded a significant finding only for psychotherapy. Further research is needed to elucidate the impact of combined medical and psychosocial approaches on improving outcomes and reducing response variability.

Despite the limitations and complexity of its design, this study achieves its goal of providing external validity to the notion that adhering to current antidepressant drug treatment guidelines results in improved clinical outcomes. Adherence with treatment guidelines may also affect the direct and indirect costs of depression. Although guideline-adherent antidepressant treatment will have higher drug acquisition costs because of longer lengths of therapy relative to early discontinuation, these costs

seem to be offset by reduction in costs for other components of care.^{18,21} Moreover, guideline-adherent treatment could substantially reduce indirect costs related to depression in terms of maintaining functional status and reduced mortality from suicides. Studies that ignore antidepressant drug use patterns or length of therapy and only compare drug acquisition costs or depression-related medical costs are misleading because they implicitly assume similar medical and nonmedical costs associated with alternative antidepressant drugs.

... CONCLUSION ...

In summary, we found that adherence to treatment guidelines is significantly associated with reduced likelihood of relapse or recurrence of depression and that choice of initial antidepressant drug is related to adherence to treatment guidelines. These findings highlight the importance of continuing medication treatment beyond the point of symptom resolution. Preventing or delaying relapse or recurrence of depressive disorders can have an economic impact by reducing costly procedures, hospitalization, and other expensive care. More important, it can have a profound clinical impact and help maintain normal functioning.

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