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Cost-Effectiveness of Antidepressant Medications

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Abstract

Background: Antidepressant medications have been shown to effectively relieve symptoms, improve interpersonal and occupational functioning and reduce disability from coexisting medical conditions. Although the newer selective serotonin reuptake inhibitors (SSRIs) have improved tolerability, are easier to take and are associated with longer lengths of therapy when compared with the tricyclic antidepressants (TCAs), the relative cost-effectiveness of alternative antidepressants remains unclear.

Aims of the Study: This study seeks to determine (i) the probability that relapse or recurrence of depression can be prevented by appropriate antidepressant choice, (ii) the cost associated with relapse or recurrence of depression and (iii) the relative cost-effectiveness of alternative antidepressants.

Methods: We use a quasi-experimental design to compare claims from a state Medicaid plan for TCA and SSRIs users.

Results: Premature discontinuation of antidepressant medication is the strongest predictor of relapse and recurrence. Antidepressant choice was not an independent predictor of relapse or recurrence. The effect of relapse and recurrence on expenditures is complex, with a non-significant trend toward lower expenditures for those who had longer periods between episodes of depression two years after initiation of treatment for the first episode. We were unable to replicate prior research results regarding the impact of SSRIs on duration of therapy in this Medicaid plan.

Conclusion: Premature discontinuation of antidepressant treatment is associated with a high probability of relapse and recurrence. Health care expenditures are not altered by preventing relapse and recurrence. We suggest that antidepressant medications associated with reduced probability of premature discontinuation should be considered cost-effective.

Implications for Health Care Provision and Use: There are very few variables which health care providers can use to improve the outcomes and associated economic consequences of depression. Among these factors, treatment choice and adherence to the prescribed treatment are likely candidates. In this paper, we suggest that adherence to antidepressant medication results in substantial improvement in the time to relapse or recurrence of depression. Choice of an SSRI may thus improve treatment outcome by lengthening remission. In addition, this choice is not associated with higher costs.

Implications for Health Policy Formulation: Depressive illnesses are associated with high rates of health service use and functional impairment. Thus, the societal burden is quite high. This paper furthers the debate regarding the relative cost-effectiveness of antidepressant medications, and our findings suggest several ways that policy makers can improve the care of depressed individuals at little additional cost. Specifically our findings highlight the importance of adherence to current recommendations regarding the length of antidepressant treatment and suggest several methods for improving this important outcome.

Implications for Further Research: The relative cost-effectiveness of alternative antidepressant medications continues to be an important and unsolved issue. We suggest the need for future research in this area using a variety of research designs appropriate to the question. The quasi-experimental approach outlined here seems promising in this regard.

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Introduction

Medical care for depressed individuals places an enormous economic and social burden on society. Depressive illnesses are among the most common disorders seen in primary care, with the lifetime prevalence of major depression approaching 17%,[1] and are associated with high rates of health service utilization when compared with other diseases seen in the general medical setting.[2–5] In addition, the functional status of patients with depression is similar to or worse than patients with many severe, chronic medical conditions.[6] Total direct and indirect costs of depression in the United States are of similar magnitude to those of other major illnesses such as cancer, AIDS and coronary heart disease,[7,8] and recent projections suggest that these total costs will place depression as the second largest medical burden to our global society by 2025.[9]

Antidepressant medications have been shown to effectively relieve symptoms, to improve interpersonal, marital and occupation functioning[11], and to reduce disability from coexisting medical conditions.[2] While one might expect new and more effective antidepressants would help alleviate some of the burden imposed by depression, this has been difficult to prove. Introduction of the selective serotonin reuptake inhibitors (SSRIs) and increasing awareness of depression as a cause of significant disability has resulted in rapid increases in expenditure for depression over the past decade. While it is clear that SSRIs are associated with fewer side effects and are easier to take than the older

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drugs,[12,13] clinical studies have failed to show that the SSRIs result in improved clinical outcomes when compared with the tricyclic antidepressant (TCA) medications.[14] Unfortunately, these comparative studies have focused on short term symptom reduction to the exclusion of longer term outcomes such as restoration of normal functioning or prevention of relapse and recurrence of depression.

Although clinical studies have failed to show differences in short term outcomes between the TCAs and the SSRIs, a growing body of literature suggests that there are meaningful differences in the way patients use the SSRIs as a result of their easy to use and more tolerable profile. Specifically, studies have reproducibly shown that SSRI recipients are more likely to achieve adequate dose and/or duration of therapy when compared with TCA recipients.[15–18] Based upon the available literature, one would expect that such improvements in the process of care should result in improved outcomes. For example, longer lengths of therapy have been shown to be associated with improvement in certain measures of work restoration.[19,20] There is also a substantial literature which suggests that longer lengths of therapy are associated with reduced likelihood of relapse or recurrence of an episode of major depression.[21–23] These results have led several guideline panels to recommend at least four to nine months of continued antidepressant treatment beyond the point of symptom relief.[10,24]

In spite of the indirect evidence that the SSRIs might be expected to be cost-effective relative to the older antidepressants, controversy remains. A number of decision analytical models of antidepressant cost-effectiveness have resulted in a virtual stalemate.[25] Parameter estimates for these analyses come primarily from clinical trials, the results of which depend heavily on the definition that one uses for drop-out from the benchmark studies. In general, if one considers only those who drop out from a clinical study because of an adverse event or failure to respond, then the SSRIs appear relatively cost-effective.[26] However, if one considers all causes of drop-out to result in similar outcomes, then the TCAs appear to be the more cost-effective alternative because of their lower acquisition prices. We now know from observational studies that patients who prematurely discontinue antidepressant medication in actual practice have very heterogeneous outcomes,[28] and so the relevance of this line of research may be questioned.[29]

The preliminary results of the only randomized, economic trial of antidepressant cost-effectiveness have recently been released.[30] This study failed to show significant differences in cost, depression symptoms, and health status over the six month observation period between the prototypic SSRI, fluoxetine, and either of two TCA cohorts. Unfortunately, many patients initially randomized to receive a TCA were quickly switched to fluoxetine, so that the results may have been subject to substitution bias. Consistent with previous observational studies, however, patients initially randomized to receive fluoxetine were more likely to remain on their initial treatment for the study period.

A third line of cost-effectiveness research has attempted to make use of the observed differences in length of therapy between the older and newer antidepressants. Several studies have looked at differences in cost for those who receive a prescribed course of therapy which adheres to the recommended standard of care. Several studies have suggested reduction in 'depression related' costs—i.e., that portion of a person's total medical expenditure which can be directly attributed to caring for depression—for those patients who fill at least some minimum number of antidepressant prescriptions in the course of the year following initiation of treatment.[31–33] More recent work has suggested that the longer lengths of therapy associated with SSRI use can be achieved at no increase in total medical costs, or in mental health specific costs, when treatment is initiated with the SSRI drugs.[18] While these studies are consistent with current recommendations, they fail to study more meaningful clinical outcomes, such as symptoms, functional status or rates of relapse or recurrence.

The research described in this paper attempts to link total medical expenditures for patients with depression with a clinically meaningful outcome, prevention of relapse and recurrence. In other words, we attempt to define the relative value of alternative antidepressant choices at the time when they are first prescribed to an individual patient. The specific goals of the research are to address three closely related questions in order to assist in decisions regarding coverage of particular treatments:

(i) What is the probability that relapse or recurrence can be prevented by choice of particular classes of antidepressants?
(ii) What is the cost associated with relapse or recurrence of an episode of depression and its prevention?
(iii) What is the cost-effectiveness of alternative antidepressant choices?

In brief, our results suggest that use of an SSRI as the initial medication has no effect on relapse or recurrence independent of their effect on length of medication. Although we did not demonstrate the effect in this study, SSRI use has been shown to reduce the probability of premature discontinuation, and they may therefore be shown to be more effective, and thus cost-effective, than the TCAs in other systems of care.

Methods

Episodes of Depression Treatment

We begin by providing background information on depression in general, including the various forms of depressive disorders and their treatment. We then define an episode of depression which we believe is faithful to the clinical syndrome.

Depressive Disorders

Clinical depression is characterized by depressed mood, loss of interest in activities and feelings of worthlessness. It is clearly a chronic illness, with most types characterized by recurrent episodes over time. The *Diagnostic and*

Statistical Manual of the American Psychiatric Association (fourth edition, DSM-IV) provides very specific guidelines regarding the diagnostic criteria for the various forms of depression, and these diagnoses link reasonably well with the *International Classification of Diseases—Ninth Edition—Clinical Modification* (ICD-9-CM) used for coding of medical claims.

Depressive disorders are part of a broader classification of mental illness known as the affective disorders, which also includes conditions such as anxiety and Bipolar Affective Disorder. The latter is more commonly known as manic–depressive illness, and although depression is a major component of this illness, the other features of mania make its clinical characteristics and treatment sufficiently different from the more common forms of depression that we exclude it from our analysis.

There are six classifications of depression based on ICD-9-CM coding. Major Depressive Disorder (MDD) is very well defined clinically and is characterized by depressive symptoms which last for at least two weeks. MDD—single episode implies that the patient is experiencing a first episode. MDD—recurrent episode suggests the presence of at least two or more episodes of major depression separated by at least two months.[24] Approximately 50% of all people who experience a first episode will experience at least one additional episode at sometime during their lifetime, and at least 70% of those who experience a second episode will at some time have a third.[34] About 25% of depressed individuals who receive their initial treatment for depression in primary care have either MDD—single episode or MDD—recurrent episode as their primary diagnosis.[35] Taken together, the major depressive disorders are the most common form of depression.[1,36,37] Most treatment guidelines for depressive disorders are based upon studies of individuals with major depression.[10,24]

The most common form of clinically well defined depression recorded on claims from primary care is dysthymia, sometimes called minor depression because symptoms tend to be less severe.[35] By definition, however, symptoms must be present for at least two years. In addition to the more typical symptoms of depression, individuals with dysthymia tend to have symptoms of an overlapping anxiety disorder. Dysthymia maps to an ICD-9-CM diagnosis of neurotic depression. The two other clinically well defined syndromes are brief depressive reaction and prolonged depressive reaction. The chronicity and reactive nature of these disorders is self-evident.

The most common depression diagnosis recorded on medical claims for patients in primary care is depressive disorder not elsewhere classified (NEC), but this diagnosis is much less frequent in the mental health specialty setting.[35,38] In this case, there is no recorded information regarding symptom classification or chronicity. In our previous studies of depression care, none of these diagnostic indicators have been found to be predictors of cost or length of therapy outcomes.[28,35,39,40] This information is important because all forms of depression tend to be treated, at least initially, in a manner similar to major depression. Also, differentiation of the clinical syndrome may be very difficult. Both of these factors are especially important in primary care where 80% of all initial care for depression is received.[37,41]

Treatments for Depression

Treatment of episodes of depression can be divided into three phases,[22] each with clearly defined objectives. The goal of the *acute phase* of treatment is symptom elimination. Newer forms of psychotherapy, such as interpersonal therapy (IPT) and cognitive behavioral therapy (CBT), the TCA medications and the SSRI medications are all equally efficacious during this acute phase,[10,42] at least for those with mild to moderate symptoms. Acute treatment lasts until symptoms are resolved and is the period when medication titration or switching occurs because of lack of response or side effects. In most cases, the acute treatment phase lasts six to eight weeks.[10]

The goal of the *continuation phase* of treatment is to achieve more complete restoration of functional status and to prevent relapse of symptoms or recurrence of a second episode. Although there are few studies, most medications appear equal when studied under strict adherence protocols, but only intensive, continued psychotherapy protocols have been found equal to medications.[10] Length of medication treatment seems to be predictive of restoration of normal functioning[19] and relapse prevention.[21] Current recommendations suggest four to nine months of continuation treatment beyond the point of symptom resolution.[10]

The third and final phase of treatment for depression is the *maintenance phase* and is currently indicated only for those individuals who have experienced three or more episodes of depression.[43] The goal of maintenance treatment is to prevent recurrent depressive episodes in those who have a very high probability for recurrence. Although not yet clearly defined, current recommendations call for a minimum of five years of treatment.

Episode Creation

We make use of the chronic, relapsing nature of depression and current treatment recommendations to construct episodes of care which can be identified in medical claims. Because our interest is in prevention of relapse or recurrence, our focus is on constructing episodes which allow us to examine those factors during the acute and continuation phases of treatment which might influence this important and clinically meaningful outcome.

Data for the study are derived from medical and pharmacy claims records from a state Medicaid population in the southern United States. Information on drug claims, inpatient hospital care, ambulatory care, laboratory tests and demographic characteristics is provided. There were no administrative restrictions on access to particular treatments of relevance to mental health care or depression during the study period. Specifically, there were no formulary or prior authorization restrictions on any of the medications we include in the analysis. The strengths and limitations of using Medicaid data have been reviewed elsewhere.[44]

The initial sample is based on Medicaid recipients for whom a diagnosis of depression had been recorded on a

medical claim or who had submitted a pharmacy claim for an antidepressant during the six year period 1989–1994. The diagnoses are identified by ICD-9-CM codes and include MDD—single episode (296.20, 1, 2, 3, 5, 6), MDD–recurrent episode (296.30, 1, 2, 3, 5, 6), neurotic depression (300.4*x*), brief depressive reaction (309.0*x*), prolonged depressive reaction (309.1*x*) and depression NEC (311.*xx*). Individuals with a diagnosis of psychosis, such as schizophrenia and psychotic depression, are excluded from the study because these patients exhibit markedly different symptoms from other depressive disorders. We include the major medications in both the TCA and SSRI classes. These include the TCAs amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protrityline, trimipramine and clomipramine. The SSRIs in the sample are fluoxetine and sertraline.

Episodes of 30 months duration are created in keeping with past research on claims based episode creation for depression.[18,45–47] Because we are interested in new episodes of depression, we require that the initial six months of each episode be free of any indication of depression or mental health specific care. The exception to this exclusion criteria is use of anxiolytic medications which have achieved very common use. Patients taking anxiolytics in the first six months of the episode are included in the sample. Although clinical definitions suggest that any symptom-free period of two months or more constitutes the end of an episode, periods of this duration during which no services are delivered may not mean that individuals are symptom free. Therefore, we have chosen a longer and more stringent definition to avoid including relapse of a existing episode. We term this first six months the *pretreatment period*.

The second six month period of the episode constitutes the *treatment period* during which we measure the nature and intensity of treatment which may then impact subsequent relapse or recurrence. The initial filling of a prescription for an antidepressant medication marks the index event for the treatment period and must occur within 30 days of a medical claim on which depression was included as a diagnosis. During the treatment period we record the type of antidepressant initially used, the pattern of use for that antidepressant, whether mental health specialty services were also used and the number of concomitant medical conditions. We consider patients who filled at least four prescriptions for the initial antidepressant, but no other antidepressant, during this first six months as *continuous users*. Those who filled at least four prescriptions for more than one antidepressant are placed in a *switched or augmented* cohort. All remaining individuals—i.e., those who filled three or fewer prescriptions for any antidepressant—are considered *premature discontinuers* because these individuals could not have received even minimally recommended care.

The final 18 months of each episode constitutes the *follow-up* period during which we look for resource utilization based evidence of relapse or recurrence. Any hospitalization or emergency room visit for mental health reasons, electroconvulsive treatment or evidence of attempted suicide following 60 days of stable anti-depressant treatment are considered evidence of relapse or recurrence. In addition, any new use of an antidepressant which follows a six-month period off any of these medications is also considered evidence of relapse or recurrence. Use of resource based measures may result in undercounting the actual occurrence of relapse or recurrence because not all symptomatic patients seek care for a current episode.[1]

In addition to understanding the rate and predictors of the clinical outcome, we are also interested in the costs associated with care. For this study, we accumulate all paid charges beginning with the index prescription, including those for both mental health specific care and for general medical care. Individuals included in the study had to be continuously enrolled in the Medicaid plan throughout the pretreatment and treatment period, and for at least the first six months of the follow-up period. The inclusion and exclusion criteria result in a sample of 3845 observations, of whom 2445 completed the entire 30 months, and 3104 completed at least 24 months.

Statistical Methods and General Estimation Strategy

To examine the impact of antidepressant choice on relapse and recurrence of depression, we use survival analysis and estimate a Cox proportional hazards model with antidepressant and other variables as covariates. Survival analysis provides the dual advantage of the ability to estimate the likelihood of an event occurring over time and the average time to occurrence of an event, and the ability to include individual observations with intermittent or truncated data due to loss of Medicaid eligibility.

Analysis of drug treatment effects on any outcome can often be complicated by selection effects regarding the choice of a particular treatment. Differences in outcomes related to comparative treatments may be correlated with both the treatment itself and the selection of patients with certain characteristics to receive one treatment over an alternative. Such selection bias is generally a consequence of unobserved variables, for if all relevant variables affecting both treatment choice and outcome could be measured, perfect comparison groups could be formed or all the effects could be controlled for statistically. Several adjustment methods for handling selection bias due to unobserved variables have recently been applied to health outcomes research.[48–50] Known collectively as instrumental variables techniques, all have the ability to correct for statistical problems characterized by explanatory variables which are correlated with the residuals. An instrumental variable is one that has the characteristic of being highly correlated with the variable for which it is intended to serve as an instrument without its being correlated with the residuals.

We recognize that not all of the differences between the SSRI and TCA cohorts can be observed in our dataset and therefore construct an instrumental variable to adjust for sample selection bias. We first model the probability of receiving an SSRI by considering factors which might influence antidepressant prescribing decisions. We hypothesize that the decision to use a TCA or an SSRI is a function

of several factors observable in our dataset which would indicate (i) general health status (age, gender, race, reason for Medicaid eligibility, number of comorbid medical conditions during the pretreatment period, any non-psychiatric hospitalizations in the pretreatment period), (ii) the characteristics of the depression and related conditions (depression diagnosis, anxiolytic use, substance abuse indicator) and (iii) certain structural features of the medical care system (provider type). Probit models were chosen as the algebraic form of the equation because the dependent variable (antidepressant choice) is binary and the random error follows a normal distribution. The predicted value of the probit model then serves as the instrumental variable in the outcomes equation.

We next use the survival models to assess the incidence of relapse or recurrence as well as the time to relapse for those who experience this outcome. We hypothesize that several factors influence relapse and recurrence, including indicators of general health status (age, gender, race, Medicaid eligibility status, number of comorbid medical conditions in the treatment and follow-up periods), severity and nature of the depression (depression type, substance abuse), provision of mental health specialty services (initial provider type, use of psychotherapy as an adjunct during the treatment period) and the propensity of an individual to seek medical care (total number of ambulatory visits for certain medical problems).

After extensive testing of various model specifications, we find that a single equation survival model—i.e., one in which all the observations are included—is most faithful to the observed data and that sample selection bias does not significantly alter the results. Therefore, the instrumental variable constructed from the antidepressant choice models is not included in the final specifications. Separate models for each drug class (SSRI and TCA), with and without the instrument, were also estimated but did not alter the results. As a final sensitivity check, we tested our results using two-stage sample selection models in which the results of the drug choice model were used to construct an inverse Mill's ratio (IMR) as described by Heckman[51,52] and as modified by us.[50] Because survival models do not easily accommodate the IMR term, we used tobit estimation for these secondary models. Like survival analysis, tobit estimation allows one to account for censored observations but lacks the other advantages of survival analysis. Thus, this sensitivity check, not reported in detail here, allows us to confirm our estimates of the probability of relapse or recurrence but not the time to relapse or recurrence.

Estimates of cost were generated using paid charges as a proxy measure. While use of this proxy does not allow us to make definitive statements regarding the 'cost' of the services provided, paid charges is a direct measure of the demand for health services and the expenditures of the payor, in this case state Medicaid programs. Estimates were generated using ordinary least squares regression with specifications similar to those for the survival models. Details of these methods can be found elsewhere.[18,50]

Results

Impact of Medication Choice on Relapse and Recurrence of Depression

Table 1 reports the means and relative frequencies for the variables hypothesized to influence time to relapse and recurrence by class of antidepressant. In general, members of the TCA and SSRI drug cohorts appear to have relatively similar characteristics. On average, members of both cohorts are in their mid-thirties, overwhelmingly female and much more likely to be black than the Medicaid population in general. More than seven in ten recipients of antidepressant medications failed to reach even minimal standards for antidepressant care.

Despite these similarities, there are statistically significant differences between the TCA and SSRI cohorts for a number of variables. TCA recipients are more likely to be in the aged/blind/disabled eligibility category, to be older, male, have a mental health provider as the initial prescriber of an antidepressant, to have received treatment for substance abuse and to have and receive care for general medical illnesses. The SSRI patients in this sample are more likely to receive ongoing psychotherapy during the treatment period, and subjects are more likely to receive the SSRI during a later year in the sample. The average time to relapse or recurrence is significantly longer for the TCA cohort.

Factors Affecting Medication Choice

Although not the major focus of this paper, the results of the drug choice models are interesting in their own right (**Table 2**). Older patients, those with other or unknown race, those with a diagnosis of depressive reaction, either brief or prolonged and those receiving initial care from a mental health specialist are more likely to receive a TCA. Patients with an indicator for MDD–single episode and those who received their initial prescription in a later year were more likely to receive an SSRI as the initial antidepressant.

Factors Affecting Relapse and Recurrence of Depression

In **Table 3** we report the parameter estimates for the final model predicting relapse and recurrence. Premature discontinuation is associated with an 82% increase in the likelihood of relapse or recurrence (hazard ratio (HR) = 1.82). Premature discontinuation of antidepressant treatment suggests substandard care, and our models would tend to confirm this point. Several other factors are significant determinants of relapse or recurrence. African Americans are less likely to receive care for relapse or recurrence (HR = 0.845). Because there do not appear to be racial differences in the epidemiology of depression, at least with regard to blacks as compared to whites,[1,53] this may be the result of cultural factors. Anxiolytic use (HR = 1.215), substance abuse (HR = 1.685) and prior psychiatric hospitalizations (HR = 2.385) suggest more severe mental illness and are associated with relapse or recurrence. The number of

Table 1. Descriptive statistics. Reported are mean (SD) for continuous variables and percent for dichotomous variables.

Variable	SSRI	TCA	*p*
Age	34·1 (10.9)	35·5 (11.0)	<0.001
Black	46.2%	48.7%	0.114
Other/unknown race	6.5%	6.7%	0.781
Aged/blind/disabled	32.4%	38.4%	0.001
Poverty related	1.4%	0.8%	0.060
Male	5.4%	8.4%	<0.001
Psychotherapy during treatment period	21.1%	15.2%	<0.001
Years from beginning of January 1989	4·3 (1.5)	3·6 (1.5)	<0.001
Mental health provider	35.5%	44.1%	<0.001
Premature discontinuation	70.9%	70.1%	0.553
Switch/augment	9.7%	11.5%	0.457
Anxiolytic use	9.7%	11.0%	0.170
Substance abuse	4.1%	6.3%	0.002
Number of psychiatric hospitalizations at any time prior to treatment	0·5 (0.1)	0·2 (0.0)	0.051
Number of non-mental-health visits in treatment and follow-up period	9·6 (8.5)	11·3 (9.2)	<0.001
Number of non-substance-abuse MDC categories	5·9 (3.1)	6·4 (3.1)	<0.001
Time to relapse or recurrence in days	292·4 (192.1)	352·6 (190.0)	<0.001
N	1917	1928	

Table 2. Probit models of antidepressant choice (1 = SSRI) ($N = 3845$).

Variable	Parameter estimate	$z = b$/s.e.
Constant	–0.238 5	–2.331
Age	–0.007 1	–3.212
Black	–0.076 1	–1.737
Other/unknown race	–0.323 5	–3.737
Male	–0.071 2	–0.785
Aged/blind/disabled	–0.047 4	–0.912
Poverty related	0.283 3	1.383
Year	0.174 23	12.348
MDD—single episode	0.463 7	6.544
MDD—recurrent episode	–0.105 5	–1.159
Neurotic depression	–0.482	–0.885
Brief depressive reaction	–0.501 2	–5.219
Prolonged depressive reaction	–0.563 5	–2.100
Anxiolytic in the pretreatment period	–0.082 6	–1.102
Number of anxiolytic prescriptions in the pretreatment period	0.008 4	0.392
Number of non-mental-health conditions in the pretreatment period	–0.010 8	–1.087
Number of psychiatric hospitalizations at any time prior to treatment	0.839 3	2.166
Mental health provider	–0.297 0	–5.462

Model $X^2 = 386.36$.

comorbid medical conditions is also predictive of relapse and recurrence (HR = 1.069).

Antidepressant choice is not associated with reduced probability of relapse or recurrence in the models independent of the indicator for early discontinuation. However, because TCA use has been shown to be associated with high rates of premature discontinuation, we ran the models without this indicator. This respecification does not result in a significant change in results, probably because TCA use is not associated with higher rates of premature discontinuation in this Medicaid system.

Impact of Drug Choice and Relapse and Recurrence on Health Care Costs

In **Table 4**, we report the results of several models which show the independent effects of treatment on total expenditures for 12, 18 and 24 months after initiating treatment, including the independent effect of relapse and recurrence on expenditure. In general, the factors which affect one-year expenditures also effect expenditures over the longer time period. African Americans tend to have lower expenditures, and expenditures for depressed individuals

Table 3. Survival model of relapse or recurrence ($N = 3845$).

Variable	Parameter estimate	Hazard ratio	X^2	p
Age	0.001	1.001	0.033	0.8560
Black	–0.169	0.845	5.875	0.015
Other/unknown race	0.168	1.183	1.833	0.176
Male	–0.051	0.950	0.114	0.736
Aged/blind/disabled	0.037	1.038	0.082	0.203
Poverty related	–1.907	0.149	3.625	0.057
Year	0.0577	1.059	2.418	0.120
Psychotherapy during treatment period	0.129	1.138	1.935	0.164
Anxiolytic use	0.195	1.215	4.096	0.043
Substance abuse	0.522	1.685	20.103	<0.001
Number of comorbid conditions (non-substance-abuse)	0.067	1.069	20.947	<0.001
Number of psychiatric hospitalizations at any time prior to treatment	0.869	2.385	4.072	0.044
Number of non-mental-health visits in treatment and follow-up period	0.129	1.138	8.647	0.003
Mental health provider	–0.034	0.997	0.166	0.683
Premature discontinuation	0.599	1.820	38.418	<0.001
Switch/augment	0.038	1.039	0.069	0.792
TCA	–0.028	0.972	0.168	0.682

Table 4. Factors which affect two-year paid charges of depressed patients.

Variable	12 months ($N = 3845$)		18 months ($N = 3104$)		24 months ($N = 2445$)	
	Coefficient	$z = b$/s.e.	Coefficient	$z = b$/s.e.	Coefficient	$z = b$/s.e.
Constant	6.530 3	78.475	6.8783	76.202	7.0833	74.651
Age	0.002 4	1.796	0.0011	0.800	–0.0001	–0.010
Black	–0.066 3	–2.616	–0.0662	–2.414	–0.0890	–2.914
Other race	0.261 2	5.221	0.2390	4.315	0.1924	2.963
Male	–0.321 3	–0.615	–0.0204	–0.369	–0.0670	–1.111
Age/blind/disabled	0.211 1	6.904	0.2109	6.410	0.2268	6.221
Year	–0.044 9	–4.782	–0.0393	–3.701	–0.0311	–2.494
Psychotherapy	0.374 1	10.804	0.3369	8.890	0.3246	7.517
Anxiolytic	0.136 5	3.274	0.1476	3.503	0.1391	3.123
MDD—single	0.039 4	0.967	–0.0016	–0.035	0.0265	0.511
MDD—recurrent	0.076 5	1.454	0.0704	1.234	0.0491	0.769
Neurotic depression	–0.029 5	–0.925	–0.0214	–0.627	–0.0149	–0.398
Brief dep. reaction	0.130 77	2.443	0.0719	1.276	0.0788	1.268
Prolonged dep. rtn	–0.082 7	–0.546	–0.1457	–0.796	–0.0488	–0.244
Substance abuse	0.486 4	8.864	0.4558	8.089	0.4459	7.459
Comorbid conditions	0.170 7	35.029	0.1522	29.028	0.1389	23.630
	0.364 7	28.538	0.3536	27.617	0.3421	25.737
Prior psych. OP visits	0.007 5	12.182	0.0076	12.326	0.0074	11.464
Mental health	0.111 1	3.474	0.1301	3.752	0.1161	3.003
Time to relapse	0.000 9	3.409	–0.0001	–0.629	–0.0002	–1.931

declined by about 4% per year over the course of the study period. Use of anxiolytics, treatment for substance abuse, the number of comorbid medical conditions, the propensity to seek care for non-mental health conditions, a past history of psychiatric hospitalization and use of mental health specialty services all tended to increase expenditures.

The effect of extending the time to relapse or recurrence is somewhat more complex. For the one year time from initiation of treatment to end of follow-up, extending the time to relapse or recurrence was associated with somewhat higher expenditures. However, at two years, this trend had reversed such that extending the time to relapse or recurrence tended to be associated with lower costs, although this latter result did not reach statistical significance. While we cannot explain the apparent paradox of increased costs related to increasing the time to relapse and recurrence, the magnitude of the change is very small. Mean expected expenditure for the 12 month cohort is about $7154 or $19 per day. A 0.1% increase in cost for each day of expected relapse free time would result in an increase of only $12.74 per year in

total medical expenditure. The potential savings over 24 months are equally small and not policy relevant.

In **Table 5**, we present the predicted paid charges from the OLS regressions over two years following initiation of antidepressant treatment. There is a trend suggesting lower costs for the SSRIs although this does not reach statistical significance in this 'intent-to-treat' fashion. These results are similar to those observed in previous cost-effectiveness research.[18]

Conclusions

SSRIs are widely acknowledged to have fewer side effects and a more tolerable pharmacological profile[12,13] making them more 'user friendly'. The finding that SSRI use is associated with longer lengths of therapy would tend to confirm their 'user-friendly' nature. Still, it has been very difficult to prove the SSRIs are more effective than the TCAs in terms of symptoms or functional status. We believe this results in part from the methods used in these prior studies. The importance of the work presented here is that we begin to bring the tools of modern economics to the challenges of medical outcomes research.

Our preliminary answer to the first question posed in the introduction is that the choice of the newer SSRI antidepressants can make a significant difference in the probability of relapse and recurrence of depression. While we cannot make this inference directly from the results presented here, we present the circumstantial case as follows. In most systems of care studied, SSRI use is associated with higher rates of achieving recommended lengths of medication treatment.[15,16,18,30] In this work we show that achieving these lengths of therapy is associated with reduced probability of relapse and recurrence. Unfortunately, because the association between antidepressant choice and length of therapy does not hold in the Medicaid system studied here, the anticipated improved effectiveness of the SSRIs remains unproven.

The answer to the second question regarding the costs associated with relapse and recurrence is more complicated. After adjusting for covariates, relapse and recurrence is not associated with economically relevant changes in total expenditures. With regard to our third question regarding antidepressant cost-effectiveness, our overall results are similar to those of Simon.[30] In this population of Medicaid recipients, we do not detect improved effectiveness related to SSRI use, and there is a trend toward reduced cost. One might anticipate, however, SSRI dominance on cost-effectiveness in populations where differences in use patterns occur, an hypothesis that invites further study.

Table 5. Predicted two-year paid charges by drug cohort ($N = 2445$).

	Parameter estimate	$z = b$/s.e.
SSRI	8.0202	1.137
TCA	8.6421	

There are very few variables which policy makers can alter in terms of affecting the economics and outcomes of individuals with depression. The major factors which can be altered to some degree are treatment choices and whether people adhere to those treatments once they are provided. Treatments which improve outcomes at no additional expenditure would be preferred, as would those which result in reduced expenditure at no loss in effectiveness. In this regard, the SSRIs appear dominant over the TCAs because they appear to result in longer lengths of remission at no additional cost in many, but not all, systems of care. Addition of mental health specialty care to the treatment mix is even more complex. Specialty care is associated with significantly higher costs (Table 4), but the additional investments may be cost-effective because they may be associated with improved patient outcomes not identified in the current study.

The work presented in this paper has implications for the field of technology assessment as it relates to new, innovative products. The SSRIs have been broadly considered as significant advances in the treatment of depression, and yet proving these advances has been, and remains, very difficult.[54] Randomized clinical trials, at least those designed to prove that the treatment has the intended effect in the hands of experts, fail to consider the broader range of effects that a new treatment might have. In other words, they have lost external validity. We believe that more consideration should be given to research designs which can accommodate the needs of society to make data driven coverage decisions.

In summary, we have analyzed the factors which affect the cost-effectiveness of depression treatment, including the relative cost-effectiveness of antidepressant medications. Our findings suggest that the SSRIs might dominate the TCAs because of their association with longer lengths of therapy. As anticipated, this increase in effectiveness may be largely due to an easy to take, more tolerable pharmacologic profile which makes them more 'user friendly'. In the future, we hope that a closer examination of new medical treatments and a broader range of study designs will allow policy makers to determine relative value of technological and other innovation.

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