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ANTIDEPRESSANT TREATMENT FOR DEPRESSION: TOTAL CHARGES AND THERAPY DURATION

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Abstract

Background: The economic costs of depression are significant, both the direct medical costs of care and the indirect costs of lost productivity. Empirical studies of antidepressant cost-effectiveness suggest that the use of selective serotonin reuptake inhibitors (SSRI) may be no more costly than tricyclic antidepressants (TCA), will improve tolerability, and is associated with longer therapy duration. However the success of depression care usually involves multiple factors, including source of care, type of care, and patient characteristics, in addition to drug choice. The cost-effective mix of antidepressant therapy components is unclear.

Aims of the Study: Our study evaluates cost and antidepressant-continuity outcomes for depressed patients receiving antidepressant therapy. Specifically, we determined the impact of provider choice for initial care, concurrent psychotherapy, and choice of SSRI versus TCA-based pharmacotherapies on the joint outcome of low treatment cost and continuous antidepressant therapy.

Methods: A database of private health insurance claims identifies 2,678 patients who received both a diagnosis of depression and a prescription for an antidepressant during 1990–1994. Patients each fall into one of four groups according to whether their health care charges are high versus low (using the median value as the break point) and by whether their antidepressant usage pattern is continuous versus they discontinued pharmacotherapy early (filling fewer than six prescriptions). A bivariate probit model controlling for patient characteristics, co-morbidities, type of depression and concurrent treatment is the primary multivariate statistical vehicle for cost-effective treatment situation.

Results: SSRIs substantially reduce the incidence of patients discontinuing pharmacotherapy while leaving charges largely unchanged. The relative effectiveness of SSRIs in depression treatment is independent of the patient's personal characteristics and dominates the consequences of other treatment dimensions such as seeing a mental health specialist and receiving concurrent psychotherapy. Initial provider specialty is irrelevant to the continuity of pharmacotherapy, and concurrent psychotherapy creates a tradeoff through reduced pharmacotherapy interruption with higher costs.

Discussion: Longer therapy duration is associated with SSRI-based pharmacotherapy (relative to TCA-based pharmacotherapy) and with concurrent psychotherapy. High cost is associated with concurrent psychotherapy and choice of a specialty provider for initial care. In our study cost-effective care includes SSRI-based pharmacotherapy initiated with a non-specialty provider. Previous treatment history and other unobserved factors that might affect antidepressant choice are not included in our model.

Implications for Health Care Provision: The decision to use an SSRI-based pharmacotherapy need not consider carefully the patient's personal characteristics. Shifting depressed patients' pharmacotherapy away from TCAs to SSRIs has the effect of improving outcomes by lowering the incidence of discontinuation of pharmacotherapy while leaving largely unchanged the likelihood of having high overall health care charges. Targeted use of concurrent psychotherapy may be additionally cost-effective.

Implications for Health Policies: The interaction of various components of depression care can alter the cost-effectiveness of antidepressant therapy. Our results demonstrate a role for the non-specialty provider in initiating care and support increased use of SSRIs as first-line therapy for depression as a way of providing cost-effective care that is consistent with APA guidelines for continuous antidepressant treatment.

Implications for Further Research: Further research that improves our understanding of how decisions regarding provider choice, concurrent psychotherapy, and drug choice are made will improve our understanding of the effects treatment choices on the cost-effectiveness of depression care. We have suggested that targeted concurrent psychotherapy may prove to be cost-effective; research to determine groups most likely to benefit from the additional treatment would further enable clinicians and healthcare policy makers to form a consensus regarding a model for treating depression.

Introduction

Depressive disorders in adults are common, and depression is among the most often seen conditions in the primary care setting (Weissman et al. 1988; Kessler et al. 1994). Depression is linked to high rates of functional disability and health service use (Von Korff et al. 1992; Simon et al. 1995; Hays et al. 1995), which makes depression an attractive candidate for cost containment and quality improvement initiatives (Agency for Health Care Policy Research 1993; American Psychiatric Association 1993). In the past decade, treatment of depression has changed substantially with the introduction of new forms of psychotherapy (APA 1993) and new medications, such as the selective serotonin reuptake inhibitors (SSRIs). There is considerable interest in determining the cost-effectiveness of the SSRIs relative to the less expensive tricyclic antidepressants, or TCAs. However, depression care is usually multi-faceted so that the medical- and cost-effectiveness of treatment depends not only on drug choice, but also on the interactions among the source of care, type of care, and patient characteristics. Using data from a retrospective study of adults treated for depression, we examine the factors that alter the cost-effectiveness of important treatment decisions, including drug choice, provider choice, and the decision to complement pharmacotherapy with concurrent psychotherapy.

Recent evidence supports the use of new medications that make a significant advance in tolerability, and at least one of the SSRIs (fluoxetine) may be cost-effectiveness relative to the less expensive tricyclic antidepressants or TCAs (Wilde and Benfield 1998). Although the medication costs of SSRIs are generally higher the literature is mixed with regards to the cost-effectiveness of SSRIs relative to TCAs as first-line treatment for depression.

The effectiveness of pharmacotherapy has often been defined by the ability of patients to tolerate and comply with the medication regimen for a specified length of time. Therapy

discontinuation is a routinely applied health outcome measure accompanying treatment cost (Anderson and Tomenson 1995; Montgomery et al. 1994; Montgomery and Kasper 1995; Song et al. 1993; Croghan et al. 1998; Isaacson et al. 1999; Croghan et al. 1997; Sclar et al. 1994). Considerable research has demonstrated reductions in relapse and recurrence (Maj et al. 1992), improved work functioning (Mintz et al. 1992), and reduced functional disability (Sturm and Wells 1995) from longer lengths of treatment in the acute phase of depression. The American Psychiatric Association has recommended 16 to 20 weeks of continuous antidepressant medication following full symptom remission when treating uncomplicated depression (APA 1993). Because randomized controlled trials are often of relatively short duration (eight weeks or less) they do not fully meter non-compliance with the APA recommended threshold of 16–20 weeks of pharmacotherapy.

Reduced side effects and improved tolerability of the SSRIs has been well established in meta-analyses of the randomized controlled trials (Montgomery et al. 1995; Montgomery and Kasper 1995; Anderson and Tomenson 1995, Anderson 2000). Although meta-analyses have demonstrated at least small improvements in therapy continuation from SSRI use relative to TCAs and heterocyclics (Song et al. 1993) and significant improvement from SSRI use relative to TCAs excluding heterocyclics (Montgomery et al. 1995; Montgomery and Kasper 1995; Anderson and Tomenson 1995), others have shown no difference in therapy discontinuation between SSRIs and TCAs (Trinidade et al. 1999). One meta-analysis has documented differences in meta-analytic results depending on location of clinical trials; comparisons of all trials and United States-only trials found a trend towards lower discontinuation rates with SSRIs relative to TCAs. A comparison of non-US trials found, instead, a trend in favor of TCA use (Bech et al. 2000). A randomized, open-label study of patients in the United Kingdom found no significant

difference in therapy duration for patients on fluoxetine (an SSRI) relative to dothiepin (Thompson et al. 2000).

More recent empirical research examines therapy duration as an effectiveness outcome within the context of large longer duration database studies, usually using prescription claims data or medical records databases to establish whether subjects were prescribed or filed claims for a sufficient duration to indicate continuity of therapy. Several studies have demonstrated the increased likelihood of continuous therapy with SSRIs versus TCAs (Isacsson et al. 1999; Croghan et al. 1997; Sclar et al. 1994, Dunn et al. 1999). In two studies demonstrating improved therapy duration, there appeared no significant differences in annual total medical charges between the SSRIs and TCAs (Croghan et al. 1997; Sclar et al. 1994). A prospective two-year study found that fluoxetine was associated with a greater likelihood of continuing on the initial medication than either desipramine or imipramine (TCAs), but that there was no difference in the likelihood of continuing therapy on any medication. Total medical costs were equivalent between medications (Simon et al. 1999).

In addition to the medication choice the initial site of care has been shown to affect the cost-effectiveness of pharmacotherapy. The direction of any care site effect is not consistently reported across the published literature. In a study of depressed patients receiving pharmacotherapy and/or psychotherapy, care initiated by a psychiatrist reduced non-psychiatric medical costs through lower emergency room use relative to any non-physician mental health specialist (Powers, Kniesner, and Croghan 2000). In an earlier simulation study depression treatment by mental health providers both improved functional outcomes and increased treatment costs, with an ambiguous cost-effectiveness implications (Sturm and Wells 1995). The effect of care by psychiatrists on compliance with APA guidelines is also ambiguous because psychiatrists are more likely to prescribe antidepressants at adequate levels and non-psychiatrists more likely to attain adequate therapy duration (Shasha et al. 1997).

The literature also does not report a consensus for the cost-effectiveness of psychotherapy for the treatment of depression. In a randomized controlled trial, depressed primary care patients randomized to receive pharmacotherapy incurred slightly lower costs with better outcomes than patients who received interpersonal psychotherapy (Lave et al. 1998). Combining pharmacotherapy with brief psychotherapy was cost-effective relative to usual care in a primary practice for patients with major depression, but combined pharmacotherapy-psychotherapy was not cost-effective for patients with minor depression (Von Korff et al. 1998). In a retrospective database study, adequate psychotherapy treatment did not affect general medical care costs in the six months immediately after diagnosis but was associated with higher costs 6–12 months after diagnosis (Powers, Kniesner, and Croghan 2000), which further emphasizes the need to research duration of treatment and duration of outcomes.

Improving the cost-effectiveness of depression care requires a better understanding of how altering the various components of anti-depression treatment affects long-term outcomes. Although many studies consider the costs or cost-effectiveness of specific therapies (Hotopf, Lewis, and Normand 1996; Mitchell et al. 1993), few studies have encompassed the collection of services that might result in more cost-effective care. Evidence does suggest that accounting for multiple aspects of treatments is important for identifying the factors that alter the likelihood of treatment success. A retrospective study of pharmacy claims found evidence for a differential impact of provider choice according to medication type. Patients taking a TCA prescribed by a psychiatrist were more likely to continue in treatment for at least one month, and at three months were more likely to be receiving a therapeutic dose than patients taking a TCA under the care of a non-psychiatrist. Treatment compliance to guidelines was not affected by provider-type for patients taking an SSRI (Fairman et al. 1998). Our research is informative because it extends the work on providing cost-effective acute and continuation phase management for depression by

estimating the consequences for total charges and continuity of therapy for a cohort of patients who are recognized then treated for depression in the private insurance sector.

Consistent with previous cost-effectiveness studies we use length of therapy as an indicator of the effectiveness of pharmacotherapy (Anderson and Tomenson 1995; Montgomery et al. 1994; Montgomery and Kasper 1995; Song et al. 1993; Croghan et al. 1997, 1998; Isaacson et al. 1999; Sclar et al. 1994). Here we group patients according to two concurrent outcomes: duration of pharmacotherapy (continuous versus discontinued) and annual health charges (high versus low). We use a bivariate probit model to estimate the likelihood that a patient will have the dually poor outcomes whereby he or she discontinues pharmacotherapy early and incurs relatively high health care charges. We are able to shed light on three core components of medication in care decisions. First, when a person is recognized as possibly depressed should care be initially directed from the specialty sector? Second, when medication is prescribed should counseling be made available? Third, does medication choice have an effect that differs importantly across typical patient groups?

Data and Methods

Our observational study uses a retrospective claims database to identify the implication on charges of different patterns of patient adherence with pharmacotherapy. We employ regression techniques to identify aspects of care that have possible implications for the cost-effectiveness of antidepressant treatment. Controlling for patient characteristics, we estimate a bivariate probit model to achieve two research objectives (1) to test our focal hypothesis that using SSRIs as a first-line treatment for major depression increases the likelihood that a patient incurs low charges and maintains continuous therapy relative to using TCAs and (2) to estimate the impact of both site of care and concurrent psychotherapy on the cost-effectiveness of pharmacotherapy.

Sample

Our data are from the Marketscan® database, which contains health insurance claims of a group of employed persons and their families in the United States. Patients were followed for one year following the onset of a new episode of depression. An indicator of a depression diagnosis on a medical insurance claim, and a prescription for an antidepressant (either an SSRI or a TCA) during a 30-day window between 1990–1994 trigger a depressive episode.

To identify a new episode of depression, patients included in the study had a period of six months prior to receiving the prescription during which there was neither a depression indicator nor any antidepressant medication. Patients were followed for one year following the onset of the new depressive episode. In the six months following the 12-month study period, an insurance claim for the patient must have been filed to ensure that someone not refilling a prescription was still covered by insurance.

Strict diagnostic exclusion criteria focus the study. We examine the population of adults aged 18 to 64 with a new depressive episode during 1990–1994. Six indicators of depression delimit the sample of depressed persons we study: single episode major depressive disorder (ICD-9-CM 296.2x, except as noted below), recurrent episode major depressive disorder (309.0x), neurotic depression (300.4x), brief depressive reaction (309.0x), prolonged depressive reaction (309.1x) and other depressive disorder (311.xx). Excluded are patients with psychotic depression (296.24, 296.34), schizophrenia (295), or substance abuse.

Outcome Measures

Our medical outcome measure, length of therapy, was defined by the number of prescriptions filled for an SSRI or TCA during the year study period; no more than three months between any two of the first six prescriptions defined continuous pharmacotherapy.

Our cost outcome measure, total health care charges paid, includes all health charges during the year following the commencement of pharmacotherapy and is our indicator of the patient's costs. Total health charges include hospitalization, medications, and outpatient visits. Indirect costs such as lost work time and productivity are ignored. Using total health care charges as an outcome frames the cost outcome issue as a comparison of how different pharmacotherapy patterns impact the patient's overall health resource use.

Data Analytic Procedures

We tested the equivalence of mean and median charges between patients on SSRIs or TCAs, and between patients with continuous versus discontinued pharmacotherapy. We also tested the equivalence of patient and treatment characteristics between patients who both discontinue therapy early and incur high (greater than the median) charges versus all other patients using SPSS v3.0.

We employed a multivariate statistical model to examine the individual and joint influences of treatment interventions on the concurrent outcomes of total charges and pharmacotherapy continuity. The dependent variables, high versus low charge and discontinued versus continuous pharmacotherapy, are binary, which necessitates a regression equation that is non-linear, in particular sinusoidal or S-shaped. We use probit models, which take the regression error terms as normally distributed. Because charges and pharmacotherapy duration were observed concurrently, and are therefore possibly correlated via unobserved common factors, we estimate the charge and duration equations simultaneously. Simultaneous modeling of two probit equations is called a bivariate probit model, and is more efficient than estimation of the two models separately.

Our bivariate probit model estimates two probit regressions allowing for correlated disturbances, or latent common stochastic factors, where one equation describes the determinants of the likelihood that an undesirable medical event occurs (pharmacotherapy is discontinued) and

the other equation describes the determinants of the likelihood that an undesirable economic event occurs (high charges)

$Disc = \beta_D X_D + \varepsilon_D$, where *Disc* = 1 if the person had discontinued pharmacotherapy,

$High = \beta_H X_H + \varepsilon_H$, where *High* = 1 if the person incurred high charges, and

$Cov(\varepsilon_D, \varepsilon_H) = \rho$.

Discontinued pharmacotherapy is defined as having fewer than six prescriptions filled, and high charges are charges greater than the median total annual medical care charge of all patients in the sample. X_D and X_H include patient characteristics (age and gender), treatment characteristics (antidepressant choice and specialty provider at initiation of treatment) pre-study medical and psychiatric co-morbidities, depressive disorder diagnoses and concurrent depression care (switched or augmented antidepressant care, and use of Benzodiazapine indicating the presence of anxiety).

As an empirical strategy to simplify estimation of the bivariate probit model by not including superfluous regressors, we initially estimated separate probit regressions with uncorrelated disturbances on the full set of independent variables. All treatment variables and the significant ($p < 0.10$) co-morbidities from the initial probit regressions (X_D and X_H) were then included in the bivariate probit model that we report and discuss.[1] We also ignored any variable with an incidence of less than 5 percent in any one of the four outcome groups.[2] An indicator for the presence of all other co-morbidities not included as separate regressors appears in the bivariate probit model, which was estimated using Limdep v7.0.

Our final empirical contribution is a set of simulations (predictions) and accompanying discussion of their implications for health care provider decisions based on the marginal effects of the indicators for concurrent psychotherapy and antidepressant choice implied by the coefficients reported in Table 2. In the simulations we are interested in inferring the likely impact

of treatment decisions for specific representative sample persons. We have chosen an older (greater than median age) man with a diagnosis of chest pain, and a younger woman with a diagnosis of back pain to test the impact of initiating therapy with an SSRI instead of a TCA on the percentage of therapy completers (those who achieve continuous therapy, as we define above). To conduct the drug choice simulations, we first estimate the marginal effect of therapy initiation with an SSRI relative to a TCA on both therapy duration and charges. Using the marginal effect of SSRI use on the likelihood of continuing therapy, we then calculate the change in the number of persons in each group (older men with chest pain and younger women with back pain) who would achieve continuous therapy if they received an SSRI prescription. Finally, we calculate the expected percentage change in the number of persons achieving continuous therapy within each group. Details of these calculations may be found in the Appendix.

Results

Table 1 reports descriptive statistics for the 2,678 patients meeting our strict inclusion criteria. The average patient we study is 41 years old. Most (74 percent) are women, and somewhat less than one-half (41 percent) had some form of psychotherapy during the study period. Most patients (89 percent) came from the North Central Region of the United States. Depressive diagnoses in the sample include single episode major depressive disorder (16 percent), recurrent episode major depressive disorder (10 percent), neurotic depression (33 percent), brief depressive reaction (10 percent), prolonged depressive reaction (1 percent) and other depressive disorder (30 percent).

Patients initially prescribed a TCA are 26 percent of the sample. The TCAs in the sample include amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine and clomipramine. The analytical file contains only an indication that a patient received a prescription for a TCA without specifying the individual TCA prescribed. The sample

includes three different SSRIs: fluoxetine (50 percent), paroxetine (5 percent) and sertraline (19 percent). The 52 percent of the patients we study who filled fewer than six prescriptions for either a TCA or an SSRI during the study year form the discontinued pharmacotherapy group.

Total annual health care charges in the sample ranged from $43 to $516,117. Mean charges were significantly higher (*t*-test, $p < 0.05$) for patients initially prescribed a TCA ($6,950) than for patients prescribed an SSRI ($5,731); median charges did not differ significantly (χ^2 test, $p > 0.05$) for patients initially prescribed a TCA ($3,619) than for patients prescribed an SSRI ($3,523).

Patients in our sample are placed into four groups according to their combined charge/use pharmacotherapy pattern. Because we are interested in identifying patient and treatment characteristics that are associated with bad outcomes, specifically high charges and early discontinuation of pharmacotherapy, we compare descriptive statistics between the 607 patients (23 per cent of the sample) incurring high charges and discontinuing pharmacotherapy early and the remaining 2,071 patients. Table 1 reports the percentages of patients with the specified characteristics and the *t*-statistics for the comparisons. Patients in the high charge/early discontinuation group are older, more likely to be women and to initiate care from a specialty provider, and less likely to receive a TCA prescription. Patients in the high charge/early discontinuation group are also more likely to have a co-morbidity and to have their pharmacotherapy switched or augmented.

Bivariate Probit Results

The bivariate probit model produces the parameters of two statistically linked probit regressions. One models high versus low charges, and the other models discontinued versus continuous pharmacotherapy with the two equations linked by possibly correlated error terms capturing unmeasured common factors. Coefficient estimates, *t*-statistics, and *p*-values for the

tests that each of the coefficients in the bivariate probit model is equal to zero appear in Table 2. The hypothesis of zero correlation between the error terms from the two equations is rejected using a *t*-test ($\rho = -0.203$, $p = 0.000$), which supports using the bivariate probit model to capture latent common factors in the economic and medical outcomes we study.

The model allows identification of the impact of the regressors on the charge and pharmacotherapy duration outcomes separately and jointly. We set the other covariates set equal to their respective overall sample means when we calculate the marginal effect of a treatment variable of interest on discontinuing therapy early and/or incurring high charges. Recall that 23 percent of the sample incurred high medical charges and discontinued therapy early. Ceteris paribus, specialty provider choice results in an increase of over six percentage points (from about 20 percent to about 27 percent), or about a one-third increase in the probability of being high charge with discontinued pharmacotherapy. The large impact of specialty provider choice on charges incurred drives the increase in the joint probability of interest. Patients with a specialty provider at the onset of treatment were only about 0.8 times as likely to have any outcome other than high charge/discontinued pharmacotherapy.

Concurrent psychotherapy slightly increased the joint probability of being a high charge patient who discontinues pharmacotherapy, from about 22 percent to 23 percent. Although concurrent psychotherapy reduced the likelihood of discontinuing pharmacotherapy the charge impact of therapy was sufficient to result in little overall change in the joint probability of our two outcomes of interest.

The final treatment effect result we mention is of choice of antidepressant. For a patient with no anxiety, an SSRI prescription reduces the likelihood of having high charges along with discontinuing pharmacotherapy by about a third, from about 27 percent to about 18 percent. The reduction in the joint probability is largely driven by a decreased likelihood of discontinuing

therapy. For a patient with anxiety, an SSRI prescription reduces the likelihood of being high charge/discontinued by just over a fourth, from about 35 percent to about 26 percent. The reduction in the joint probability of poor medical and economic outcomes is again largely driven by a decreased likelihood of discontinuing pharmacotherapy, although the presence of anxiety significantly increases charges. A person on an SSRI is about 1.4 times more likely not to have the joint high charge/discontinued pharmacotherapy outcome.

Simulation Results

We now use our estimated bivariate probit coefficients to examine the main effects of pharmacotherapy on the concurrent charge and treatment continuity outcomes and compare the effects of drug choice to the effects of specialty provider care and concurrent psychotherapy. We seek to clarify how typical medical decisions can possibly be re-focused to reduce the proportion of patients who have high charges and discontinue APA recommended treatment.

The estimated marginal effect of a change in the treatment intervention variables (such as SSRI use and concurrent psychotherapy) is conditional on the values of the other independent variables that describe the patient. We calculate the expected percentage point differences in outcomes for SSRI versus TCA use for two typical patients, an older (age greater than the sample mean, 42) man with chest pain and a younger woman with back pain. Both patients are assumed to have no anxiety, and the remaining variables are set equal to their overall means in our simulations.

Table 3 presents the percentage point change in outcomes for the prototypical male patients when treated with an SSRI versus when treated with a TCA. An older man had a slightly increased likelihood of having high medical care charges. SSRI use by the older man with chest pain was also associated with a 20-percentage point predicted reduction in the likelihood of discontinuing pharmacotherapy. The outcomes in Table 4 for the younger woman with back pain are similar to the outcomes for the older men. There is a 20-percentage point reduction in the

likelihood of a younger woman with back pain discontinuing pharmacotherapy and a 2.5 percentage point increase in the likelihood of having high medical care charges if the woman begins therapy on an SSRI instead of a TCA. The wider societal implications of our simulation results in Tables 3 and 4 are that if all patients on a TCA were switched to an SSRI about 14 percent more of the typical depressed older men treated would continue rather than discontinue treatment. About 11 percent more of the younger women with back pain would also continue rather than discontinue treatment. (See the Appendix for all calculation details.)

In contrast to the effects of an SSRI, which are to lower the likelihood of discontinuing pharmacotherapy and leave charges relatively unchanged, the effects of concurrent psychotherapy in Table 5 are mixed from a medical decision making standpoint. Psychotherapy lowers the likelihood of discontinuing pharmacotherapy by about 11 percentage points but increases the likelihood of having high overall charges by about 10 percentage points. There is a tradeoff in deciding to complement pharmacotherapy with psychotherapy. The typical depressed patient undergoing concurrent psychotherapy has a 10 percentage point greater chance of increasing total health care charges by about 258 percent, so that psychotherapy raises the expected health care charges of the typical patient by 26 percentage points. From the social perspective on medical decision making, because about 60 percent of the sample members were not undergoing concurrent psychotherapy, if everyone eligible were to receive concurrent psychotherapy the expected total charge of care would increase by about 16 percentage points as the incidence of interrupting pharmacotherapy falls by about 7 percentage points.

Discussion

Recent empirical studies of antidepressant cost-effectiveness (Simon et al. 1995; Sclar et al. 1994) have suggested that SSRI use may be no more costly than TCA use and that SSRIs benefit the patient through fewer side effects and a greater chance of completing recommended

pharmacotherapy. However, other studies have failed to demonstrate significant benefits to SSRI use. Differences in inclusion criteria, outcome definitions, research design, and analytic methods each have probably contributed to the inconsistency in reported results. A better empirical understanding of the long-term cost-effectiveness of various aspects of depression treatment is therefore useful. Our research contributes by examining the joint charge/pharmacotherapy completion outcome, in turn inferring the cost-effectiveness implications of antidepressant care.

Our study is informative because of its quantitative predictions regarding the effect of specific treatment choices. Specialty provider choice appears to result in a small increase in the probability of being high charge/pharmacotherapy discontinued, dominated by its impact on charges. Our finding that using a psychiatrist or other mental health specialty provider is more expensive with no significant impact on medical outcome is different than has been previously observed (Sturm and Wells 1995). The addition of psychotherapy independently predicts better adherence to recommended length of therapy, but at some additional cost. Choice of an SSRI over a TCA predictably moves patients into the continuous antidepressant use cohort where some will incur higher charges due to longer length of treatment, and others will incur lower health care charges due to fewer side effects.

Our results have multiple implications for health plans. Access to counseling following initiation of medication management clearly results in longer lengths of therapy albeit at incremental cost, which would be considered valuable by most consumers. Because of the cost implications of concurrent psychotherapy, further research is required to predict which patients are likely to benefit the most from the additional counseling. Targeting of referrals could potentially reduce costs. Our research suggests that specialty provider choice largely impacts cost of care, with no significant effect on outcome as measured by completion of pharmacotherapy. Finally, the initial medication choice between an SSRI and a TCA appears to

result in substantial improvements in quality of care with little net effect on overall medical care expenditures.

As with any observational study, ours may have the situation that treatment choices are determined by decisions that try to look ahead to the outcomes of interest. Several features of the regression model should tend to mitigate parameter bias. First, indicators of comorbid medical and psychiatric conditions and previous expenditures as adjusters for severity are control covariates (Iezzoni 1990; Baum et al. 1993). Second, switching or augmenting pharmacotherapy has previously been shown to be associated with high medical expenditure (Thompson et al. 1996) so that including whether a patient switched or augmented pharmacotherapy as an independent variable should, and did, have a significant predictive effect in our probit regressions. Perhaps more importantly, therefore, our including an indicator of switching or augmenting pharmacotherapy should adjust for differences in severity of depression that could be correlated with failure to respond to medications.

At issue are unobserved factors that might influence both the decision to use a particular antidepressant and the outcomes of interest. The one factor not directly incorporated here most likely to affect the concurrent charge/duration outcomes is a history of success or failure related to prior use of a particular antidepressant. If a person has experienced a successful course of treatment in some prior period (for example, due to lack of side effects) physicians are most likely to begin treatment again with that medication under the proper belief that the patient will again experience a successful course of treatment. Prior treatment for the period 1990–1994 would probably have been a TCA due to the recent availability of the SSRI medication, so that our regression results if at all biased would favor the TCAs, thus minimizing the differences in medication effects we have observed. Conversely, if a person had a poor experience with a particular class of medications in a prior period, most physicians would prescribe a different

class of the medications for a new episode. The patients with a change in medication based on previous experience are at least as likely to experience a poor outcome and discontinue treatment as they were during their first episodes. The result is again a possible bias in favor of the TCAs.

We also addressed empirically the issue of possible endogeneity bias in the estimated effects of SSRI versus TCA assignment by instrumental variables (IV) estimation. The instrumental variable approach here involves positing variables (instruments) that one believes determine drug choice but are not themselves related to the medical and cost outcomes of interest and which do not directly affect the medical and cost outcomes. The instruments then identify the effect of an exogenous change in drug because the instruments independently alter drug choice and also do not influence outcomes directly but rather only indirectly through drug choice (See Deaton 1997, Chapter 2 for a discussion of instrumental variables estimation). In particular, we estimated a two-stage model where the predicted likelihood of using an SSRI from a first-step regression entered the second stage probit of charge/treatment continuity. The results were largely uninformative. Because it is difficult to find statistically significant predictors of SSRI versus TCA assignment the resulting predicted likelihood of SSRI across patients is close to a constant (the sample mean). The nearly constant predicted value for the pharmacotherapy variable in turn necessarily produces a statistically insignificant effect of SSRI versus TCA on the dual charge/pharmacotherapy continuity patient outcomes. We interpret the lack of differential effect of drug in the instrumental variables approach not as the result of simultaneity bias but rather as the result of a poor predictor of drug used or a so-called weak instruments in an IV estimator.

Other variables possibly subject to endogeneity problems include the two remaining treatment variables: specialty provider choice and concurrent psychotherapy. In each case, the unobserved factor most likely to affect the joint charge/duration outcomes is again a history of success of failure related to prior decisions regarding site of care and the use of psychotherapy.

For example, addition of psychotherapy is reasonable when the prior course of the illness is chronic or characterized by poor inter-episode recovery, treatment has been only partially effective, the patient has a history of chronic psychosocial problems distinct from an episode of acute depression, and a history of non-compliance with medications. We also applied the instrumental variables approach discussed above to estimating the effects of provider choice and concurrent psychotherapy. Similar to our findings with drug choice, the decisions to seek care from a specialty provider and to use concurrent psychotherapy were not well differentiated by the variables available in our database; therefore the predicted provider choice and use of psychotherapy concurrently from exogenous information did not significantly impact upon the joint charge/pharmacotherapy continuity outcomes in the ultimate probits of interest.

Although our data have the advantage of capturing actual treatment decisions and charges experienced by patients in a naturalistic setting the use of observational data also has limitations. Drug choice may depend on both diagnosis and depression severity. We are unable to verify the reliability and validity of our diagnosis indicators; no measure of depression severity is available in our database. If the use of TCAs is associated with more severe cases, then our inability to capture severity may lead to an overstatement of the effectiveness of SSRIs.

Significant within-group variation in cost and effectiveness can exist within our drug categories that may hamper our ability to make comparisons between the groups. Previous research has demonstrated important differences between medications usually grouped together. A significantly greater likelihood of treatment response was found for patients on sertraline than for patients on fluoxetine in a retrospective study of a clinical practice setting in Spain (Hylan et al. 1999). In a meta-analysis of randomized controlled trials, SSRIs and TCAs were found to be equally effective for most patients, but SSRIs were less effective than one TCA, amitriptyline (Anderson 2000). Our study does not consider medications individually and may in turn mask differences between medications.

Our data include only patients with private health insurance who are unlikely to be representative of the population as a whole. The employed population we study is less likely to experience barriers to healthcare, and is therefore more likely to receive adequate care. Finally, our data are drawn from health claims submitted between 1990 and 1994. Advances in the care of depression may have altered prescription patterns as well as the type and frequency of use of psychotherapy.

One would like to see if our parameter estimates could receive corroborating evidence from a randomized study. That our results regarding the central tendency of charges and use patterns agree with the conclusions of a prospective randomized naturalistic study (Simon et al. 1996) provides a measure of external validity to our findings. Together with Simon's, our results indicate that SSRI use goes with longer durations of continuous monotherapy and mean charges that are about the same as mean charges associated with TCA use.

Previous research using simulation methods to examine cost effectiveness of alternative depression treatments has rested on data collected as part of the Medical Outcomes Study (Sturm and Wells 1995) or on data from randomized controlled trials of depression treatment (Kamlet et al. 1995). Our data are from a database with insurance claims information for a large group of employed persons and their families. The result is the greater realism we can provide for our predicted outcomes because of the more diverse set of patient and treatment attributes we can consider. Our most important findings are that the decision to use an SSRI is more important than complementary treatment input choices, that the effectiveness of SSRIs stems largely from reducing early discontinuation of pharmacotherapy, and that SSRI effectiveness is largely independent of patients' personal characteristics.

Appendix: Calculations

Pharmacotherapy Choice Simulation Calculations

Societal implications of switching initiation of pharmacotherapy from a TCA to an SSRI on the proportion of patients achieving continuous therapy are presented for the average older man with chest pain and the average younger woman with back pain. The calculations are summarized here.

The number of additional patients who would achieve continuous therapy if therapy were initiated with an SSRI instead of TCA equals the number of patients in the sample on a TCA times the increase in the likelihood of achieving continuous therapy.

The proportionate increase in the number of patients who would achieve continuous therapy equals the number of patients achieving continuous therapy if all were on SSRIs minus the observed number of patients achieving continuous therapy divided by the observed number of patients achieving continuous therapy

Older Man with Chest Pain. 125 older male patients had chest pain: 40 were on TCAs and 85 were on SSRIs; 56 had continuous pharmacotherapy and 69 discontinued therapy. A 20 percentage point reduction in probability of discontinuing therapy for patients on an SSRI instead of a TCA means $40 \times 0.2 = 8$ additional men would be expected to have continuous therapy if therapy were initiated with an SSRI instead of a TCA. The result is a $(64 - 56)/56 = 14$ percent increase in the total number of older men with chest pain who are expected to have continuous therapy.

Younger Woman with Back Pain. 327 younger female patients had back pain: 85 were on TCAs and 242 were on SSRIs; 151 had continuous pharmacotherapy and 176 discontinued therapy. A 20 percentage point reduction in probability of discontinuing therapy for patients on an SSRI instead of a TCA means that $85 \times 0.2 = 17$ additional women expected to

have continuous therapy if therapy was initiated with an SSRI instead of a TCA. The result is a (168 – 151)/151 = 11 percent increase in the total number of younger women with back pain who are expected to have continuous therapy.

Concurrent Psychotherapy Simulation Calculation

Because complementing pharmacotherapy with psychotherapy has implications for improved treatment at significant cost, we calculated the expected impact on overall charges and rates of continuous therapy if all patients in the sample received concurrent psychotherapy.

Impact of Concurrent Psychotherapy on Charges. Key facts are that 1,067 out of 2,678 total patients received concurrent psychotherapy, and that we estimated a 10 percentage point increase in the probability of incurring high medical charges for patients with concurrent psychotherapy. The (median) charges were $1,787 and $6,396 for the low and high cost groups, a difference of 258 percent.

The predicted increase in charges per patient moving from low to high charge group then equals the percentage point increase in health care charges from moving from low to high charge group times the proportionate increase in the likelihood of having high charges, so that our results imply a 258 percent × 0.1 = 26 percent increase in charges per patient moved from low to high charges

The expected increase in charges per patient in the sample if everyone were to get concurrent psychotherapy equals the percentage of patients in sample with no concurrent psychotherapy observed times the proportionate increase in charges per patient from moving from low to high charge group, so that a 26 percent × 0.6 = 16 percent increase in charges per patient would be anticipated if all patients were to receive concurrent psychotherapy.

Impact of Concurrent Psychotherapy on Likelihood of Continuing Therapy. Once again, the calculation uses the fact that 1,067/2,678 patients received concurrent

psychotherapy, which was associated with an 11 percentage point increase in the likelihood of continuing pharmacotherapy. The resulting expected increase in the likelihood of continuing therapy if everyone has concurrent psychotherapy equals the percentage of patients in the sample with no concurrent psychotherapy observed times the proportionate increase in the likelihood of continuing therapy, which is a $11 \times 0.6 = 7$ percent increase in the incidence of pharmacotherapy continuation if all patients received concurrent psychotherapy.

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Endnotes

1. To accentuate positive medical and economic outcomes we use the low cost/continuous pharmacotherapy case as the baseline. The base case chosen is of no practical consequence in the bivariate probit because the estimated values of $\beta_D = -\beta_{Continuous}$ and the estimated values of $\beta_H = -\beta_{Low}$. In the interest of space we note, but do not elaborate on algebraically, that estimates of how the outcomes are affected by treatment interventions depend nonlinearly on the parameters of the joint normal distribution and the values of the independent variables. For details see Greene (2000).

2. Excluding geographic region indicators should be of little consequence as there is little geographic variation in the sample.

Table 1. Descriptive Statistics: Percentage of Patients with Characteristic

	All Patients *n* = 2678	High Charge/ Discontinued (HC/DC) Antidepressant Therapy *n* = 2071	All Others *n* = 607	Comparison of HC/DC versus all others *t*-statistic
Patient Characteristics				
Female**	74	78	73	–2.603
Age* (in years)		42.7	41.7	–2.219
Treatment Characteristics				
SSRI**	74	66	77	–4.972
Concurrent Psychotherapy	40	39	40	0.645
Specialty Provider**	42	48	40	–3.532
Pre-Study Co-morbidities				
Nervous system**	12	15	11	–3.210
Ear, nose, mouth, and throat**	32	41	30	–4.829
Respiratory system**	18	24	16	–4.308
Circulatory system**	22	27	20	–3.935
Digestive system	17	21	16	–3.185
Musculoskeletal system**	37	47	34	–5.908
Skin, subcutaneous tissue	32	34	31	–1.338
Endocrine, nutritional, metabolic**	24	30	22	–3.821
Kidney, urinary tract**	11	15	10	–3.301
Female reproductive system**	22	26	21	–2.767
Blood, immunological disorders**	9	12	8	–3.432
Infectious and parasitic diseases**	7	9	6	–2.964
Mental diseases and disorders	67	70	66	–1.870
Injuries, poison, toxic drug effects**	6	8	5	–2.868
Other factors	27	29	26	–0.996
Depressive Disorder Diagnosis				
Major depression, single	16	15	16	0.547
Major depression, recurrent	10	10	10	0.110
Neurotic depression**	33	38	31	–3.395
Brief depression reaction	10	11	9	–1.189
Concurrent Depression Care				
Switched/Augmented**	26	31	24	–3.502
Benzodiazapine prescription**	31	39	29	–4.549

*differences between HC/DC and all others are statistically significant at $\alpha = 0.05$

**differences HC/DC and all others are statistically significant at $\alpha = 0.01$

Source: Authors' calculations using the Marketscan® database.

Table 2. Bivariate Probit Results

Regressor	Coefficient	Standard Error	*t*-statistic
Equation for Discontinued Use			
Constant	0.749	0.095	7.889*
SSRI	–0.523	0.070	–7.447*
SSRI/Benzodiazapine Interaction	0.161	0.124	1.302
Concurrent psychotherapy	–0.272	0.053	–5.099*
Specialty provider	0.037	0.053	0.695
Female	–0.120	0.058	–2.052*
Age (> 41 years)	–0.111	0.050	–2.228*
Digestive system	0.123	0.066	1.876
Mental diseases and disorders	–0.139	0.054	–2.596*
Other pre-study co-morbidities	0.098	0.057	1.171
Brief depressive reaction	0.126	0.085	1.483
Switched/Augmented	–0.133	0.056	–2.354*
Benzodiazapine prescription	–0.037	0.107	–0.347
July-December 1992	–0.133	0.064	–2.075*
Equation for High Charges			
Constant	–1.199	0.094	–12.756*
SSRI	0.062	0.071	0.876
SSRI/Benzodiazapine Interaction	–0.090	0.128	–0.697
Concurrent psychotherapy	0.245	0.055	4.434*
Specialty Provider	0.261	0.056	4.694*
Female	0.218	0.060	3.624*
Ear, nose, mouth, and throat	0.175	0.056	3.137*
Respiratory system	0.160	0.070	2.278*
Circulatory system	0.238	0.065	3.652*
Musculoskeletal system	0.362	0.054	6.739*
Endocrine, nutritional, and metabolic system	0.129	0.064	2.035*
Blood, immunological disorders	0.229	0.094	2.449*
Mental diseases and disorders	0.284	0.055	–5.132*
Injuries, poisonings, and toxic effects of drugs	0.280	0.118	2.380*
Other pre-study co-morbidities	–0.117	0.060	–1.972*
Neurotic depression	0.258	0.057	4.538*
Brief depressive reaction	0.199	0.090	2.206*
Switched/Augmented	0.394	0.060	6.600*
Benzodiazapine prescription	0.346	0.111	3.120*
Disturbance correlation	–0.203	0.031	–6.439*

*Statistically significant at $\alpha = 0.05$

Source: Authors' calculations using the Marketscan® database.

Table 3. Estimated Changes in Outcomes Percentage Point Difference between SSRI and TCA Use Older Man with Chest Pain

	High Cost of Care	Low Cost of Care	Row Sum
Discontinued Pharmacotherapy	–8.5	–11.8	–20.3
Continuous Pharmacotherapy	+10.9	+9.3	+20.2
Column Sum	+2.5	–2.5	

Source: Authors' calculations using the estimates in Table 2. Column and row sum totals may not equal zero due to rounding.

Table 4. Estimated Changes in Outcomes Percentage Point Difference between SSRI and TCA Use Younger Woman with Back Pain

	High Cost of Care	Low Cost of Care	Row Sum
Discontinued Pharmacotherapy	–8.8	–11.5	–20.3
Continuous Pharmacotherapy	+11.3	+9.0	+20.3
Column Sum	+2.5	–2.5	

Source: Authors' calculations using the estimates in Table 2. Column and row sum totals may not equal zero due to rounding.

Table 5. Estimated Changes in Outcomes Percentage Point Difference if Have Concurrent Psychotherapy

	High Cost of Care	Low Cost of Care	Row Sum
Discontinued Pharmacotherapy	–0.6	–10.3	–10.9
Continuous Pharmacotherapy	+10.3	+0.5	+10.8
Column Sum	+9.7	–9.8	

Source: Authors' calculations using the estimates in Table 2. Column and row sum totals may not equal zero due to rounding.

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