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Controlling for Systematic Selection in Retrospective Analyses: An Application to Fluoxetine and Sertraline Prescribing in the United Kingdom

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ABSTRACT

Background: Criticism has been made of observational studies in clinical practice because of their failure to control for unobserved factors that correlate with both initial treatment selection and observed outcomes.

Method: A two-stage statistical model was applied to data obtained from a large general practitioner medical records database (DIN-LINK) to estimate the effect of initial antidepressant selection on the duration of antidepressant therapy and on the likelihood of being prescribed an average daily dose above the minimum recommended dose. The statistical model controlled for unobserved factors correlated with initial treatment selection and the observed outcomes as well as for observed confounders.

Results: Unobserved factors correlated with treatment selection were not a statistically significant determinant of the number of days of antidepressant therapy. However, unobserved factors correlated with treatment selection were a statistically significant determinant of the likelihood of receiving an average dose during therapy greater than the minimum recommended. After controlling for relevant confounders, those patients who began treatment with sertraline as opposed to fluoxetine had fewer days of antidepressant therapy and were more likely to receive average doses greater than the minimum recommended during therapy.

Conclusion: Unobserved factors correlated with treatment selection can impact outcomes in observational studies and should be tested and controlled for whenever possible.

Keywords: antidepressants, econometric methods, self-selection models, SSRIs.

Introduction

To ensure a high degree of internal validity, controlled clinical trials of pharmaceuticals hold individuals' behavioral and health system effects constant. Yet variability in the behavior of patients and prescribers can ultimately lead to variability in outcomes between treatments in clinical practice. As a result, prospective naturalistic trials and retrospective database studies conducted in clinical practice settings are frequently used in pharmacological assessments to complement findings from randomized clinical trials. An important contribution of retrospective database studies is that they can identify associations between treatment selection and outcomes in the context of patient and prescriber behavior.

In controlled trials, initial random assignment theoretically mitigates potential biases due to the influence of both observed and unobserved factors because the randomization process is ignorant of the particular characteristics of the patients being assigned. Criticism has been directed at retrospective studies that use data collected in nonrandomized environments for their failure to control for not only observed factors, but also unobserved factors that may be correlated with both the initial treatment selection and observed outcomes [1,2]. If this type of unobserved confounder influences the outcome, but is ignored in the analysis, then estimates of the effects of alternative drug treatments on the outcome will be statistically biased. Nonrandom selection of patients for alternative drug treatments will result in erroneous inferences concerning the relative effectiveness of alternative treatments.

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Statistical methods can be applied to retrospective data to control for unobserved factors correlated with initial treatment selection, as well as for observed factors that influence the subsequent outcomes. The purpose of this study is to illustrate how sample selection modeling may be used in retrospective database studies examining the impact of alternative treatments on health care outcomes, specifically in cases where the outcome variable of interest may not necessarily be normally distributed.

Heckman [3] proposed a two-step approach for testing and correcting sample selection bias. Recent empirical studies of retrospective data in pharmacoeconomics have used this method to assess health care outcomes associated with alternative antidepressant treatments [4–6]. The first step involves estimation of a treatment selection model. The study sample is segmented in this step into mutually exclusive categories for the dependent variable (e.g., those that are and are not treated). The estimated probabilities of treatment from this regression are used to calculate the risk of not receiving a particular treatment, given that treatment was an option. In the second step, an outcome equation is estimated by ordinary least squares and this risk variable entered as an additional explanatory variable. Standard errors of parameter estimates of the outcome equation must account for additional variability introduced by the estimated selection term.

The risk variable (also known as the selection term) controls for the effect of unobserved variables correlated with treatment selection on the outcome variable. The statistical significance of selection bias is assessed by the *t*-statistic associated with the parameter estimate of the outcome equation selection term. Specifically, a significant finding rejects the null hypothesis that unobserved factors correlated with treatment choice do not affect the outcome under study. If the selection term is significant then unbiased parameter estimates are obtained from the selection-corrected regression. If, however, the selection term is insignificant, unbiased results are obtained from a regression that excludes the selection term from the set of explanatory variables.

Heckman's two-step method implementation is relatively easy. For research applications concerning health care, however, the model is somewhat limited. Consistent parameter estimates are ensured only if the outcome variable is normally distributed. As such, outcome variables that are discrete counts (e.g., the number of therapy days) or indicators (e.g., whether or not an average dose is greater than the recommended dose) cannot be handled with this procedure. Count data is typically bounded by zero and often naturally skewed. Applying linear regression to an indicator variable may result in predicted probabilities that lie outside the unit interval as well as estimated variances that are negative.

Sample selection correction methods that apply less parametric structure to the problem have been developed in response. The least restrictive of these include the semiparametric and series-expansion (semi-nonparametric) methods of Lee [7] and Ichimura and Lee [8]; however, such methods can be quite difficult to estimate. The generalized method of moments estimator of Mullahy [9] is another alternative, although in some cases it is less efficient in a statistical sense than those that impose some structure [10].

The methodology applied below accounts for the joint determination of treatment choice and levels of the outcome measures of interest. In addition, it tests and corrects for the influence of systematic sample selection on these levels. The sample selection algorithm used [11] is appropriate for many types of outcome measures. The method yields consistent parameter estimates not only for those measures that are continuous and normally distributed, but also for those that represent discrete integers (e.g., number of days of therapy) with distributions that may contain a large frequency of zero valued observations (e.g., the number of hospitalizations). It is also appropriate for variables that are binary (e.g., whether or not the dose prescribed is above the minimum recommended dose).

In this paper, this method is illustrated using data from the United Kingdom on prescribing patterns for primary care patients to ascertain whether the duration of antidepressant therapy and dosing differed among those who initiated therapy on fluoxetine as opposed to sertraline. Fluoxetine and sertraline are among the most common selective serotonin reuptake inhibitors (SSRIs) prescribed in clinical practice. Their use in this setting has been extensively studied [12–18]. These analyses have found differences between the two drugs in terms of prescribing patterns, as measured by the duration of therapy and dosing. However, none of these studies controlled for the possibility that differences may have resulted merely from the influence of nonrandom treatment selection. As such, results from these previous studies may be biased [19,20]. Application of the sample selection methodology described below allows testing of whether sample

selection bias exists and results in estimates appropriately adjusted for the presence of such bias.

Methods

Statistical Model

A two-stage statistical model developed by Terza [11] was used to estimate the number of therapy days and probability that the average prescribed daily dose during treatment was greater than the minimum recommended daily dose. This two-stage method of moments estimator is statistically consistent and asymptotically normal for a broad class of nonlinear second stage regressions. Second-stage regressions estimated by ordinary least squares for continuous variables, probit or logit for binary variables, or nonlinear least squares exponential regression for count variables, are included within this class.

As with the Heckman procedure, the first stage of the model involves estimating the probability that a patient receives sertraline as opposed to fluoxetine by a maximum likelihood procedure (probit or logit). For this study, the treatment choice of sertraline versus fluoxetine was modeled as a function of patient characteristics (e.g., age, gender, and indicators of disease severity) and two variables that proxy for general practice antidepressant prescribing patterns. Previous studies showed that variables such as these appear to be important determinants of initial antidepressant selection [6,17,21].

Physician prescribing patterns may be shaped by a number of influences, including previous experience and information received about the product and its use. Simon and Fishman [21] found that habitual prescribing preferences were a stronger determinant of initial antidepressant drug selection than patient characteristics. Evidence also suggests that general practitioners (GPs) may prescribe the same antidepressant for all patients rather than consider individual patient characteristics when selecting a treatment [22]. Similar to the Simon and Fishman approach, the two variables used in this study to capture these effects were defined as the percentage of the general practice study antidepressant prescriptions that were fluoxetine and sertraline on the date of the patient's initiation of therapy.

As with Heckman's procedure, the two-stage methods of moments estimation involves calculation of a sample selection correction term. This term will control for biases that arise from the selection of patients into alternative antidepressant categories based on unobservables that are uncorrelated with other (exogenous) explanatory variables in the model. One component of the term is a parameter that captures the correlation between unobserved factors (e.g., patient and/or prescriber characteristics) that influence initial treatment selection and the outcome of interest (either therapy days or the likelihood of being prescribed an average daily dose above the minimum recommended dose). The estimate of this parameter, referred to as theta in Terza's paper, will reflect the existence (or nonexistence) of selection bias. In particular, a significant estimate rejects the null hypothesis that unobserved factors correlated with treatment choice do not affect the outcome under study.

Two-stage method of moments regression models were estimated to test the null hypothesis of no difference between fluoxetine and sertraline patients in the duration of initial antidepressant therapy and the likelihood of receiving an average daily dose above the minimum recommended. The duration of therapy dependent variable was constructed as a count of the number of antidepressant prescription days during the 180 days following the initiation of treatment. An exponential specification was used, and the regression was estimated by nonlinear least squares. The exponential specification is appropriate for non-negative, integer-valued measures [23]. The dosing binary dependent variable was set equal to one if the patient's average daily dose during treatment was greater than the minimum recommended dose and set equal to zero otherwise. A probit specification was used to judge the parameter estimates associated with the explanatory factors of the dichotomous variable regression model.

Minimum recommended daily doses used were those quoted in the British National Formulary [24], 20 mg for fluoxetine and 50 mg for sertraline. The minimum recommended dose can optimize the risk:benefit ratio of a drug, and is often based on evidence from controlled clinical trials. Replication in clinical practice of efficacy rates, side-effect profiles, and drop-out rates obtained in such stylized settings is unlikely. As such, actual doses used in clinical practice may be guided by physician experience with patient outcomes and tolerability. There are economic consequences of dosing decisions in clinical practice. List prices in the United Kingdom for 1997 (Monthly Index of Medical Specialties, 1998) indicated that the monthly cost of fluoxetine (20 mg) was £20.77 while the monthly cost of sertraline (50 mg) was £26.51. Differences in prescribed daily doses could alter this price differential.

The main explanatory variable in the second-stage equations was a binary indicator of drug choice set equal to one for sertraline and set equal to zero for fluoxetine (the more frequently prescribed antidepressant). Variables were also included to control for baseline differences in patient demographics (age and gender) and location in the country. Other variables were included to control for patient baseline comorbid conditions at the index date or in the prior period: four binary indicators for depression diagnosis at the index date, i.e., endogenous depression, reactive depression, depressed, and on examination depressed, with depression not otherwise specified as the reference group; binary indicators for coronary artery disease and diabetes in the 180-day period prior to initiation of therapy (diseases that are often comorbid with depression); counts of the number of anxiolytic, sedative-hypnotic, antipsychotic, and other medicine prescriptions in the 180-day prior period; GP visits; GP, psychotherapy, and lab referrals in the 180-day prior period; psychiatric accident and emergency (A & E), general A & E, general non-A & E admissions in the 180-day prior period; and a count of the number of unique Psychiatric Diagnostic Groups (PDGs) [25] that a patient had in the 180-day prior period. PDGs are a method of classifying major psychiatric conditions and serve in the regression context as proxies for general mental health. Note that although the model is theoretically identified on the basis of nonlinearities, the exclusion of the proxies for general practice prescribing preferences from the second stage regressions assists in identification.

As described above, the parameter theta was estimated to test and control for the potential self-selection into the two different antidepressants. If theta is statistically significant, then selection bias is an important factor to consider in the outcome equations. By including both the observed factors and adjusting for unobserved factors correlated with initial treatment selection, the estimated effect of the antidepressant will be free of selection bias that is attributable to unobserved factors uncorrelated with the exogenous explanatory variables in the model. If the selection parameter is insignificant then the null hypothesis of no sample selection cannot be rejected. In this case, unbiased parameter estimates can be obtained from regressions that do not estimate theta.

The incremental or marginal impact of initiating therapy on sertraline as opposed to fluoxetine on either outcome was calculated as the difference between the predicted outcome evaluated with the sertraline indicator variable set equal to one and the predicted outcome with the sertraline indicator set equal to zero. Other explanatory variables were set equal to the overall sample mean values (or modal values for qualitative variables) in these calculations. Standard errors associated with the marginal effects were calculated using the delta method [26]. Software to estimate the statistical model was provided by Joseph Terza Econometric Consulting, Inc. (State College, Pennsylvania USA).

Data

The analysis file used in this study was constructed from the 1992–1997 panels of the Doctors' Independent Network (DIN-LINK), maintained by CompuFile Ltd. (Woking, UK). These files contain standardized medical and prescription records for approximately 750,000 patients from 100 general practices in the United Kingdom.

To ensure that the antidepressant prescribing behaviors studied were not part of an earlier episode of treatment, each patient had to have a 6-month antidepressant-free prior period. An episode of antidepressant therapy was then constructed using an intent-to-treat design, since the hypotheses of the study concerned the impact of initial drug selection on subsequent outcomes. Under this design, patients' subsequent experiences in the study period are attributed to the original drug selected [27].

An index date was defined as the date on which the first prescription for the study antidepressant (fluoxetine or sertraline) was prescribed, accompanied by a depression-related diagnosis within a 30-day period. Five depression-related diagnoses were collected, including endogenous depression, reactive depression, depressed, on examination depressed, or depression not otherwise specified. These diagnoses are consistent with those used and validated in earlier analyses of the DIN-LINK data [14,15]. The period examined for each patient was 6 months. The end of the patient's treatment coincided with the duration of the last prescription for any antidepressant.

Patients were excluded from the final sample if they:

- did not have a 180-day prestudy period;
- did not have a minimum of 180 days of continuous health care coverage in the same GP practice after the index date;
- were prescribed more than one index study antidepressant at the index date;
- had used antidepressants in the 180-day prior period;

- had multiple records of the study antidepressant on the index date;
- were younger than 18 on the index date.

The final analytical file included 4555 patients in 99 practice groups that were prescribed either fluoxetine ($N = 3817$) or sertraline ($N = 738$) for the treatment of depression.

The SAS package (SAS Institute, Cary, NC USA) was used to construct the final analytical file.

Results

In the sample, 83.8% ($N = 3817$) of patients initiated therapy with fluoxetine as compared to 16.2% ($N = 738$) with sertraline (Table 1). The average number of days of antidepressant therapy for those who initiated therapy on fluoxetine was 90.9 with standard deviation of 57.2, while for those who initiated on sertraline, the mean number was 77.3 with standard deviation of 57.3 ($P < .0001$). Approximately 49% of sertraline patients and 36% of the fluoxetine patients discontinued therapy with their original antidepressant and were not given another prescription for their original antidepressant for the remainder of the study period. The final analytical sample included all patients, irrespective of actual therapy length.

While most of the patients who initiated therapy on fluoxetine (95.4%) had an average prescribed daily dose equal to the minimum recommended dose of 20 mg, 4.6% of patients had a prescribed average daily dose above this minimum. A majority of sertraline patients (58.9%) had a prescribed average daily dose equal to the minimum recommended dose (50 mg); approximately 41% of patients in this group had a prescribed average daily dose above the minimum recommended dose.

Table 1 Descriptive statistics by drug selection

	Fluoxetine ($N = 3817$)		Sertraline ($N = 738$)		
	N	Percentage	*N*	Percentage	*P* value
Average drug dose greater than minimum recommended dose					
Yes	175	4.6	303	41.1	.001
No	3642	95.4	435	58.9	
Index depression diagnosis					
Depression not otherwise specified	1847	48.4	339	45.9	.007
Endogenous depression	946	24.8	167	22.6	
Reactive depression	519	13.6	109	14.8	
Depressed	430	11.3	94	12.7	
On examination depressed	75	1.96	29	3.9	
Location					
Southern England	1959	51.3	332	45.0	.001
Northern England & Scotland	1557	40.8	313	42.4	
Wales	301	7.9	93	12.6	
Gender					
Male	982	25.7	198	26.8	.532
Female	2835	74.3	540	73.2	
Indicators of other medical conditions in the 180-day prior period					
Coronary artery disease	187	4.9	41	5.6	.454
Diabetes	84	2.2	16	2.2	.956
Days of antidepressant therapy	90.88	57.2	77.31	57.3	.000
Age (years)	44.52	17.3	46.14	18.8	.030
Number of medical occurrences in the 180-day prior period					
Anxiolytic prescriptions	0.09	0.7	0.12	0.9	.365
Sedative-hypnotics prescriptions	0.22	1.0	0.28	1.1	.212
Antipsychotic prescriptions	0.07	0.57	0.02	0.3	.001
Other prescriptions	17.26	18.7	16.98	18.0	.705
General Practitioner visits	6.80	6.1	6.76	6.0	.859
General Practitioner referrals	1.01	2.4	1.18	2.7	.106
Psychotherapy referrals	0.08	0.5	0.14	0.7	.028
Lab referrals	0.09	0.8	0.10	0.6	.519
Psychiatric A & E admissions	0.01	0.1	0.02	0.2	.060
General A & E admissions	0.05	0.3	0.06	0.4	.737
General non-A & E admissions	0.13	0.7	0.15	0.8	.518
PDG occurrence in the 180-day prior period (count of number of unique PDGs)	0.26	0.5	0.26	0.5	.916
General practice drug preference					
Frequency of general practice fluoxetine prescriptions	0.22	0.08	0.17	0.07	.000
Frequency of general practice sertraline prescriptions	0.04	0.04	0.08	0.05	.000

P values for indicator variables are based on chi-square tests of independence. All other *P* values are based on *t*-tests.

For the first prescription, 98.4% of patients in the fluoxetine group were prescribed a daily dose of 20 mg, with the remainder of prescriptions at higher doses. For sertraline patients, 63.7% were prescribed a daily dose of 50 mg at the first prescription. An additional 15.8% of sertraline patients received 100 mg, 20.2% received 150 mg, with the remainder at other dose levels. Similar average daily dose patterns were observed for subsequent prescriptions. Patients who initiated therapy on fluoxetine had an average daily dose prescribed during treatment of 20.8 mg ($SD = 5.6$). Patients who initiated therapy on sertraline had an average daily dose prescribed during treatment of 79.0 mg ($SD = 38.9$).

Descriptive statistics for the explanatory variables noted in the methods section are also depicted in Table 1. Patients initiating therapy on fluoxetine were slightly younger, on average, than their counterparts that began therapy on sertraline. These subsamples also appear to be different in terms of where they resided and the diagnosis they received. In terms of medical events in the six months prior to their depression treatment, fluoxetine patients had significantly more antipsychotic prescriptions and fewer psychotherapy referrals, on average. As expected, fluoxetine patients were more likely to receive their prescription from a GP practice that tended to prescribe fluoxetine more frequently; the same held true for sertraline patients visiting practices that tended to prescribe sertraline more frequently.

Results for the first stage antidepressant selection equation are reported in Table 2. The sign on the coefficients indicates the directional effect of the characteristic on the change in probability of being prescribed sertraline versus fluoxetine. The two variables capturing the likelihood of the practices to prescribe the two drugs are highly significant and of the expected signs, a finding consistent with an earlier study [17]. Patients whose general practice tended to prescribe sertraline (fluoxetine)

Table 2 Coefficients and *t*-statistics from 1st stage model of drug choice

Variable	Coefficients†	*t*-statistics
Demographics		
Age at index date	0.005	3.479*
Female indicator	0.014	0.244
Location		
Wales indicator	−0.149	−1.434
Southern England indicator	−0.221	−4.087*
Index depression diagnosis		
Endogenous depression	0.003	0.048
Reactive depression	0.155	1.972*
Depressed	0.095	1.196
On examination depressed	0.490	3.353*
Counts of medical occurrences in the 180-day prior period		
Anxiolytic prescriptions	0.024	0.722
Sedative-hypnotics prescriptions	0.033	1.376
Antipsychotic prescriptions	−0.192	−2.695*
Other prescriptions	−0.002	−0.532
General Practitioner visits	0.001	0.101
General Practitioner referrals	0.004	0.351
Psychotherapy referrals	0.088	2.098*
Lab referrals	−0.010	−0.289
Psychiatric A & E admissions	0.472	2.809*
General A & E admissions	−0.048	−0.608
General non-A & E admissions	0.035	1.011
PDG occurrence in the 180-day prior period		
Number of unique PDGs	−0.006	−0.113
Indicators of other medical conditions in the 180-day prior period		
Coronary artery disease	0.022	0.184
Diabetes	−0.027	−0.156
General Practitioner drug preference		
Frequency of General Practitioner sertraline prescriptions	12.117	21.394*
Frequency of General Practitioner fluoxetine prescritptions	−3.818	−11.275*
% correctly predicted		
Overall	85.005	
Likelihood ratio test statistic (d.f. = 24)	813.426	

*Indicates $P < .01$.

†The sign on the coefficient indicates the direction of the change in probability of being prescribed sertraline relative to fluoxetine that is associated with the characteristic.

PDG, Psychiatric Diganostic Groups

had a higher probability of being prescribed sertraline (fluoxetine), all else being equal. Older individuals, as well as patients in the diagnosis categories "reactive depression" and "on examination depressed" were more likely to receive sertraline as opposed to fluoxetine. Subjects residing in southern England were less likely to initiate therapy on sertraline. Patients with more antipsychotic prescriptions, fewer psychotherapy referrals, and psychiatric A & E admissions in the 180-day prior period were also less likely to initiate treatment for depression on sertraline.

Tables 3 and 4 present the second stage results for duration and dosing analyses, respectively. Columns 1 and 2 in each table display the results unadjusted for selection, while columns 3 and 4 display those from the selection model. In Table 3, the sign on the coefficients indicates the direction of the effects of characteristics on the duration of therapy. In Table 4, the sign on the coefficients indicates the direction of the change in probability of being prescribed an average daily dose during treatment higher than the minimum recommended dose.

Patients who began therapy on sertraline were more likely to have a shorter duration of therapy after controlling for observable confounders (Table 3). This finding rejects a main null hypothesis of this study, namely that there is no difference between those initiating therapy on sertraline as opposed to fluoxetine in terms of therapy duration. The significance and sign of this result was generally robust to alternative specifications of the explanatory variables in the statistical model. The selection parameter theta was statistically insignificant. This result implies that unobserved factors correlated with initial treatment selection and duration are not a significant determinant of the duration of therapy for these primary care patients.

Since selection bias did not appear to be an issue for this outcome measure in this sample, the parameter estimates from the unadjusted model were used to obtain an estimate of the size of the

Table 3 Coefficients and *t*-statistics from 2nd stage model of days of antidepressant therapy

	Unadjusted Results		Selection Model Results	
Variable	Coefficients†	*t*-statistics	Coefficients†	*t*-statistics
Demographics				
Age at index date	0.003	4.466*	0.003	4.428*
Female indicator	−0.018	−0.845	−0.018	−0.848
Location				
Wales indicator	−0.098	−2.519*	−0.099	−2.536*
Southern England indicator	0.004	0.174	0.004	0.200
Index depression diagnosis				
Endogenous depression	0.033	1.416	0.033	1.426
Reactive depression	−0.081	−2.575*	−0.081	−2.584*
Depressed	−0.084	−2.625*	−0.084	−2.636*
On examination depressed	−0.056	−0.921	−0.058	−0.946
Counts of medical occurrences in the 180-day prior period				
Anxiolytic prescriptions	−0.001	−0.037	−0.001	−0.044
Sedative-hypnotics prescriptions	−0.013	−1.278	−0.013	−1.288
Antipsychotic prescriptions	0.021	1.350	0.022	1.377
Other prescriptions	0.000	−0.112	0.000	−0.107
General Practitioner visits	0.003	1.033	0.003	1.041
General Practitioner referrals	−0.001	−0.154	−0.001	−0.173
Psychotherapy referrals	0.023	1.445	0.023	1.411
Lab referrals	−0.015	−0.875	−0.015	−0.881
Psychiatric A & E admissions	0.018	0.258	0.016	0.227
General A & E admissions	0.007	0.285	0.007	0.281
General non-A & E admissions	0.013	1.150	0.013	1.136
PDG occurrence in the 180-day prior period				
Number of unique PDGs	0.075	3.854*	0.075	3.850*
Indicators of other medical conditions in the 180-day prior period				
Coronary artery disease	−0.020	−0.446	−0.020	−0.446
Diabetes	0.010	0.148	0.010	0.152
Drug choice				
Sertraline	−0.148	−5.115*	−0.131	−2.054*
Selection parameter				
Theta	—	—	−0.011	−0.290
Sums of squared residuals	14,605,024		14,604,748	

* Indicates $P < .01$.
†The sign on the coefficient indicates the direction of the change in duration that is associated with the characteristic.
PDG, Psychiatric Diganostic Groups

Table 4 Coefficients and *t*-statistics from 2nd stage model of average dosage greater than the minimum

	Unadjusted Results		Selection Model Results	
Variable	Coefficients†	*t*-statistics	Coefficients†	*t*-statistics
Demographics				
Age at index date	−0.003	−1.603	−0.002	−1.016
Female indicator	−0.111	−1.678	−0.132	−1.590
Location				
Wales indicator	−0.512	−4.356**	−0.308	−2.090**
Southern England indicator	−0.292	−4.805**	−0.204	−2.581**
Index depression diagnosis				
Endogenous depression	−0.041	−0.566	−0.027	−0.296
Reactive depression	0.017	0.187	−0.004	−0.033
Depressed	−0.261	−2.570**	−0.334	−2.453**
On examination depressed	0.175	1.060	−0.001	−0.005
Counts of medical occurrences in the 180-day prior period				
Anxiolytic prescriptions	−0.011	−0.280	−0.050	−1.016
Sedative-hypnotics prescriptions	−0.086	−2.559**	−0.103	−2.275**
Antipsychotic prescriptions	0.124	2.878**	0.121	2.326*
Other prescriptions	−0.004	−1.273	−0.006	−1.278
General Practitioner visits	0.012	1.151	0.014	1.000
General Practitioner referrals	0.005	0.445	0.009	0.589
Psychotherapy referrals	0.077	1.858	0.086	1.800
Lab referrals	0.036	1.256	0.049	1.389
Psychiatric A & E admissions	0.427	2.297**	0.473	2.267**
General A & E admissions	0.056	0.670	0.053	0.452
General non-A & E admissions	−0.029	−0.632	−0.054	−0.900
PDG occurrence in the 180-day prior period				
Number of unique PDGs	0.214	3.621**	0.187	2.514**
Indicators of other medical conditions in the 180-day prior period				
Coronary artery disease	0.091	0.655	0.055	0.291
Diabetes	0.126	0.639	0.116	0.447
Drug choice				
Sertraline	1.525	24.976**	1.158	8.286**
Selection parameter				
Theta		—	0.269	2.579**
Sums of squared residuals % correctly predicted				
Overall	89.835		333.063	
Likelihood ratio test statistic (d.f. = 23)	742.647			

*Indicates $P < .05$; **indicates $P < .01$.
†The sign on the coefficient indicates the direction of the change in probability of being prescribed an average dose during treatment higher than the minimum recommended dose that is associated with the characteristic.
PDG, Psychiatric Diganostic Groups

incremental effect. For the average subject in the sample, the parameter estimates from this model imply an incremental effect of −11.289 days (*SE* 4.352 days). In other words, initiating therapy on sertraline as opposed to fluoxetine for the average patient would be expected to result in 11.289 fewer days of antidepressant therapy.

Other statistically significant variables in this model included: age, location, reactive depression and depressed, as well as the prior period PDG count. Older patients as well as those with a greater number of unique PDGs during the 6 months prior to treatment had more days of therapy. Patients residing in Wales as opposed to Northern England or Scotland and subjects diagnosed with reactive depression or depressed as opposed to "depression not otherwise specified" had shorter durations.

Patients beginning therapy on sertraline were also more likely to have an average daily dose during treatment greater than the minimum recommended dose after controlling for observable and unobservable factors correlated with drug selection (Table 4, column 3). This finding rejects the other main null hypothesis of this study, namely that there is no difference between those initiating therapy on sertraline as opposed to fluoxetine in terms of receiving an average dose greater than the recommended minimum dose during treatment. The selection parameter theta was statistically significant. Unobserved factors correlated with initial treatment selection and dosing appear to have been a significant determinant whether doses received were greater than the minimum recommended. These results were robust to alternative specifications of the explanatory variables in the statistical model.

Using the parameter estimates from the model adjusted for sample selection (Table 4, column 3)

results in an incremental effect of 22.85% (*SE* 5.27%) for the average patient in the sample. If sample selection had not been controlled, the incremental effect would have been substantially higher at −33.88% (*SE* 2.23%).

Other results of the dosing model indicated that patients who resided outside Northern England or Scotland or who were diagnosed as depressed versus "depression not otherwise specified" were more likely to have the minimum recommended average daily dose during treatment. Patients with fewer sedative-hypnotic prescriptions, more antipsychotic prescriptions, more unique PDGs, and more psychiatric A & E admissions in the preperiod had an increased likelihood of an average daily dose greater than the minimum recommended dose.

Discussion

This study showed differences in the treatment duration and likelihood of being prescribed a daily dose above the minimum recommended dose for patients who initiated therapy on sertraline and fluoxetine in primary care in the United Kingdom. Features of this study included the use of data from clinical practice and controls for both observed and unobserved factors correlated with both treatment selection and the outcomes under study—prescribed daily doses and the duration of therapy. Although all the SSRIs have equal efficacy, their use in clinical practice can vary due to differences in tolerability, dosing regimen, ease of use, and other factors.

A previous study also found differences among the SSRIs in the duration of initial antidepressant therapy [28]. Differences in the side-effects profiles, which may be more pronounced at higher doses, can contribute to differences in therapy length among the SSRIs [29]. Longer duration of therapy is often associated with improved clinical outcomes [30].

The dosing results reported here are consistent with another study [18] that analyzed data from a primary care psychiatry setting in Spain. This study also found that patients who initiated therapy on sertraline as opposed to fluoxetine were more likely to have an average daily dose above the minimum recommended dose. In the Spanish study, patients met DSM-IIIR criteria for major depressive disorder and had no baseline differences by initial antidepressant in disease severity as measured by the Hamilton Depression Rating and Clinical Global Impression scales. Although antidepressant doses higher than the minimum recommended may provide a greater clinical effect in some patients, higher doses may also increase the likelihood of side effects and lead to higher antidepressant costs.

The parameter estimate of theta was statistically significant in the model that considered the likelihood of having an average dose during therapy greater than the minimum recommended. This result suggests that unobserved factors such as patient and prescriber characteristics not measured in the data, but correlated with initial treatment selection and observed doses, are a significant determinant of the likelihood of being prescribed an average daily dose above the minimum recommended. Since the statistical method controls for unobserved factors correlated with treatment choice, they cannot explain the significant effect of initial antidepressant selection on the dose outcome. In addition, the size of the effect of patients initiating therapy on sertraline as opposed to fluoxetine on the likelihood of receiving an average daily dose above the minimum recommended dose would have been biased if sample selection methods were not used. Unobserved factors correlated with initial drug choice were not found to be a significant determinant of the duration of therapy, although treatment type did matter. The statistical methodology applied here addresses concerns raised in earlier literature about the need to control for the potential effect of unobserved factors when comparing outcomes on fluoxetine and sertraline [19,20].

It is not possible with these data to identify the reason for the differential between the two antidepressants in the duration of therapy or the likelihood of receiving an average daily dose above the minimum recommended dose. Nor is it possible to evaluate patient-associated clinical outcomes with the observed regimen since clinical symptomatology data were unavailable in DIN-LINK. It is conceivable that some patients in the study sample did not meet the clinical criteria for major depressive disorder and that some patients who were receiving their antidepressant for major depressive disorders were excluded. While the diagnoses of affective disorders are not perfect in these data, it is unlikely that there is systematic bias across the fluoxetine and sertraline groups. Similarly, it is unlikely that a systematic bias due to miscoding of depression diagnoses exists in these data. While it was impossible to know whether patients were taking their medications, it is further unlikely that any differences in compliance were systematic across the treatment groups.

Future research might include randomized, prospective analysis comparing these outcomes among

the SSRIs as a way to further validate the retrospective analysis presented here. As occurred with the development of the Heckman model [31,32], further theoretical work extending the Terza model to allow for polychotomous choices in the treatment choice equation would be valuable as well. The statistical methods applied in this study would be useful in other areas of pharmacoeconomics and health outcomes research such as in the evaluation of health, utilization, and cost outcomes in clinical practice settings across alternative therapies.

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