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Does the Use of SSRIs Reduce Medical Care Utilization and Expenditures?

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Abstract

Background: Although selective serotonin reuptake inhibitors (SSRIs) are more expensive than tricyclic antidepressants (TCAs), SSRIs may reduce overall health costs compared with TCAs through improved compliance and reduced need for other medical care services. Economic evaluation studies using clinical trial or claims data have not accurately estimated the actual costs associated with antidepressants because they did not appropriately address two issues: the heterogeneity of SSRI and TCA users and the use of antidepressants for non-indicated symptoms.

Aims of the Study: This study estimates the relative substitution effect of SSRIs on the overall utilization of outpatient and inpatient care and other prescription drugs compared to TCAs. This study identifies and controls for heterogeneities in diagnosis among SSRI and TCA users and looks for variations in substitution effects across utilization.

Methods: To estimate the direct effect of SSRIs compared with TCAs on the utilization of other medical care resources in a naturalistic setting, this study uses the Medical Expenditure Panel Survey, national panel survey data, from 1996 to 1998. The main model of analysis is a two-part regression: the first part is a probit model of any use and the second part is a log linear model of expenditures among users. Baseline physical health status, depression severity, and socioeconomic factors that could affect antidepressant choice and medical care utilization are controlled for.

Results: A considerable fraction of antidepressant use, especially among TCA users, is for reasons other than depression. After controlling for the heterogeneity in SSRI and TCA users, this study does not find consistent evidence of the substitution of SSRIs for other medical care. Although SSRIs, compared with TCAs, reduce overall outpatient visits and other prescription drugs, they increase the utilization of these services for depression. Antidepressant choice does not influence the utilization or expenditure level for inpatient services which composed the largest part of medical expenditure in this study sample. Results are robust when the analysis is restricted to the SSRI or TCA users with a depression diagnosis.

Discussion: The potential cost-incremental effect of SSRIs over TCAs for the treatment of depression can be compromised by the reduced utilization for symptoms other than depression among SSRI users. This study uses national survey data and takes into account the heterogeneity of SSRI and TCA users so the results can be generalized to real clinical practice.

Implications for Health Care Provision: The costs associated with antidepressants are not only for the treatment of depression symptoms. Antidepressants are commonly prescribed for conditions for which the clinical and economic benefits are not established. This practice may lead to significant unnecessary healthcare expenses.

Implications for Health Policies: Antidepressant prescriptions for non-indicated conditions should be considered in setting policies designed to control costs associated with antidepressants and in developing clinical guidelines for antidepressant prescription.

Implications for Future Research: Future research on the economic evaluation of antidepressants should consider the use of antidepressants for health conditions other than depression. The economic incentives for and clinical benefits of the prescription of antidepressants for non-indicated conditions could be explored in future research.

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Introduction

Spending on prescriptions, and in particular those for psychiatric medications, has been one of the fastest-growing components of health care expenditure.[1] The volume of SSRI prescription has increased substantially since its introduction in 1988 and the annual expenditure for SSRIs constitutes about 80% of the 3.5 billion US dollar antidepressant market in the US in 1995[2] and is growing 25% per year.[3] Newer drugs typically cost more than older ones which are available as generic versions. Among antidepressants, the newer drug Sertraline, an SSRI, is almost nine times more costly than a previous popular treatment, Amitriptyline, a TCA.[4] One reason for the rapid market penetration of SSRIs may be the relatively benign side effects of SSRIs. Meta-analyses of clinical trials have shown that significantly fewer patients receiving an SSRI discontinued treatments because of an adverse side effect compared with those receiving a TCA,[5-6] although others showed no difference in the discontinuation rates of SSRIs and TCAs.[7]

Increased compliance could ultimately improve patient functioning and reduce total healthcare expenditures.[8]

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Because expenditures on prescriptions represent only 9% of total health care spending,[9] it is possible that increased demand for prescription drugs would reduce overall health care costs by substituting for the use of more costly psychiatric therapies or by reducing hospitalizations. Thus, the overall cost profile of using the newer antidepressants is determined by the relative substitutability of a certain drug for other health care sector expenditures as well as by its own cost relative to alternative antidepressants.

The objective of this study is to examine the relative substitutability of SSRIs as compared to TCAs for other medical care services. To estimate the incremental effect of SSRIs on the utilization and expenditures incurred in other medical care sectors in a realistic setting, this study uses national survey data from the Medical Expenditure Panel Survey (MEPS).

Economic evaluation studies on SSRIs and TCAs typically use one of two types of study designs: retrospective administrative data analysis and clinical decision analysis models. Retrospective reviews generally use a claims database, and the majority of them have concluded that SSRIs have a cost-saving advantage over TCAs.[10-12] Some studies have found the opposite to be true[13] or no difference between the two drug types.[14] Decision analysis modeling has been extensively used to evaluate the cost-effectiveness of SSRIs compared with TCAs and results from most decision analysis studies indicate the cost-effectiveness of SSRIs.[15-18]

Using claims data as source of cost information involves treatment assignment selection according to disease severity. Some researchers addressed the selection problem by restricting the sample to new episodes of depression because information on the severity of depression symptoms is rarely available.[19] External validity of results from this approach is limited because patients with depression are usually treated for recurrent symptoms or as part of ongoing maintenance therapy.

Claims data represent demographically homogeneous populations and are often available only for enrollees in private insurance plans. Patients who are privately insured are likely to be younger and healthier than those with public insurance or without insurance.[20] Perspectives of the studies using claims data are generally those of the payer or health plan, and cost-shifting to patients or other public parties has not been appropriately addressed.[21]

A modeling approach often incorporates unrealistic assumptions and is vulnerable to bias in source data, which counteracts the advantage of flexibility in study design.[22] Results are usually extrapolated beyond the time frame of available data in simulations representing a 12-month or longer period.[23] According to a review reported by AHRQ, over 90% of the clinical trials of SSRIs and TCAs were 6 to 8 weeks in duration which is far shorter than the 4- to 9-month duration of pharmacotherapy which AHRQ guidelines suggest for treatment of depression.[24] A study using 24-month clinical data found no difference in medical costs between SSRIs and TCAs.[25] Furthermore, all the published studies are sponsored by manufacturers of newer drugs making the validity of the results questionable.[26]

Effectiveness parameters in decision analyses are generally derived from published studies based on randomized controlled trials (RCTs). Although prospective RCTs capitalize on the strengths of experimental designs which can provide evidence of causality between drug use and outcomes, strict inclusion criteria and the contrived nature of controlled clinical trials do not mimic routine clinical practice.[27,28] Patients in psychiatric care usually have comorbid psychiatric and general medical conditions and are on concomitant therapies. Such patients are often excluded from RCTs. Clinical trials also exert special efforts to retain patients; clinic visits are more frequent than usual care and dosage regimens are strictly enforced. Consequently, compliance in clinical trials may not be the same as it is in practical settings.

This study has several advantages over previous economic evaluation studies on SSRIs and TCAs using claims data or clinical study results. First, the study sample represents the population taking SSRIs or TCAs, including patients with diverse levels of depression symptoms and other comorbidities. Results can also be generalized to heterogeneous demographic groups with different insurance status, employment status, income, and age levels. Second, utilization patterns in observational data resemble those in real practice with flexible dosage, concomitant medications and psychotherapy. Third, this study takes a broad societal perspective by considering medical care costs including third party reimbursement as well as out of pocket payments.

To estimate the direct effect of SSRIs using the observational data, heterogeneities in individual characteristics affecting drug choice and medical care utilization are controlled for. The analytic methods used in this study take advantage of the individual panel structure and information on diagnoses, utilization, and costs associated with each medical event provided by the MEPS data. This study uses two subclasses of study subjects: (i) people who are using an SSRI or a TCA and (ii) SSRI or TCA users with depression; and two utilization measures: (i) overall service use and (ii) service use for depression. The results of the evaluation for the two subclasses and two utilization measures are compared to understand robustness of the substitution effect of SSRIs in different study settings.

Methods

Data

The MEPS data from 1996 to 1998 are used for the entire analysis. The MEPS survey is conducted 5 times for each respondent during 2 calendar years. Thus, there are up to 5 rounds of surveys for participants who joined the survey in 1996 and 1997 and up to 2 rounds for those who joined the survey in 1998. Data on medical expenditures associated with all types of medical services utilization including inpatient and outpatient care and prescription drugs were first collected from the Household Component (HC) survey and then verified and corrected using the Medical Provider Component (MPC) survey. The MPC sample includes all

hospitals, hospital physicians, and pharmacies, and about 50% of office-based physicians reported in the HC. The HC survey was conducted through in-person interviews and the MPC survey was through telephone interviews and mailed survey materials.[29] The MEPS uses a weighted sequential hot-deck procedure for imputing missing data on expenditures.[30]

In the MEPS, prescription drugs are coded by national drug codes (NDC) and medication names, both of which are used to identify SSRI or TCA prescription events for this study. All SSRI or TCA drugs available in the market during 1996 to 1998 are considered. The SSRIs used in the study sample include fluoxetine, fluvoxamine, citalopram, paroxetine, and sertraline, and the TCAs include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, mirtazapine, protriptyline and trimipramine. Drug choice is defined at the baseline round. Among the available sample of SSRI or TCA users at baseline (n = 2,085), 13.7% (n = 195) of SSRI users and 2.9% (n = 23) of TCA users who were taking more than one class of antidepressants (e.g. an SSRI and a TCA, an SSRI and other antidepressants, a TCA and other antidepressants) are excluded. SSRI users compose 62% and TCA users compose 38% of the overall analysis sample (n = 1,997).

Utilization and expenditures are described by the variables for the indication of any use, frequency of use, expenditure among any users (separately for inpatient and outpatient care) and the indication of any use and expenditure level for other prescription drugs. Utilization and expenditures are defined as total and average values during the post-baseline period, respectively. The *any use* indicator specifies whether or not an individual has ever used any services during the post-baseline period. The average length of the post-baseline period for each individual is 13.2 months and is about the same for SSRI and TCA users with no statistical difference (p=0.39). *Inpatient days* and *outpatient visits* represent the frequencies of inpatient days and outpatient visits during the post-baseline period. *Expenditure* of each service is the average expenditure per round (4.8 months on average) among those who ever used each service during the post-baseline period. Expenditures include total cost of care no matter who paid for it but do not include insurance premiums. All expenditure values are adjusted to 1998 US dollars using the Consumer Price Index-Urban.[31] The same set of variables is created for those services associated with a depression diagnosis.

The MEPS uses the International Classification of Diseases - 9th revision (ICD-9) and the Clinical Classification Codes (CCC; developed by AHRQ[32]) for the classification of medical conditions. Medical conditions were reported by household respondents and recorded by interviewers as verbatim text, then coded to fully-specified ICD-9 codes by professional coders. The public MEPS data provide the abbreviated 3-digit ICD-9 codes. The accuracy of diagnosis codes was verified and error rates do not exceed 2.5% for any coder.[29] This study uses a combination of ICD-9 and CCC for selecting prescriptions and medical events associated with depression. Depression conditions included are manic-depressive disorder, neurotic depression, depressive reaction, and other depressive disorders with corresponding ICD-9 codes of 296, 300 (accompanied by CCC 69), 309 (accompanied by CCC 72), and 311. With this classification scheme, 70% (n = 865) of SSRI users and 24% (n = 186) of TCA users are identified as having a depression diagnosis.

Empirical Model Specification

A two-part model is used in the estimation of incremental medical services utilization and expenditures related to SSRIs. The first part is a probit regression of the indicator for any use, and the second part is a linear regression of expenditures among users. In each part, separate models for outpatient, inpatient, and other prescription drug expenditures are used to produce more precise estimates for each service category.

$$[\text{Any Medical Service Use}]_t = f(SSRI_{t-1}, SEVERITY_{t-1}, ACCESS_t, OTHER\ DEMOGRAPHIC_t) \quad (1)$$

$$[\text{Expenditure on Medical Service} \mid \text{Medical Service} > 0]_t = g(SSRI_{t-1}, SEVERITY_{t-1}, ACCESS_t, OTHER\ DEMOGRAPHIC_t) \quad (2)$$

In the empirical specification described in equations (1) and (2), the *SSRI* variable indicates whether one is taking an SSRI or a TCA (=1 if SSRI). The sign and magnitude of the estimate on *SSRI* indicate the incremental effect of SSRIs on other medical services use. Variables indicating *SEVERITY*, which represents severity of health problems, are self-rated health status (=1 if fair or poor), any limitation in activities of daily living (ADL), and a major depression diagnosis (=1 if having diagnosis of ICD-9 296 or 311). The *ACCESS* variable represents factors affecting access to medical care and includes insurance type, area of residence (=1 if living in a metropolitan statistical area (MSA)), and household income.[33,34] Variables used to represent *OTHER DEMOGRAPHIC* factors are age, gender, race, education level, marital status, and survey years which are associated with antidepressant choice and medical care utilization.[35,36] Year fixed effects control for the simultaneous trends in medical care utilization and antidepressant prescriptions during the study period. The same regression framework is used for utilization and expenditures associated with depression diagnosis and for the overall utilization and expenditures in the subgroup of individuals with depression.

Data Analytic Procedures

Examination of the Endogeneity of Drug Choice with Instrumental Variables Method

The challenge of using non-experimental data for estimating the causal effect of treatment on outcome variables lies in the heterogeneity that is correlated with both treatment and outcomes among the comparing groups. Failure to control for the heterogeneity leads to a biased estimation capturing spurious relationships between drug choice and utilization. For example, if patients with more severe depression symptoms are more likely to take an SSRI, the observed

higher utilization and costs among SSRI users can be explained by the underlying difference in depression symptoms that would have incurred higher medical costs regardless of SSRI use. To identify the direct effect of SSRIs, this study defines the drug choice at baseline in order to estimate utilization during the following period. With this approach, reverse causality of medical care utilization to drug choice can be minimized. Indicators of physical health conditions and depression severity are also defined at the baseline round.

An instrumental variable (IV) method is used to examine the potential endogeneity of drug choice. Market age and drug class specific adverse effects are examined as potential instruments. Market age is defined as 'years between the date a drug is first approved in the US and the prescription date.' FDA approval date is defined at the generic name level.[37] Adverse effects are represented by three variables indicating the occurrence of comorbid conditions that are known as adverse effects of TCAs and SSRIs (nausea, insomnia, and hypotension). Comorbidities are identified using medical conditions coded with ICD-9. Although many physician-side characteristics are suggested as potentially valid instruments in the literature,[38] they are not available in the MEPS data.

The identification assumption of the IV method is that instruments are highly correlated with *SSRI* and are correlated with utilization and expenditure level only through the instrumented variable, *SSRI*. Because newer drugs are more likely to be SSRIs, *SSRI* is highly correlated with market age. However, it is not likely that market age independently determines utilization and expenditure levels. Regarding adverse effects, SSRI users may have nausea or insomnia more often than TCA users as these are common side-effects of SSRIs. Similarly, TCA users are expected to be more likely than SSRI users to report anticholinergic symptoms such as hypotension.[39,40]

Specification tests are used to select valid instruments and to compare the estimates with and without instruments. The IV estimation is conducted with a two-stage linear regression. In the first stage, market age is a strong predictor ($p < 0.001$) of *SSRI*, but none of the adverse effects are strong predictors. None of these adverse effects instruments pass the Hausman tests or Lagrange multiplier tests of overidentification ($p < 0.001$). Using the *market age* as a valid instrument, all the regression models of any use and expenditures for each service category are estimated. In the comparison of the IV estimates and estimates without instruments, Hausman tests do not reject the null hypothesis of the exogeneity of *SSRI* for all dependent variables. Based on the specification tests results, this study takes the estimates from the models without instruments as the main results.

Selection of Functional Forms and Calculation of Marginal Effects

In the estimation of expenditure models, the logged linear model, generalized linear model (GLM), and OLS with un-logged expenditure are examined to select a correct functional form of the expenditure data. The Box Cox test[41] and Wooldridge tests[42] show that the models with logged expenditures are superior to those with un-logged expenditures in terms of overall model fit. The error term shows kurtosis greater than 3 for all the dependent variables, indicating potential inconsistency of GLM estimates.[43] Based on these results, logged expenditures were chosen for all of the expenditure models.

In the retransformation of the logged expenditures into level values, error distributions deviating from the normal curve are adjusted with the smearing factor.[44] All the logged models pass the White test and Lagrange multiplier test of heteroskedasticity,[45,46] and a smearing factor is applied to the entire sample for each expenditure variable. To calculate the marginal effects of SSRIs and statistical inferences of the marginal effects, correct standard errors are estimated using the bootstrapping method with 200 replications.[47]

Results

Unadjusted Sample Statistics of SSRI and TCA Users

Table 1 reports sample means of utilization and expenditures for inpatient care, outpatient visits and prescription drugs. Utilization rates and mean expenditures among SSRI or TCA users are shown in the first two columns and those among SSRI or TCA users with a depression diagnosis are in the middle two columns. Sixty percent of SSRI users and 23% of TCA users taking these antidepressants had a depression diagnosis. The last two columns show the utilization and expenditures associated with depression among SSRI or TCA users.

When overall utilization is taken into account, SSRI users in general and the subset with a depression diagnosis are less likely to use outpatient care compared with TCA users. However, this trend is reversed when utilization and expenditures only for depression are considered. The average utilization and expenditures for inpatient services are not statistically different across all three criteria.

About 95% of the sample used medications other than antidepressants and 90% of the sample used outpatient services during the post-baseline period. Although the probability of using inpatient care is relatively low (18%), expenditures for the inpatient care compose half of the total medical care expenditure. On the other hand, prescription costs for SSRIs and TCAs are only 7.0% and 1.5% of overall medical care expenditure, respectively. Although the prescription drug costs for SSRIs are about 5 times as high as those for TCAs, this difference contributes little to overall expenditure. Overall medical care expenditure does not differ between the two groups. The subsample of SSRI or TCA users with depression shows a similar pattern but with a higher level of utilization.

Unadjusted sample statistics show substantial differences between SSRI and TCA users in the variables representing health status, access and other demographic characteristics (**Table 2**). SSRI users rate their health better but more frequently report symptoms classified as major depression.

Table 1. Sample Means of Medical Service Utilization and Expenditures[a]

Variables	Overall utilization among SSRI or TCA users		Utilization for depression among SSRI or TCA users		Overall utilization among SSRI or TCA users with depression	
	SSRI N = 1,228	TCA N = 769	SSRI N = 1,228	TCA N = 769	SSRI N = 771	TCA N = 171
Service received:						
Any inpatient care	0.18	0.19	0.02	0.01	0.18	0.18
Inpatient days	0.74 (4.3)	1.1 (4.3)	0.09	0.11	0.91 (5.4)	1.6 (6.6)
Any outpatient visit	0.88*	0.91	0.33**	0.15	0.90**	0.98
Number of outpatient visits	6.6 (9.3)	7.2 (9.8)	1.5** (3.9)	0.73 (3.2)	7.3 (10.2)	8.1 (9.3)
Any other prescription drug use	0.93**	0.97	0.24**	0.14	0.90**	0.98
Expenditures ($) on:						
Inpatient care	1481 (5255)	1844 (6296)	131 (1406)	182 (2057)	1740 (6043)	2386 (6748)
Outpatient visits	771 (1652)	764 (1182)	89** (314)	54 (266)	778 (1473)	816 (1151)
Other prescription drugs	410* (619)	469 (582)	41** (156)	18 (76)	434 (665)	394 (459)
SSRI or TCA	200**(240)	46 (130)	147**(224)	19 (100)	279**(245)	100 (209)
Total medical care	2862 (6041)	3122 (6624)	408 (1580)	273 (2253)	3232 (258)	3695 (7250)

* Significant at 5% level and ** significant at 1% level based on the t-statistic with unequal variance for the continuous variables and Fisher's exact test statistic for the dichotomous variables.
[a] Standard deviations for continuous variables are in parentheses.

Table 2. Sample Means of Individual Characteristics

Variables	SSRI users[a]	TCA users[a]
Health status		
Self-rated health (=1 if fair or poor)	0.37**	0.49
Any ADL limitation	0.09	0.09
Severe depression (=1 if having diagnosis of ICD-9 296 or 311)	0.60**	0.19
Insurance type[b]		
Medicaid	0.20**	0.27
Medicare/CHAMPUS	0.28**	0.43
Private insurance	0.69**	0.58
No insurance	0.07	0.07
Other demographics		
Age	47** (18)	53 (20)
Female	0.29	0.32
White	0.92**	0.87
High school: (=1 if 12 or more years of education)	0.72**	0.63
Married	0.51	0.50
MSA	0.75**	0.68
Income (unit: $1,000)	21** (23)	17 (21)
Total number of observation	1,228	769

* Significant at 5% level and ** significant at 1% level based on the t-statistic with unequal variance for the continuous variables and Fisher's exact test statistic for the dichotomous variables.
[a] Standard deviations for the continuous variables are in parentheses.
[b] Insurance categories are not mutually exclusive and sum of the fractions in each category is more than 1.

SSRI users are more likely to have private insurance whereas TCA users are more likely to be covered by Medicaid or Medicare/CHAMPUS. Compared with TCA users, SSRI users tend to be younger, more educated, and white, and are more likely to live in metropolitan statistical areas and have higher incomes.

Utilization and Expenditures among Any SSRI or TCA Users

The main two-part regressions show that SSRIs decrease the use of outpatient care and other prescription drugs (**Table 3**). SSRIs reduce the chance of using other prescription drugs by 6.3% ($p < 0.01$). The decreased chance of outpatient visits (0.9%) with SSRIs is very small and, inferring from the bootstrapped standard errors, is not statistically different from zero. There is no incremental effect of SSRIs on the chance of using inpatient care. Expenditure levels among people using any service do not differ by antidepressant

Table 3. Medical Care Utilization and Expenditures by Service Type among Any TCA or SSRI Users[a]

	Inpatient service		Outpatient service		Other prescription drug	
	Any use	Expenditure	Any use	Expenditure	Any use	Expenditure
SSRI	0.100	0.018	−0.194*	−0.080	−0.353**	0.042
	(0.079)	(0.130)	(0.095)	(0.070)	(0.125)	(0.068)
Marginal effect of SSRI	0.039*	1237	−0.009	265	−0.063**	431
	(0.019)	(3511)	(0.013)	(231)	(0.010)	(221)
Health Status						
Self-rated health: fair/poor	0.378**	0.133	0.211*	0.330**	0.283*	0.625**
	(0.073)	(0.116)	(0.094)	(0.066)	(0.119)	(0.064)
Any ADL limitation	0.061	−0.081	−0.357*	0.226*	0.643	0.281*
	(0.115)	(0.199)	(0.146)	(0.110)	(0.401)	(0.110)
Severe depression	−0.026	0.102	0.143	0.137*	0.043	−0.027
	(0.076)	(0.126)	(0.090)	(0.067)	(0.108)	(0.067)
Insurance Type						
Medicaid	0.163	0.076	0.203	0.182	0.260	0.237*
	(0.104)	(0.184)	(0.143)	(0.103)	(0.193)	(0.099)
Medicare/CHAMPUS	0.156	0.065	0.319**	0.088	−0.176	0.064
	(0.100)	(0.158)	(0.115)	(0.087)	(0.145)	(0.085)
Private insurance	−0.098	0.291	0.081	0.252**	−0.012	0.154
	(0.093)	(0.155)	(0.125)	(0.090)	(0.161)	(0.082)
Other demographics						
Age	0.008**	0.011*	0.005	0.001	0.027**	0.018**
	(0.003)	(0.005)	(0.003)	(0.002)	(0.004)	(0.002)
Female	0.011	0.290*	−0.249**	0.003	−0.192	0.008
	(0.075)	(0.123)	(0.087)	(0.069)	(0.107)	(0.068)
High school	0.042	−0.250	0.008	0.348**	0.040	0.123
	(0.079)	(0.138)	(0.098)	(0.073)	(0.128)	(0.072)
White	−0.013	0.045	0.255	0.059	−0.065	−0.028
	(0.113)	(0.157)	(0.131)	(0.104)	(0.198)	(0.099)
Married	−0.023	−0.093	0.083	−0.062	−0.279*	0.022
	(0.073)	(0.119)	(0.090)	(0.064)	(0.112)	(0.062)
MSA	−0.016	0.070	0.230**	0.071	−0.061	−0.040
	(0.077)	(0.125)	(0.089)	(0.071)	(0.125)	(0.068)
Income (/10K)	−0.005**	0.001	0.003	0.001	−0.000	0.000
	(0.002)	(0.004)	(0.002)	(0.001)	(0.002)	(0.002)
Year = 1997	−0.045	−0.274*	−0.274*	−0.136	−0.010	−0.013
	(0.083)	(0.128)	(0.116)	(0.071)	(0.134)	(0.074)
Year = 1998	−0.404**	−0.299	−0.528**	−0.167*	−0.102	−0.059
	(0.096)	(0.157)	(0.118)	(0.081)	(0.137)	(0.081)
Constant	−1.407**	7.951**	0.824**	5.271**	0.952**	3.946**
	(0.204)	(0.348)	(0.245)	(0.191)	(0.310)	(0.184)
Observations	1997	355	1997	1817	1997	1896
R-squared		0.100		0.043		0.150

* Significant at 5% level and ** significant at 1% level.

[a] For each service category, probit regression is used for *any use* and log linear regression is used for the *expenditures* among users.
Robust standard errors are in parentheses.
Marginal effect of *SSRI* in the expenditure model is calculated with the retransformation of the estimate of *SSRI* multiplied by smearing factor. Smearing factors for inpatient, outpatient and drug expenditure models are 1.56, 2.23 and 1.97, respectively.
Robust standard errors for the marginal effects are obtained by bootstrapping with 200 replications.

Table 4. Medical Care Utilization and Expenditures among Patients with Depression[a]

	Inpatient service		Outpatient service		Other prescription drug	
	Any use	Expenditure	Any use	Expenditure	Any use	Expenditure
Coefficient on SSRI	0.130	−0.150	−0.370*	−0.198	−0.576*	0.115
	(0.126)	(0.213)	(0.183)	(0.105)	(0.261)	(0.106)
Marginal effect of SSRI	0.056*	−4443	−0.057**	−487	−0.068**	−25.5
	0.027	(7818)	(0.015)	(366)	(0.016)	(161)
Observations	1051	179	1051	966	1051	988
R-squared		0.150		0.038		0.167

* Significant at 5% level and ** significant at 1% level.

[a] For each service category, probit regression is used for *any use* and log linear regression is used for the *expenditures* among users.
Robust standard errors are in parentheses.
Marginal effect of *SSRI* in the expenditure model is calculated with the retransformation of the estimate of *SSRI* multiplied by smearing factor. Smearing factors for inpatient, outpatient and drug expenditure models are 1.26, 2.20 and 2.25, respectively.
Robust standard errors for the marginal effects are obtained by bootstrapping with 200 replications.
All other covariates presented in **Table 3** are retained in the regressions but not displayed in this table.

choice for all three service categories.

Indicators of poor physical health status at baseline are strong predictors of medical care utilization and expenditures. Fair or poor self-rated health status increases the chances of inpatient care, outpatient visits, and other prescription drug use while also increasing expenditures for those using outpatient visits or prescription drugs. Any ADL limitation increases outpatient and other prescription drug expenditures among those using these services, but decreases the chance of using outpatient services. Severe depression increases expenditure during outpatient visits but does not have a significant effect on services in other categories. In comparison with those having no insurance, those who are eligible for Medicare are more likely to use inpatient services; those with private insurance tend to spend more on outpatient visits; and those with Medicaid tend to spend more on prescription drugs. Other demographic factors show directions consistent with those expected from the literature.[33-36]

Utilization and Expenditures among SSRI or TCA Users with Depression

Analyses based on the subsample of patients with depression produce results similar to the results of the overall sample (**Table 4**). SSRIs reduce the chances of using outpatient care by 5.7% and using other prescription drugs by 6.8%, as is indicated by the bootstrapped marginal effects and standard errors ($p < 0.01$). Consistent with the overall sample analyses results, there is no incremental effect of SSRIs on inpatient service use or on the expenditures among people using any type of service. Other covariates not reported in the table show the same directions as the overall sample analyses presented in **Table 3**.

Utilization and Expenditures for Depression among Any SSRI or TCA Users

When utilization and expenditures only for depression are taken into account, SSRIs increases the chance of outpatient visits by 19.2% and the chance of other prescription drug use by 11.5% ($p < 0.01$) (**Table 5**). In the results not reported in the table, the variable indicating severe depression diagnosis is a strong predictor of outpatient visits and other prescription drug use.

Frequency of Inpatient and Outpatient Care Utilization

Results from the linear regressions for the number of inpatient days and outpatient visits are consistent with those from the part probit regressions of the overall sample (**Table 6**). One difference is that the increase in the outpatient visits for depression with SSRI is not statistically significant. On average, SSRIs reduce outpatient visits by 1.1 visits compared with TCAs for the overall sample, and by 1.7 visits in the subsample of patients with depression.

Discussion

The objective of this study is to examine the relative substitution effect of SSRIs over TCAs in terms of medical care utilization and expenditures. After controlling for heterogeneity between SSRI and TCA users using regression analyses exploiting the longitudinal structure of the MEPS, this study finds that SSRIs reduce overall outpatient visits and other prescription drugs while it increases the chance of using these services for depression. Antidepressant choice does not affect the utilization or expenditures for inpatient services which constitute the largest fraction of overall medical expenditures.

It is surprising to find that the majority of patients take antidepressants for conditions other than depression, although most SSRI and TCA drugs are indicated only for depression. In addition to the predominant diagnosis (ICD-9) of depressive disorders (311) and neurotic disorders (300), non-psychiatric chronic conditions such as diabetes (250)

Table 5. Medical Care Utilization and Expenditure for Depression among Any TCA or SSRI users[a]

	Inpatient service		Outpatient service		Other prescription drug	
	Any use	Expenditure	Any use	Expenditure	Any use	Expenditure
Coefficient on SSRI	0.190	−1.447	0.341**	−0.184	0.223**	0.234
	(0.170)	(0.751)	(0.077)	(0.140)	(0.081)	(0.155)
Marginal effect of SSRI	0.014	−18321	0.192**	−394*	0.115**	21.9
	(0.007)	(29792)	(0.019)	(164)	(0.019)	(79.2)
Observations	1997	36	1997	533	1997	411
R-squared		0.593		0.069		0.081

* Significant at 5% level and ** significant at 1% level.

[a] For each service category, probit regression is used for *any use* and log linear regression is used for the *expenditures* among users.
Robust standard errors are in parentheses.
Marginal effect of *SSRI* in the expenditure model is calculated with the retransformation of the estimate of *SSRI*. multiplied by smearing factor. Smearing factors for inpatient, outpatient and drug expenditure models are 1.25, 2.06 and 2.08, respectively.
Robust standard errors for the marginal effects are obtained by bootstrapping with 200 replications.
All other covariates presented in **Table 3** are retained in the regressions but not displayed in this table.

Table 6. Inpatient Days and Number of Outpatient Visits - OLS Estimates[a]

	Overall utilization among any SSRI or TCA users		Overall utilization among SSRI or TCA users with depression diagnosis		Utilization for depression among any SSRI or TCA users	
	Inpatient days	Outpatient visits	Inpatient days	Outpatient visits	Inpatient days	Outpatient visits
Coefficient on SSRI	0.009	−1.092*	−0.205	−1.740*	−0.002	0.049
	(0.224)	(0.449)	(0.326)	(0.829)	(0.087)	(0.165)
Observations	1997	1997	1051	1051	1997	1997
R-squared	0.044	0.058	0.072	0.076	0.007	0.094

* Significant at 5% level and ** significant at 1% level.

[a] Robust standard errors are in parentheses.
All other covariates presented in **Table 3** are retained in the regressions but not displayed in this table.

and migraine (346) are commonly reported among TCA users. For SSRI users the commonly reported symptoms other than depression are other psychiatric symptoms such as acute reaction to stress (308), hyperkinetic syndrome of childhood (314), and Alzheimer's disease or dementia (331). The percentage of people who do not report depression symptoms is higher among TCA users (77%) than SSRI users (40%). Compared with SSRI users, TCA users more frequently rate their general health status as fair or poor and are less likely to report symptoms classified as major depression. This trend holds even among the subsample of patients with depression. This implies that evidence from clinical trials focusing on patients with indicated symptoms with a restricted range of comorbid conditions would represent only a strict subset of antidepressant users.

Provided that drug choice is not endogenously determined in the regression, one possible pathway by which TCAs lead to increased outpatient visits and other prescription drug use is through the higher risk of adverse events associated with TCAs. Notice that utilization during the post-baseline period is treated as being associated with the baseline drug choice. Thus, additional medical care utilization arising from adverse events is linked to the drug choice at baseline. However, this study does not explicitly estimate the incremental cost ascribed to adverse events or discontinuation; future studies using experiments in a naturalistic setting may be able to quantify the incremental medical care utilization and expenditures due to adverse effects associated with antidepressant choice.

The increase in outpatient visits and other prescription drug use for depression among those using SSRIs indicates that SSRIs induce other medical care for the treatment of depression rather than substituting for it. However, if this increased outpatient visits is from the increased use of psychotherapy, then SSRIs could potentially substitute for more costly inpatient utilization in the long-run. Psychotherapy in combination with antidepressants is found to be more effective than mono-therapy, although its cost-effectiveness has not been established.[48] In this study sample, the probability of using psychotherapy among SSRI users (30%) is almost twice as high as that for TCAs (16%) with statistical significance ($p < 0.001$).

Most medical care utilization among SSRI or TCA users is for conditions other than depression. Inpatient days and outpatient visits associated with depression compose only 12% and 23% of overall utilization by SSRI users, and 10% of the utilization for both types of services by TCA users. Because the prevalence of physical comorbidities and the utilization of medical care for conditions other than depression are disproportionately higher among TCA users than SSRI users, the cost-effectiveness ratio combining overall medical care cost with clinical outcomes measured by only depressive symptoms between these heterogeneous groups would be misleading. However, practically, it is difficult to identify costs specific to depression because most patients with depression have diverse physical comorbidities and use concomitant therapies. Outcome measures for overall physical and other psychiatric conditions as well as depression symptoms should be incorporated to make a fair comparison.

The analysis sample of this study includes individuals taking other psychotropic drugs (other than antidepressants) or other medications for physical comorbidity. Nearly all SSRI and TCA users (95%) in this study sample were taking psychotropic drugs other than antidepressants. Among SSRI users, 11% were taking antipsychotics and 27% were taking other anxiolytics or sedatives. These frequencies were similar among TCA users with no statistical difference. The observed high utilization of other prescription drugs in this study also implies that cost-effectiveness studies using data from clinical trials with strict inclusion criteria may not reflect cost and effectiveness profiles of antidepressants in real practice.

Several limitations of this study are worth noting. First, this study uses observational data where two comparison groups are different in characteristics associated with utilization and expenditures. Only some of these differences are observable. However, this study adopts several analytical strategies to deal with the limitation inherent in observational data, and the evidence indicates the insignificance of the potential endogeneity. The equivalence of estimates with and without instruments supports the exogeneity of drug choice. The results for the subgroup of patients with depression, where most of the heterogeneity between the two comparison groups is eliminated, are similar to the results for the overall sample.

Second, information on health services utilization and expenditures in MEPS is based primarily on self-reported information and is verified by a provider survey. Self-reported services utilization data may not be as accurate as those based on administrative records and could be correlated with utilization level.[49,50] However, even if there are errors in reporting after the verification with the provider survey, regression results would not be biased unless reporting errors were systematically different between SSRI and TCA users. On the other hand, self-reported data have an advantage over administrative data in cost analyses because they capture a wide array of services use which is common among patients with behavioral health problems.[51]

Third, depression diagnosis in this study could have been underreported if patients have a tendency to attribute depression symptoms to causes other than depression. Diagnosis of clinical symptoms in the MEPS is based on self reports and is represented by ICD-9 codes. The high accuracy of coding is verified and therefore the potential inaccuracy of diagnosis codes in the MEPS could be mostly from the limited ability of household respondents to report clinical conditions.[52] Stigma associated with mental health problems would also have caused the underreporting of depression symptom in self-reporting.

Fourth, the sample in the analysis excludes individuals taking more than one class of antidepressants, which weakens the external validity of this study. Individuals who took both an SSRI and a TCA during the baseline period could have either switched drugs between a TCA and an SSRI or stayed on SSRI and TCA combination therapy during that period. Exclusion of the former case may have affected estimates if switchers to an SSRI and switchers to a TCA are systematically different in their use of medical care. However, this might not be the case in this study. Individuals who were excluded because they were taking both an SSRI and a TCA at the same period compose only 4% ($n = 88$) of the remaining sample, and their outpatient and inpatient care utilizations were not different from the utilizations among SSRI or TCA only users. A previous study also has shown that most of the treatment changes between a TCA and an SSRI occurred during the initial 3 months of antidepressant therapy and had no difference in other medical costs between the two groups.[53]

The study sample also excludes those who were taking other classes of anti-depressants along with an SSRI or a TCA during the baseline survey round (n=130; 6%). If those taking other antidepressants are randomly assigned to one of the two comparison groups, the inclusion of these cases does not change the regression estimates. However, the data show that users of multiple antidepressants are more likely to take an SSRI than a TCA and are more likely to use other medical care. This implies that the inclusion of these high volume users could have led to a bias toward higher utilization with SSRIs.

Finally, the population of this study sample is civilian and noninstitutionalized, and, as a result, a significant fraction of patients with severe depression symptoms is not included in the study. Future research could include institutionalized patients to more accurately represent the population using SSRIs and TCAs.

Findings of this study suggest several areas for future investigation. First, effectiveness of antidepressants for conditions not approved by the FDA should be better understood. For example, the most frequently reported non-depression diagnosis for outpatient visits among TCA users are diabetes and hypertension. Although there is some evidence suggesting the usefulness of TCAs for relieving pain related to diabetic neuropathy and treatment of hypertension and heart disease,[54-56] none of the TCA drugs has an approved indication for these conditions. Second, economic incentives that lead practitioners to prescribe TCAs improperly for these conditions could also be explored in future research. Previous literature suggests that physician characteristics, such as physician specialty, contracts with

health care plans, or years of practice, are strong predictors of antidepressant choice.[38] Antidepressant use for conditions that are not approved could be better understood using other data with information on the physician side. Third, incorporation of longer-term clinical outcomes not only in terms of depression but also in terms of other physical comorbidities could improve the generalizability of antidepressant cost-effectiveness evaluation studies.

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