

Course and Cost of Treatment for Depression with Fluoxetine, Paroxetine, and Sertraline

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Abstract

Objective: To compare depression-related treatment costs and total healthcare costs for patients diagnosed with depression and treated with either sertraline, paroxetine, or fluoxetine.

Patients and Methods: Claims records from a national database of patients diagnosed with depression who began treatment with an SSRI in 1995, following an antidepressant medication-free period of at least 6 months, were included. Treatment course and associated depression-related treatment and total healthcare costs during the subsequent 12-month treatment period were examined using univariate and multivariate methods.

Results: Nine-hundred five (905) patients taking sertraline, 492 on paroxetine, and 945 on fluoxetine met inclusion criteria. The groups were similar and representative with respect to gender and age. Mean dose over the 12-month treatment period increased 24%, indicating significant titration in all cohorts. Patients treated with paroxetine had shorter treatment duration (157.0 days) than did patients treated with fluoxetine (192.6 days) or sertraline (166.9 days, $P < 0.001$). Patients receiving index treatment with paroxetine were most likely to switch to another SSRI (21.3%); those taking sertraline were second most likely to switch (16.1%); and those on fluoxetine were least likely (12.4%, $P = 0.001$). Mean costs for depression-related outpatient visits and hospital-

izations were similar. Mean antidepressant prescription costs differed, being \$586, \$419, and \$446 for fluoxetine, paroxetine and sertraline cohorts, respectively ($P < 0.001$). In this sample, the fluoxetine cohort did not have lower nonpharmaceutical healthcare costs to offset higher pharmaceutical acquisition costs. Conclusions from median and multivariate analyses were robust to these findings.

Conclusions: During this study period when fluoxetine, paroxetine, and sertraline were all well-established agents, similar depression-related treatment courses and cost characteristics among all 3 drugs were observed.

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Depression affects millions of individuals each year and is a serious debilitating illness with far-reaching economic consequences.¹ Greenberg et al estimate the 1990 annual costs in the United States at \$43.7 billion: \$12.4 billion as a result of direct costs for medical care and pharmaceuticals, and the remaining \$31.3 billion associated with productivity losses in the workplace and premature death from depression-related suicides.² The need for cost-effective treatments is strongly supported by the substantial costs associated with depressive illness.³⁻⁷

Table 1. Definitions of Terms as Used in This Study

Term	Definition
Antidepressant and other prescription costs	Total receipts to pharmacy = insurer payment + patient copay, coinsurance, and deductibles
Outpatient visit costs	Total payment to providers for outpatient professional services, including insurer payment, deductibles, coinsurance, co-pays, and laboratory costs
Hospitalization costs	Total payment to hospitals and providers for inpatient services, including insurer payment, deductibles, coinsurance, and co-pays
Total depression-related treatment costs	Outpatient, inpatient, and laboratory costs associated with a depression (ICD-9) diagnosis code (296.2, 296.3, 300.4, 311) and antidepressant pharmaceutical costs
Total healthcare costs	All outpatient, inpatient, laboratory, and pharmaceutical costs, irrespective of diagnosis, including depression-related treatment costs
Total daily dose	Total milligrams dispensed divided by days supply
Titration	Change in total daily dose from previous prescription by more than 5%
Index prescription	First prescription with fluoxetine, paroxetine, or sertraline from January 1 through December 31, 1995, after 6-month antidepressant-free period
Pretreatment period	6-month period prior to date of index (first) SSRI prescription
Treatment period	12-month period following date of index SSRI prescription
Treatment duration	$(\text{Date}_{\text{Final Rx in Treatment Period}} - \text{date}_{\text{Index Rx}}) + \text{days supply}_{\text{Final Rx}}$
Switching	Change to another SSRI antidepressant from the index SSRI in the 12-month treatment period
Early discontinuation	Patients who received a total of no more than 60 days of antidepressant therapy with index SSRI during the 12-month treatment period
Augmentation	Patients who received another antidepressant in addition to index SSRI during the 12-month treatment period

SSRI= Selective serotonin reuptake inhibitor.

The development of selective serotonin reuptake inhibitors (SSRIs) represents a major advance in the treatment of depression.⁸⁻¹² There is a significant body of evidence that SSRIs are cost-effective treatments relative to tricyclic antidepressants (TCAs).^{7,13-36} The benefits of increased tolerability and associated increased compliance rates compared with TCAs typically outweigh the higher pharmaceutical acquisition costs associated with SSRIs.^{9-12,15,37-39}

Additional studies have been designed to evaluate and compare the direct healthcare expenditures for depressed patients who are prescribed fluoxetine, paroxetine, or sertraline. These compounds all have similar efficacy, compliance, and tolerability.^{12,13,40-45} Studies comparing the SSRIs with a focus on antidepressant pharmaceutical acquisition costs have generally concluded that paroxetine and sertraline are less costly than fluoxetine.⁴⁶⁻⁴⁸ In the only 6-month prospective, randomized, controlled, economic clinical trial comparing SSRIs published to date, fluoxetine patients utilized more medical resources.⁴³ However, it is not known whether this difference was statistically significant. Conversely, recent retrospective database analyses have reported that the higher acquisition costs for fluoxetine are more than offset by lower depression-related⁴⁹ or total healthcare expenditures.³⁷ In a comprehensive pharmacoeconomic review of fluoxetine, Wilde and Benfield stated that more evidence was needed before pharmacoeconomic conclusions could be made about the economic advantages of fluoxetine over other SSRIs.⁵⁰

Several previous retrospective medical claims studies have compared the SSRIs using data over a time period (1992 to 1994) when sertraline and paroxetine were newly approved agents. If the newer

agents were prescribed preferentially for refractory patients who required more intensive clinical management, then higher treatment costs would be expected to be associated with the clinical characteristics of the patient treated and not with the antidepressant chosen. Similar negative economic influences have been evaluated and confirmed for fluoxetine when it was a new antidepressant,¹⁷ so we hypothesize that these same factors would likely exist for sertraline and paroxetine when they were newly approved agents. This may bias cost estimates upward for sertraline and paroxetine. Therefore, previous cost estimates derived from a time period when sertraline and paroxetine were not well established should be interpreted with caution.⁵⁰

The present study was designed to compare treatment course, depression-related treatment costs, and total healthcare expenditures for patients diagnosed with depression who began treatment with one of the 3 SSRIs in 1995. A listing of terms used in this study is found in Table 1. We hypothesize that during a time period when all 3 SSRIs were well-established agents, depression disease management and total healthcare costs were similar for patients treated with these SSRIs.

portions of patients switching from the index SSRI to another SSRI. Depression-related and total healthcare expenditures included pharmaceutical acquisition costs, outpatient visit costs, hospitalization costs, and laboratory costs.

Data Analysis

Chi-square tests were conducted to determine whether differences among treatment groups existed for titration rates, SSRI switch rates, and monthly SSRI prescription expenditure rates. The independent *t*-test was used to assess differences among treatment groups for mean number of titrations and for average healthcare costs (depression-related and overall prescription, outpatient, inpatient, and total healthcare expenditures). The median test, a non-parametric test for the differences in location of the median between the SSRI treatment groups, was computed for each variable of interest. The number of observations above and below the median for the combined samples was computed, with the sum of the scores having an asymptotically normal distribution. Cochran-Mantel-Haenszel methods were used to determine if the proportion of antidepressant prescriptions requiring 2 or more tablets per day was different.

... METHODS ...

A publicly available fee-for-service medical claims database (MarketScan®) of more than 600,000 lives was used to estimate total and depression-related healthcare costs from 1995 and 1996. Records of 2342 patients diagnosed with depression who began treatment with an SSRI in 1995 were identified (Table 2). Treatment course and associated depression-related expenditures were examined for 6 months prior to and 12 months following initial antidepressant therapy with fluoxetine, paroxetine, or sertraline. Analysis of patients' treatment course included average antidepressant dose, titration rates for index SSRI, treatment duration, hospitalization rates, frequency of outpatient contacts, and the pro-

Table 2. Selection Criteria for Patient Population

Criteria	n
Age 18-65 and a prescription for an antidepressant in 1995	50,031
Treatment with fluoxetine, paroxetine, or sertraline and diagnosed with a depressive disorder (ICD-9 code of 296.2, 296.3, 300.4, 311.0) in 1995	9990
No antidepressant use in the 6-month period prior to date of the index (first) SSRI prescription	4410
Continuous enrollment for 6 months prior to the index SSRI prescription	3459
No prescriptions for antipsychotics, mood stabilizers, anticonvulsants, substance abuse agents, or Parkinsonian agents at any time	3087
No substance abuse diagnoses at any time	3072
Continuous enrollment in the healthcare plan for 12 months after the index SSRI prescription	2342

SSRI = Selective serotonin reuptake inhibitor.

With the logarithm of costs as the dependent variable, linear multiple regression was employed to determine whether any of the following factors were significant predictors of total and depression-related healthcare costs: patient age, gender, number of general comorbid medical conditions, logarithm of 6-month pretreatment depression-related costs, index treatment by a psychiatrist, and index SSRI prescribed (fluoxetine, paroxetine, sertraline). Based on these estimated models, predicted values of log costs were computed and evaluated at the sample means of explanatory variables pooled across the 3 drugs.

The SAS system for Windows, version 6.12, (Cary, NC) was used to perform all statistical analysis.

... RESULTS ...

Treatment Course Characteristics

Nine-hundred five (905) patients taking sertraline, 492 on paroxetine, and 945 on fluoxetine met inclusion criteria. Table 3 presents the demographic characteristics, type of provider that initiated antidepressant treatment, and type of health plan coverage for patients who met the selection criteria. Patient groups were similar with respect to gender, age distribution, health plan type, and provider type at time of index prescription. The majority of patients were female, the mean age was 41 years, most had traditional fee-for-service health plans, and the provider at index prescription was predom-

inantly a nonpsychiatrist.

The patients who were prescribed sertraline at index had higher 6-month pretreatment depression-related costs and were more likely to have been hospitalized for depression during this time. Seven patients (0.7%) on fluoxetine, 7 (1.4%) on paroxetine, and 23 (2.5%) on sertraline were hospitalized for depression in the 6-month pre-index treatment period in this sample. A previous report suggests that these higher depression-related pretreatment period costs may predispose this group of patients to higher costs during the treatment period.⁵¹

On average, patients had 6.8 depression-related outpatient visits with an average cost of \$117 per visit. Slightly more than 2% of patients were hospitalized for depression with a median length of stay of 5 days for patients on fluoxetine or sertraline, and 6 days for those on paroxetine at an average cost of \$1126 per hospital day. Supplemental antidepressants to augment treatment were used in 17.5%, 20.5%, and 16.9% of patients on fluoxetine, paroxetine, and sertraline, respectively. Patients treated with paroxetine had shorter treatment duration (157.0 days) than did patients treated with fluoxetine (192.6 days) or sertraline (166.9 days, $P < 0.001$). Patients receiving index treatment with paroxetine were most likely to switch to another SSRI (21.3%). Those on sertraline were second most likely to switch (16.1%), and those on fluoxetine were least likely to do so (12.4%, $P = 0.001$).

The mean antidepressant dose at index was 21.4 mg, 21.6 mg, and 63.7 mg for fluoxetine, paroxetine, and sertraline, respectively. At the last observation during the treatment period, the mean dose had changed to 26.2 mg, 24.9 mg, and 85.2 mg for fluoxetine, paroxetine, and sertraline, respectively, demonstrating a significant amount of titration in each cohort.

The percent of individuals titrated was 43.5%, 35.6%, and 47.5% for fluoxetine, paroxetine, and sertraline, respectively ($P = 0.001$) (Figure 1).

Table 3. Demographic Characteristics, Index Provider Type, and Health Plan Type

	Fluoxetine (n = 945)	Paroxetine (n = 492)	Sertraline (n = 905)	P value
Age (standard deviation)	41.3 (11.3)	41.7 (12.0)	41.6 (11.2)	0.498
% Female	70.3%	67.3%	69.6%	0.498
Provider at index				0.129
Psychiatrist	34.7%	30.5%	31.3%	
Nonpsychiatrist	65.3%	69.5%	68.7%	
Type of health plan				0.313
Basic major medical	17.2%	17.9%	19.7%	
Comprehensive	62.9%	63.0%	62.0%	
Point of service	3.9%	4.5%	5.1%	
Preferred provider	9.5%	9.8%	7.1%	
Unknown	6.5%	4.9%	6.2%	

Fluoxetine and sertraline had similar titration rates. Of those patients whose medications were titrated, the mean number of titrations was 1.8, 1.6, and 1.7 ($P = 0.049$) in the fluoxetine, paroxetine, and sertraline cohorts, respectively.

Pharmaceutical Acquisition Costs

Total antidepressant prescription costs were significantly higher for fluoxetine than for paroxetine or sertraline ($P < 0.001$). The mean index SSRI costs were \$514, \$304, and \$370 and mean total antidepressant prescription costs, including additional antidepressant augmentation treatments, were \$586, \$419, and \$446 for fluoxetine, paroxetine, and sertraline cohorts, respectively.

The fluoxetine cohort had the highest proportion of antidepressant prescriptions requiring 2 or more tablets/capsules per day (Figure 2). Sertraline and paroxetine are available in formulations up to twice the recommended initial dose at approximately the same acquisition cost, but this is not the case for fluoxetine. The drug acquisition cost for patients taking 30 mg or more of fluoxetine per day is about double that of patients taking 20 mg per day.

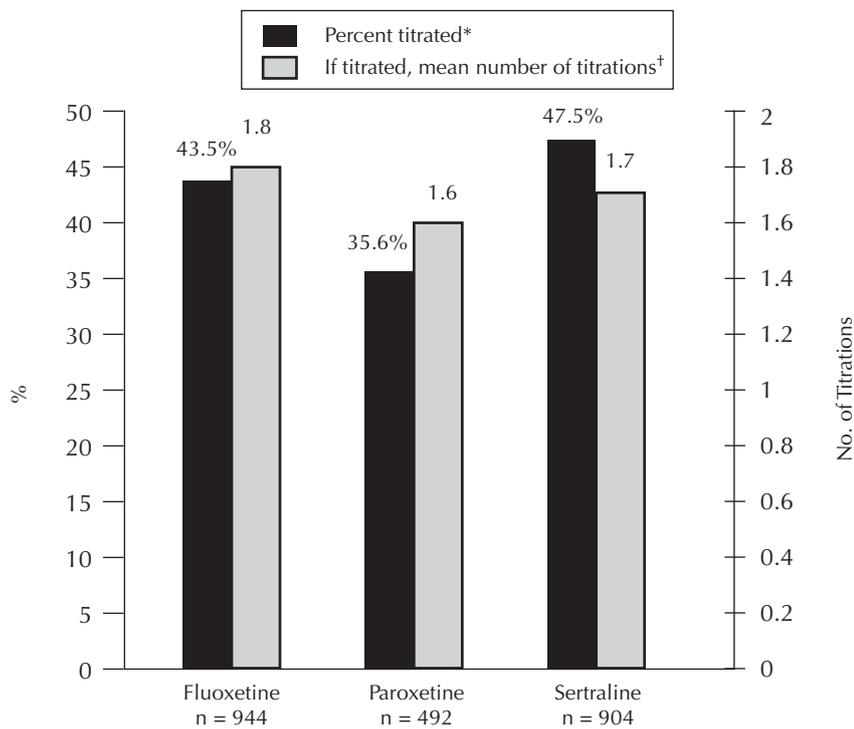
Total Depression-Related Treatment Costs

In the 12-month treatment period, average total costs for depression-related outpatient visits were \$640 for fluoxetine, \$685 for paroxetine, and \$630 for sertraline cohorts ($P = 0.605$) (Table 4). Of the 2342 patients who met inclusion criteria, only 53 were hospitalized for depression; of those the mean hospitalization costs (standard deviation) were \$7525

(\$10,123) for fluoxetine, \$5733 (\$6209) for paroxetine, and \$5220 (\$3658) for sertraline. These differences were not statistically significant. Laboratory costs were negligible in all groups.

Mean depression-related outpatient and hospitalization costs did not differ significantly among the different cohorts when pharmaceutical costs were excluded, being \$799.20, \$812.90, and \$756.80 ($P = 0.816$) for fluoxetine, paroxetine, and sertraline, respectively. However, when antidepressant acquisition costs were included, total depression-related treatment costs for the 12-month treatment period were different. Fluoxetine was highest at \$1385, paroxetine at \$1231, and sertraline at \$1203 (fluoxetine vs paroxetine, $P = 0.141$; fluoxetine vs sertraline, $P = 0.037$).

Figure 1. Titration Rates for Index SSRIs



*Fluoxetine vs paroxetine $P = 0.004$; fluoxetine vs sertraline $P = 0.084$; paroxetine vs sertraline; $P = 0.001$.

†Fluoxetine vs paroxetine $P = 0.021$; fluoxetine vs sertraline $P = 0.092$; paroxetine vs sertraline $P = 0.305$.

One individual in both the fluoxetine and sertraline groups did not have daily dose information.

Figure 2. Proportion of Antidepressant Prescriptions Requiring 2 or More Tablets/Capsules per Day During a 12-Month Treatment Period

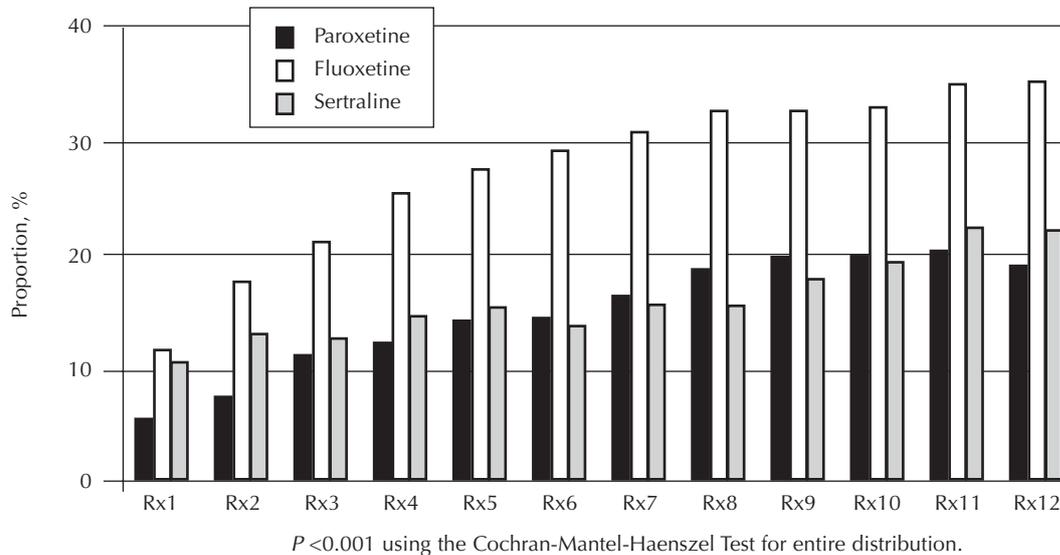


Table 4. Depression-Related and Total Healthcare Costs

Types of Costs	Healthcare Costs (US \$)			Statistical Significance* P Values for Comparison of		
	Fluoxetine (n = 945)	Paroxetine (n = 492)	Sertraline (n = 905)	Fluoxetine vs Paroxetine	Fluoxetine vs Sertraline	Paroxetine vs Sertraline
Depression-related healthcare costs						
Mean cost (standard deviation)						
Pharmaceutical	586.1 (429.6)	418.5 (319.7)	446.3 (341.6)	<0.001	<0.001	0.187
Outpatient/laboratory	639.9 (1007)	684.7 (994.6)	629.9 (994.8)	0.420	0.831	0.328
Hospitalization	159.3 (1799)	128.2 (1227)	126.9 (978.7)	0.692	0.622	0.987
Total	1385 (2221)	1231 (1690)	1203 (1555)	0.140	0.037	0.788
Median cost [†]						
Pharmaceutical	542.7	371.2	392.1	<0.001	<0.001	0.381
Outpatient/laboratory	224	248.5	210	0.260	0.217	0.053
Total	868.1	692.6	735.3	<0.001	<0.001	0.323
Total healthcare costs						
Mean cost (standard deviation)						
Pharmaceutical	1166 (893.7)	1045 (1014.0)	1015 (856.0)	0.016	<0.001	0.562
Outpatient/laboratory	2468 (2919)	2486 (2567)	2528 (3491)	0.918	0.680	0.810
Hospitalization	1046 (9988)	555.5 (2483)	832.4 (3807)	0.199	0.504	0.472
Total	4680 (10,925)	4086 (4721)	4375 (6400)	0.197	0.429	0.534
Median cost [†]						
Pharmaceutical	952	786	799	0.004	<0.001	0.927
Outpatient laboratory	1578	1711	1664	0.564	0.484	0.807
Total	2739	2721	2659	0.927	0.429	0.562

*Statistically significant P values are in bold print.

[†]Since 97.7% of sample was not hospitalized, median hospitalization cost is equal to 0 and not reported here.

Median depression-related outpatient costs were similar for all cohorts. Median pharmaceutical ($P < 0.001$) and total depression-related treatment costs ($P < 0.001$) were highest for the fluoxetine cohort. These higher depression-related treatment costs for the fluoxetine cohort were a direct result of higher pharmaceutical acquisition costs as a result of a higher proportion of fluoxetine patients requiring 2 or more tablets/capsules per day.

Total Healthcare Costs

There were no significant differences in mean or median outpatient and hospitalization costs among the different cohorts. In this sample, the longer treatment duration and lower switch rates in the fluoxetine group did not result in a reduction of total healthcare costs to offset the higher pharmaceutical acquisition costs.

Multivariate Estimates of Healthcare Costs

Multivariate models similar to those used previously were used to control for potential confounds such as age, gender, medical comorbidity, provider type, and pretreatment depression-related healthcare expenditures (Tables 5 and 6). In these models, total depression-related treatment cost estimates were lower for those individuals who began treatment with sertraline ($P < 0.001$) or paroxetine ($P = 0.002$). The model estimates are also very similar to the observed median values reported in Table 4. No significant difference was observed for estimates of total healthcare costs.

... DISCUSSION ...

A major finding of this study is that similar treatment course and depression-related nonpharmaceutical healthcare costs were observed irrespective of the index SSRI chosen. The only difference observed was the higher pharmaceutical acquisition costs for fluoxetine; similar results have been reported and reviewed elsewhere.^{46-48,52} These findings directly contradict previous retrospective medical claims analyses that have reported lower depression-related healthcare costs⁴⁹ and total healthcare costs³⁷ for patients treated with fluoxetine.

A possible reason for this contradiction is the different study time period between this investigation and the previously reported retrospective analyses. Hylan et al³⁷ and Sclar et al⁴⁹ utilized claims data from 1990 to 1994 and 1989 to 1994, respectively, when sertraline and paroxetine were unapproved or newly approved antidepressants. Physicians were unable to choose from the 3 agents during the beginning of these study periods and may have had inadequate experience using the newer agents during the later part of these time periods. This may have increased the likelihood of the use of paroxetine or sertraline in patients whose depression was refractory to treatment. Sclar et al report potential differences in disease severity when they report mean hospital costs in Table 1 of their article.⁴⁹ Patients in the paroxetine and sertraline cohorts had statistically different mean hospital costs that were 6.8 and 6.3 times greater, respectively, than those of the fluox-

Table 5. Log Linear Multiple Regression Estimated Costs

	Fluoxetine (n = 945)		Paroxetine (n = 492)		Sertraline (n = 905)	
	Total	Depression-Related	Total	Depression-Related	Total	Depression-Related
Model estimated costs	2816.9*	835.5 [†]	2681.6*	704.1 [†]	2608.7*	700.5 [†]

*Ln (Total cost) = $y + \beta_1$ (paroxetine) + β_2 (sertraline) + β_3 (age) + β_4 (gender) + β_5 (# of comorbid medical conditions) + β_6 (provider type) + β_7 (ln of pretreatment costs); $R^2 = 0.3514$.

[†]Ln (Depression-related cost) = $y + \beta_1$ (paroxetine) + β_2 (sertraline) + β_3 (age) + β_4 (gender) + β_5 (# of comorbid medical conditions) + β_6 (provider type) + β_7 (ln of pretreatment costs); $R^2 = 0.150$.

Note: See Table 6 for parameter estimates and statistical significance.

etine cohort. If there were differences in disease severity among the cohorts in this study, this would have affected other economic measurements of depression-related treatment, as well.

Another potential explanation for the differences in findings between our study and previous studies is dosage titration. A need for dosage titration, often found with SSRIs, may correlate with increased depression-related healthcare expenditures.⁵¹ In our study the likelihood of patients having their medication titrated was 43.5%, 35.6%, and 47.5% for fluoxetine, paroxetine, and sertraline, respectively. Sclar et al⁴⁹ found that patients on paroxetine or sertraline had more dosage titrations (28.1% and 40.3%, respectively) than did patients prescribed fluoxetine (16.1%). Our study, based on more recent data, does not support the finding that fluoxetine is less likely to be titrated than the other SSRIs.

Like other retrospective analyses,^{30,32,49} our study confirms that most antidepressant treatment with SSRIs is provided in the primary care setting. Paroxetine and sertraline are more likely to be prescribed by primary care physicians than fluoxetine ($P = 0.129$; Table 3). Since treatment by a psychiatrist is more expensive, this difference was evaluated and controlled for in our multivariate models and did not account for the difference observed in depression-related treatment costs for the fluoxetine cohort.

A limitation of this study is a lack of information on disease severity and clinical outcome. As with any retrospective claims analysis or cost-identification

study, disease severity and clinical outcomes are not known. Cost-identification studies should only be used when compounds have well-established and similar efficacy in the condition under study. This and other studies like it must rely on careful study design, replication, and multiple regression techniques to control for biases that may result from known confounds and factors. We have reported these results in Tables 5 and 6. However, there may be unobserved or unknown factors that may bias the results. These factors include, but are not limited to, baseline disease severity, clinical outcome, physicians' previous treatment experiences and prescribing preferences, patient preferences, and market forces.¹⁷ As with any retrospective analysis, an inability to randomly assign individuals to a treatment condition and to measure the effect of unknown factors are limitations of this study and others like it.

It would be useful to examine further the total depression-related treatment costs for each SSRI cohort using other sources of data and even more recent data to determine if the outcome of these analyses can be replicated. Further study may elucidate whether other factors not yet identified are contributing to the differences and similarities observed in this study.

... CONCLUSION ...

Similar treatment course, nonpharmaceutical depression-related treatment costs, and total healthcare

Table 6. Log Linear Multiple Regression Parameter Estimates and Statistical Significance

	Total Costs		Depression-Related Costs	
	Parameter Estimates/B	P value	Parameter Estimates/B	P value
Intercept	6.759	<0.001	6.459	<0.001
Paroxetine	-0.049	0.260	-0.170	0.002
Sertraline	-0.076	0.036	-0.174	<0.001
Age	0.005	<0.001	-0.002	0.237
Gender	-0.112	0.002	-0.040	0.375
# of comorbid medical conditions	0.206	<0.001	0.031	<0.001
Psychiatrist	0.300	<0.001	0.794	<0.001
Ln of pretreatment costs	0.002	0.436	0.010	<0.001

costs were observed irrespective of which SSRI was used to treat depression in this cohort of patients. Total depression-related treatment costs were highest for the fluoxetine group as a direct result of higher pharmaceutical costs associated with a greater proportion of patients requiring a daily dosage of 2 or more tablets/capsules.

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... REFERENCES ...

1. Greenberg PE, Stiglin LE, Finkelstein SN, et al. Depression: A neglected major illness. *J Clin Psychiatry* 1993;54:419-424.
2. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. *J Clin Psychiatry* 1993;54:405-418.
3. Gabbard GO. The cost effectiveness of treating depression. *Psychiatr Ann* 1998;28:98-101.
4. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* 1992;267:1478-1483.
5. Conti DJ, Burton WN. The economic impact of depression in a workplace. *JOM* 1994;36:983-988.
6. Lane R, McDonald G. Reducing the economic burden of depression. *Int Clin Psychopharmacol* 1994;9:229-243.
7. Jonsson B, Bebbington PE. What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment. *Br J Psychiatry* 1994;164:665-673.
8. Andrews JM, Nemeroff CB. Contemporary management of depression. *Am J Med* 1994;97:24S-32S.
9. Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. *Drug Safety* 1994;10:18-46.
10. Leonard BE. Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. *Drugs* 1992;43:3-10.
11. Leonard BE. The comparative pharmacology of new antidepressants. *J Clin Psychiatry* 1993;54:3-15.
12. Finley PR. Selective serotonin reuptake inhibitors: Pharmacologic profiles and potential therapeutic distinctions. *Ann Pharmacother* 1994;28:1359-1369.
13. Wilde MI, Whittington R. Paroxetine: A pharmacoeconomic evaluation of its use in depression. *PharmacoEconomics* 1995;8:62-81.
14. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care. *JAMA* 1996;275:1897-1902.
15. Simon GE, Fishman P. Cost implications of initial antidepressant selection in primary care. *PharmacoEconomics* 1998;13:61-70.
16. Forder J, Kavanagh S, Fenyo A. A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care. *J Affective Disord* 1996;38:97-111.
17. Crown WH, Hylan TR, Meneades L. Antidepressant selection and use and healthcare expenditures. *PharmacoEconomics* 1998;13:435-448.
18. Revicki DA, Palmer CS, Phillips SD, et al. Acute medical costs of fluoxetine versus tricyclic antidepressants: A prospective multicentre study of antidepressant drug overdoses. *PharmacoEconomics* 1997;11:48-55.
19. Freemantle N, House A, Song F, et al. Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. *Br Med J* 1994;309:249-253.
20. Song F, Freemantle N, Sheldon TA, et al. Selective serotonin reuptake inhibitors: Meta-analysis of efficacy and acceptability. *Br Med J* 1993;306:683-687.
21. Hotopf M, Lewis G, Normand C. Are SSRIs a cost-effective alternative to tricyclics? *Br J Psychiatry* 1996;168:404-409.
22. Le Pen C, Levy E, Ravily V, et al. The cost of treatment dropout in depression. A cost-benefit analysis of fluoxetine vs tricyclics. *J Affective Disord* 1994;31:1-18.
23. Stewart A. Antidepressant pharmacotherapy: Cost comparison of SSRIs and TCAs. *Br J Med Econ* 1994;7:67-79.
24. Bentkover JD, Feighner JP. Cost analysis of paroxetine versus imipramine in major depression. *PharmacoEconomics* 1995;8:223-232.
25. LaPierre Y, Bentkover J, Schainbaum S, et al. Direct cost of depression: Analysis of treatment costs of paroxetine versus imipramine in Canada. *Can J Psychiatry* 1995;40:370-377.
26. Hylan TR, Kotsanos JG, Andersen JS, et al. Comparison of a decision analytic model with results from a naturalistic economic clinical trial: An application to evaluating alternative antidepressants. *Am J Managed Care* 1996;2:1211-1223.
27. John DN, Wright T, Berti C. Is there an economic advantage in the use of SSRIs over TCAs in the treatment of depression? *J Serot Res* 1996;4:225-235.
28. Woods SW, Rizzo JA. Cost-effectiveness of antidepressant treatment reassessed. *Br J Psychiatry* 1997;170:257-263.
29. Hatzianandreu EJ, Brown RE, Revicki DA, et al. Cost utility of maintenance treatment of recurrent depression with sertraline versus episodic treatment with dothiepin. *PharmacoEconomics* 1994;5:249-264.
30. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: Economic outcomes in a health maintenance organization. *Clin Ther* 1994;16:715-730.
31. Sclar DA, Skaer TL, Robison LM, et al. Economic outcomes with antidepressant pharmacotherapy: A retrospective intent-to-treat analysis. *J Clin Psychiatry* 1998;59(suppl 2):13-17.
32. Skaer TL, Sclar DA, Robison LM, et al. Economic valuation of amitriptyline, desipramine, nortriptyline, and sertraline in the management of patients with depression. *Curr Ther Res* 1996;56:556-567.
33. Croghan TW, Lair TJ, Engelhart L, et al. Effect of antidepressant therapy on health care utilization and costs in primary care. *Psychiatr Serv* 1997;48:1420-1426.
34. Hylan TR, Crown WH, Meneades L, et al. SSRI and TCA antidepressant selection and health care costs: A multivariate analyses. *J Affective Disord* 1998;47:71-79.

35. Melton ST, Kirkwood CK, Farrar TW, et al. Economic evaluation of paroxetine and imipramine in depressed outpatients. *Psychopharmacol Bull* 1997;33:93-100.
36. Crown WH, Obenchain RL, Englehart L, et al. The application of sample selection models to outcomes research: The case of evaluating the effects of antidepressant therapy on resource utilization. *Stat Med* 1998;17:1943-1958.
37. Hylan TR, Crown WH, Meneades L, et al. Tricyclic antidepressant and selective serotonin reuptake inhibitors: Antidepressant selection and health care costs in the naturalistic setting: A multivariate analysis. *J Affective Disord* 1998;47:71-79.
38. Montgomery SA, Kasper S. Comparison of compliance between serotonin reuptake inhibitors and tricyclic antidepressants: A meta-analysis. *Int Clin Psychopharmacol* 1995;9:33-40.
39. Kasper S, Fuger J, Moller HJ. Comparative efficacy of antidepressants. *Drugs* 1992;43:11-23.
40. Tignol J. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. *J Clin Psychopharmacol* 1993;13:18S-22S.
41. DeWilde J, Spiers R, Mertens C, et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand* 1993;87:141-145.
42. Schone W, Ludwig M. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. *J Clin Psychopharmacol* 1993;13:34S-39S.
43. Boyer P, Danion JM, Bisslerbe JC, et al. Clinical and economic comparison of sertraline and fluoxetine in the treatment of depression. *Pharmacoeconomics* 1998;13:157-169.
44. Aguglia E, Casacchia M, Cassano GB, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. *Int Clin Psychopharmacol* 1993;8:197-202.
45. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. *J Clin Psychiatry* 1995;56:229-237.
46. Smith W, Sherrill A. A pharmacoeconomic study of the management of major depression: Patients in a TennCare HMO. *Med Interface* 1996;88-92.
47. Singletary T, North DS, Weiss M, et al. A cost-effective approach to the use of selective serotonin reuptake inhibitors in a veterans affairs medical center. *Am J Managed Care* 1997;3:125-129.
48. Viale GL. An economic analysis of physicians' prescribing of selective serotonin reuptake inhibitors. *Hosp Pharm* 1998;33:847-850.
49. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: Economic evaluation of fluoxetine, paroxetine and sertraline in a health maintenance organization. *J Int Med Res* 1995;23:395-412.
50. Wilde MI, Benfield P. Fluoxetine. A pharmacoeconomic review of its use in depression. *Pharmacoeconomics* 1998;13:543-561.
51. Thompson D, Buesching D, Gregor KJ, et al. Patterns of antidepressant use and their relation to costs of care. *Am J Managed Care* 1996;2:1239-1246.
52. Hylan TR, Buesching DP, Tollefson GD. Health economic evaluations of antidepressants: A review. *Depression Anxiety* 1998;7:53-64.