Duration of Therapy and Health Care Costs of Fluoxetine, Paroxetine, and Sertraline in 6 Health Plans

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Background: Previous studies comparing fluoxetine, paroxetine, and sertraline, the 3 most common selective serotonin reuptake inhibitors (SSRIs), in naturalistic settings have produced conflicting results. With this study, we provide new evidence as to the similarities and differences among these SSRI therapies with respect to the duration of use and health care costs.

Method: Data from 6 health maintenance organizations were used to identify patients with new-onset major depression, number of days with filled prescriptions, and total health care and depression-related costs. The sample consisted of 1771 patients given initial prescriptions for sertraline (N = 386), fluoxetine (N = 840), or paroxetine (N = 545) in the period from July 1, 1994, to March 31, 1997. Analyses included Cox proportional hazards models (for duration of initial therapy) and ordinary least squares regression (for cost).

Results: Patients who initiated therapy with fluoxetine were more likely to have a later interruption of therapy than patients who initiated therapy with sertraline (p = .03) and paroxetine (p = .001). Total 1-year costs did not differ statistically between the treatment groups, but 1-year depression-related costs were significantly lower for patients who initiated therapy with sertraline or paroxetine than for those who initiated therapy with fluoxetine ($332 less for sertraline, 95% confidence interval [CI] = $125 to $562; $339 less for paroxetine, 95% CI = $144 to $416).

Limitations: A limitation of this observational study, as well as of observational studies in general, is that unobserved characteristics of the patients may lead to biased estimates of the impact of treatment on adherence or cost, even with controls for observed characteristics.

Conclusion: We found no significant differences in total health care costs among the 3 SSRIs, but noted significant differences in depression-related costs (the costs of fluoxetine are greater than those of sertraline and paroxetine). Importantly, there was no relationship between treatment interruption and increased health care or depression-related costs, in contrast to the findings of some, but not all, prior studies.

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Major depressive disorders are highly prevalent[1] and have a serious social impact in terms of morbidity,[2–4] burden in the workplace,[5] and economic costs. These costs can be substantial both for the health care system[3,6–8] and for society.[6,9] One means available for reducing these costs is the adoption of cost-effective therapies. Sturm and Wells[10] have reported that one of the best strategies for making care for depression more cost-effective is through quality improvement, which includes appropriate use of antidepressant medications.

Antidepressant medications relieve the symptoms of depression,[11] improve social and employment functioning,[12,13] and reduce the disability caused by coexisting medical conditions.[14] The more recently developed selective serotonin reuptake inhibitors (SSRIs) have been shown to have increased tolerability, and thus increased compliance rates, compared with tricyclic antidepressants. They have also been shown to have equivalent or better clinical and economic outcomes[6,7,15–19] than tricyclics, although not all studies have been positive.[20] Given the variety of SSRIs on the market, information about the relative cost-effectiveness of different SSRIs will lead to more cost-effective delivery of treatment for depression.

Evidence from the randomized clinical trials that have made direct comparisons of SSRIs has shown that they have similar efficacy, compliance, and tolerability.[21–26] While such evidence is important early in the life of new pharmaceuticals, once the drugs have been marketed,

more may be learned by studying their use in naturalistic settings. First, the pattern of use of SSRIs in clinical practice can differ from that in controlled trials due to issues of convenience, tolerability, and the patient-provider relationship. Second, in naturalistic studies one is often able to observe patterns of use for substantially longer time periods than are available for most clinical trials. Third, the treatments used in randomized trials (and thus the cost of such treatments) may differ from those that would be used in the usual care of patients. Finally, the evidence from trials may not be generalizable to a managed care setting.

Naturalistic observational studies that have compared fluoxetine, paroxetine, and sertraline have evaluated the duration of SSRI use and health care costs. In these studies, the evidence of equivalence has been less clear cut than it has been in randomized trials. For example, while the few studies that have evaluated duration of therapy are not conclusive, they have generally found longer duration for patients initiating therapy with fluoxetine.[27–31] In addition, the observational studies that have analyzed differences in costs have found paroxetine and sertraline to have lower pharmaceutical acquisition costs than fluoxetine.[32–34] However, when other health care expenditures are included, some studies have found fluoxetine to be less expensive,[30,35] while others have found similar costs among the 3 therapies.[36] After a review of the evidence, Wilde and Benfield[37] concluded that more pharmacoeconomic evidence was needed.

Our objective, therefore, was to add to this body of evidence by specifically investigating the relative tolerability and costs associated with paroxetine, an interest of the pharmaceutical manufacturer that supported this study. We used data from 6 health maintenance organizations to compare adherence to therapy, depression-related costs, and total health care costs in the year after initiation of therapy with fluoxetine, paroxetine, and sertraline.

METHOD

Data Sources

Data were obtained from an administrative database maintained by Diversified Pharmaceutical Services, Inc, Bloomington, Minn. This database is a set of linked data sets, derived from claims records from 6 health plans, that represents approximately 2.6 million enrollees for the period from July 1, 1992, to March 31, 1998. Demographic characteristics of the prescribing physicians' practice locations (based on ZIP codes of the physicians' practices) were obtained from the 1990 U.S. Census.[38]

Study Sample

Study participants were identified from patients who started antidepressant pharmacotherapy with fluoxetine, paroxetine, or sertraline from July 1, 1994, to March 31, 1997. Data for patients initiating therapy before this period were not used because only a subset of the 3 SSRIs was available in this earlier period.

Patients were candidates for the study if they satisfied the entry criteria listed in Table 1. No minimum length of therapy with SSRIs was required for inclusion in the study (i.e., patients could discontinue therapy after their first prescription), nor was any limitation imposed on patients switching from one SSRI to another.

Table 1. Entry Criteria Used to Identify Study Candidates[a]

Claims record listed an ICD-9-CM diagnosis code of single-episode (296.2) or recurrent (296.3) major depression (referred to as the index diagnosis)
Aged 18 to 64 years at the time of the index diagnosis
Had no diagnosis of depression or prescriptions for SSRIs or other antidepressants in the 6 months before the index diagnosis (to ensure that the index episode represented a new episode of treatment)
Initiated therapy (ie, filled a prescription) with an SSRI within 30 days before or after the index diagnosis
Remained eligible for the health plan for 6 months before and 12 months after the date of the index diagnosis
Claims record did not include ICD-9-CM codes for dementia or other organic psychotic conditions (ICD-9-CM codes 290.xx and 310), schizophrenia (295.xx), delusional disorder (297), chronic psychotic disorders (298 and 299), bipolar spectrum disorders (296.0x, 296.1x, 296.4x to 296.9x, and 301.1x), substance-induced psychosis (acute) (291.x to 293.x), substance use disorders (chronic) (303.x to 305.x), or panic disorder (300.01). (This criterion was established to ensure a sample whose primary problem was mood disorder and who would therefore be expected to respond to SSRIs)

[a]Abbreviations: ICD-9-CM = *International Classification of Diseases*, Ninth Revision, Clinical Modification, SSRI = selective serotonin reuptake inhibitor.

Measurements

Patient characteristics. Demographic and clinical variables describing the patients were abstracted, including age, sex, whether the diagnosis of depression was for a single or recurrent episode, the date of the index diagnosis, whether the patient had used SSRIs in the period more than 6 months before the date of the index diagnosis, costs in the 6 months before the index diagnosis, the health plan in which the patient was enrolled, psychiatric comorbid conditions (personality disorders [*International Classification of Diseases*, Ninth Revision, Clinical Modification codes 301.xx, except 301.1x], dysthymia [300.4], other depressive disorders [311.xx], other chronic disorders [302.xx, 306.xx, 307.xx, 312.xx, and 316.xx], and other acute disorders [308.xx and 309.xx]), and nonpsychiatric comorbid conditions (summarized by using the Charlson comorbidity index[39]).

Physician characteristics. The specialty of the prescribing physician and the number of the physician's patients with a diagnosis of depression, a filled prescription for an SSRI, and a combination of a diagnosis of depression and a prescription for an SSRI were identified.

On the basis of the ZIP code of the prescribing physician, socioeconomic information about the community in which the physician practiced was also obtained. Abstracted data were the region of the country in which the physician practiced (and thus in which the patient lived), the distributions of age and educational levels of the population, the proportion of white persons, the median income, the percentage of the community receiving public assistance, and the proportion of the community who rented their housing. A prior study has indicated that these data may be a good proxy for individual-level data on socioeconomic status.[40]

Outcomes. The outcome measures of this study were the number of days during the year for which prescriptions were filled, the length of time (i.e., days for which prescriptions were filled) the patients received uninterrupted therapy with their initial SSRI, and total and depression-related health care costs during the year after the initiation of SSRI therapy.

Costs were determined from the expenditure profile of health services provided by the managed care organization. Total health care costs include all medical services recorded by the health plans. Depression-related costs include medical services rendered during visits associated with a primary *International Classification of Diseases*, Ninth Revision, Clinical Modification code for depression (296.2 or 296.3). All costs are expressed in 1997 U.S. dollars; the medical care component of the consumer price index was used to adjust costs to a common year.[41]

Analysis

Characteristics of patients and physicians by SSRI. We report means and standard deviations (for continuous variables) and proportions (for categorical variables) for the characteristics of patients and physicians separately for each of the 3 SSRIs. Differences among these characteristics for the 3 drugs were assessed by using 1-way analysis of variance (for continuous variables) and chi-square tests (for categorical variables).

Because these tests treat each characteristic as if it were independent of the others, differences in characteristics of those receiving the different SSRIs were reassessed using logistic regression. Three regression models were used, 1 each comparing the characteristics of those who received sertraline versus fluoxetine, sertraline versus paroxetine, and fluoxetine versus paroxetine.

Time on therapy. We report the proportions of patients who used the SSRIs, stratified by their initial SSRI prescription. We also report the mean number of days for which prescriptions were filled during the year after initiation of therapy and the proportion of patients who switched SSRIs. A Cox proportional hazards model was used to predict time to first interruption of therapy. An interruption was defined as a 30-day lapse in prescriptions for the initial SSRI. Explanatory variables were patient and physician characteristics.

Health care costs. We report the mean, median, and standard deviation of all health care costs and depression-related costs. We also report these statistics for costs of office visits, hospitalization, SSRIs, other drugs, emergency department visits, and laboratory and x-ray services. Because the cost data are skewed, we report the mean, median, and standard deviation of the log of costs. Statistical differences in costs among the SSRIs were tested for using Student t tests; multivariable ordinary least squares regression was used to predict differences in the log of costs. We report differences among the SSRIs in their predicted costs (rather than predicted log of costs) and 95% confidence intervals (CIs) around the differences. To avoid potential biases in estimating predicted costs from the predicted log of costs, a smearing procedure for this transformation was used.[42] As with the prior multivariable analyses, explanatory variables were patient and physician characteristics.

RESULTS

Study Sample

A total of 63,985 patients with diagnoses of major depression were identified, and 78,545 patients had prescriptions for 1 of the 3 SSRIs; 13,053 had both a diagnosis of major depression and a prescription for an SSRI. Of these 13,053 patients, 7435 were excluded because of prior therapy for major depression within 6 months of the date of the index diagnosis, 3216 were excluded because they were not continuously enrolled in their health plan for 6 months before and 12 months after the diagnosis of major depression, and 631 were excluded because of conflicting or confounding secondary diagnoses. Thus, our final sample consisted of 1771 patients with initial prescriptions for sertraline (N = 386), fluoxetine (N = 840), or paroxetine (N = 545).

Characteristics of Patients and Physicians by SSRI

Tables 2A and 2B show characteristics of the patients and physicians, stratified by initial SSRI prescription. Significant differences among the SSRIs were observed in the proportion of patients with a diagnosis of a single episode of depression (p = .02), proportion of patients with dysthymia (p = .04) and other acute psychiatric disorders (p = .04), use of SSRIs in the period more than 6 months before the date of the index diagnosis (p = .001), number of days of SSRI use more than 6 months before the date of the index diagnosis (p = .003), health plans in which the patients were enrolled (p = .001), date of the index diagnosis (p = .001), region of the country in which patients were treated (p = .001), number of comorbid conditions (p = .03), and 3 characteristics of the location in which the physicians practiced: the median income (p = .006), the proportion of residents receiving public assistance (p = .001), and the proportion of renters (p = .02).

Table 2A. Characteristics of the Study Sample[a]

Variable	Sertraline	Fluoxetine	Paroxetine	p Value
Patients, N	386	840	545	
Physicians, N	167	356	247	
Age, %				.15
18–24 years	8.6	11.0	9.4	
25–34 years	29.3	28.8	26.8	
35–44 years	33.2	36.6	36.0	
45–54 years	23.1	19.9	20.7	
55–64 years	6.0	3.8	7.2	
Women, %	69.4	73.7	71.7	.29
Major depression, single episode, %	60.6	55.5	62.6	.02
Psychiatric comorbid conditions, %				
Personality disorders	1.8	2.0	1.5	.75
Dysthymia	14.0	17.7	13.0	.04
Other depressive disorders	21.2	17.9	17.1	.24
Other chronic disorders	27.7	31.0	33.0	.23
Other acute disorders	24.4	20.6	26.4	.04
Any prior use of an SSRI, %	0.5	3.5	1.3	.001
Patient is subscriber to health plan, %	63.7	61.7	63.9	.65
Prescriber specialty, %				.86
Psychiatry	37.6	35.7	36.2	
Family practice	7.8	10.2	9.2	
Internal medicine	1.6	1.9	2.2	
Other	53.1	52.1	52.5	
Health plan, %				.001
1	3.6	8.3	9.5	
2	1.8	1.4	0.9	
3	71.5	46.2	39.5	
4	9.1	21.4	25.9	
5	6.2	9.2	9.0	
6	7.8	13.5	15.2	
Date of index diagnosis, %				.001
Months 1–6	17.8	16.1	8.6	
Months 7–12	15.8	16.2	13.4	
Months 13–18	19.2	20.5	24.4	
Months 19–24	20.0	17.1	20.0	
Months 25–30	18.4	19.3	20.0	
Months 31–33	8.8	10.8	13.6	
Region of United States, %				.001
Midwest	78.2	58.9	53.6	
Mountain	6.2	9.2	8.6	
New England	9.1	21.1	25.7	
South	6.5	10.8	12.1	

[a]p Values derived from chi-square tests. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

The logistic regressions used to assess differences in characteristics between the drugs indicated that fluoxetine was significantly less likely than sertraline (p = .005) or paroxetine (p = .003) to be prescribed among patients who were older, and it was significantly more likely to be prescribed among patients who had previously received therapy with SSRIs (p = .003 vs. sertraline and p = .05 vs. paroxetine). Sertraline was significantly less likely than fluoxetine (p = .03) or paroxetine (p = .001) to be prescribed among those for whom drug costs made up a high proportion of prior costs. Paroxetine was significantly more likely than fluoxetine (p = .001) to be prescribed among patients who experienced other acute psychiatric comorbid conditions.

Fluoxetine and paroxetine were prescribed in similar proportions across the 6 health plans, whereas sertraline was used significantly more frequently in health plan 3 (p = .0001 vs. both fluoxetine and paroxetine) and significantly less frequently in health plan 4 (p = .05 vs. fluoxetine and p = .002 vs. paroxetine). Evidence also suggested that prescribing patterns were significantly associated with characteristics of the community in which the physician practiced.

Time on Therapy

Patients who initiated therapy with fluoxetine filled prescriptions for the most days (fluoxetine prescriptions were filled for a mean of 201 days); those who initiated therapy with paroxetine filled prescriptions for the fewest days (paroxetine prescriptions were filled for a mean of 157 days) (Table 3). The proportions of patients who switched therapy with SSRIs were 12.5%, 18.1%, and

Table 2B. Characteristics of the Study Sample: Mean ± SD Values[a]

	Sertraline		Fluoxetine		Paroxetine		
Variable	Mean	SD	Mean	SD	Mean	SD	p Value
Age, y	38.4	10.1	37.3	9.6	38.3	10.4	.11
Charlson comorbidity index	0.15	0.54	0.20	0.75	0.26	0.82	.09
No. of comorbid conditions	0.12	0.38	0.12	0.35	0.18	0.44	.03
Days of prior SSRI use	1.32	18.4	5.76	38.6	0.99	11.8	.003
Days of prior data availability	395	269	417	269	431	271	.14
Costs before the index date, $							
Total	1576	3604	1368	3323	1671	3976	.28
Office visits	753	1596	710	2348	804	2713	.75
Emergency department	43	178	40	165	52	229	.47
Inpatient	438	2439	238	1634	389	2157	.18
Drugs	327	911	363	677	412	911	.27
Laboratory/x-ray	15	98	17	67	13	49	.60
Physician characteristics							
Patients with major depression diagnosis	86	412	61	190	58	246	.52
Patients with SSRI prescriptions	89	194	99	182	77	138	.30
Patients with SSRI prescriptions and major depression diagnosis	38	169	28	67	20	59	.20
Patients in study	2	5	2	4	2	3	.72
Location characteristics							
Age, %							
< 30 years	38.6	18.2	40.3	16.2	39.8	15.2	.22
30–64 years	47.3	14.0	46.1	12.4	46.4	11.7	.30
65+ years	14.1	6.0	13.6	5.8	13.8	5.7	.31
Education, %							
Less than high school	15.9	8.6	17.2	9.4	17.0	9.2	.06
High school	31.1	12.3	29.9	11.4	29.5	11.2	.10
Some college	28.4	4.9	27.6	5.8	27.4	5.8	.02
College	24.6	17.4	25.3	17.2	26.0	16.7	.43
White, %	87.8	13.4	88.4	14.3	88.6	15.5	.67
Urban area, %	91.0	26.4	89.7	27.8	88.4	29.0	.38
Median income (in $1000s)	29.5	16.7	32.4	16.7	32.6	15.3	.006
% of community receiving public assistance	9.3	8.0	8.1	7.2	7.5	6.9	.001
% of community renting their housing	49.3	30.1	45.6	27.8	44.3	26.4	.02

[a]p Values derived from 1-way analysis of variance. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

19.4% for those who initiated therapy with fluoxetine, paroxetine, and sertraline, respectively. These differences were statistically significant ($p < .001$).

The results from the Cox proportional hazards model that predicted time to first interruption of therapy indicated that after controlling for other variables, patients who initiated therapy with fluoxetine were least likely to experience an interruption (hazard ratio for interruption, 0.79 compared with sertraline, $p = .001$). Those who initiated therapy with paroxetine were most likely to experience one (hazard ratio for an interruption, 1.18 compared with sertraline, $p = .03$).

Other variables in the regression that were found to be predictors of greater adherence to therapy were older age, a diagnosis of a recurrent episode of major depression, the patient's health plan, a prescription by a family practitioner (as compared with physicians other than internists and psychiatrists), earlier initiation of therapy (as represented by the date of the index diagnosis), and the number of patients in the physicians' practices with a diagnosis of major depression (data not shown).

Health Care Costs

Tables 4 and 5 show summary statistics by treatment group of total health care costs and depression-related costs, respectively. Mean total costs were $5358 for patients who initiated sertraline therapy, $4313 for those who initiated fluoxetine therapy, and $4224 for those who initiated paroxetine therapy. While the costs of sertraline are higher than for the other 2 therapies, the differences are not statistically significant. For median total costs, on the other hand, patients who initiated sertraline therapy

Table 3. SSRIs Used During the 12 Months Following Initiation of Treatment[a]

	Sertraline		Fluoxetine		Paroxetine		
Initial SSRI	% Who Used	Mean Number of Days in Year on Therapy	% Who Used	Mean Number of Days in Year on Therapy	% Who Used	Mean Number of Days in Year on Therapy	Total Days in Year on Therapy
Sertraline	100.0	181	10.1	21	9.3	30	232
Fluoxetine	4.2	22	100.0	201	8.3	27	250
Paroxetine	6.4	26	11.7	28	100.0	157	211

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 4. Total Health Care Costs During the 12 Months After the Index Diagnosis[a]

	Sertraline			Fluoxetine			Paroxetine		
Cost Variable	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
Total, $	5358	2261	19188	4313	2514	8463	4224	2480	6037
Office visits, $	2467	906	7855	2031	944	7153	1841	1048	2776
Hospital, $	1584	0	13088	593	0	2836	921	0	3660
SSRI, $	611	406	653	935	601	1032	551	336	655
Other drugs, $	583	269	946	619	251	1142	760	333	1841
Emergency department, $	96	0	279	105	0	304	111	0	345
Laboratory/x-ray, $	18	0	51	31	0	130	39	0	133
Log, total costs	7.77	7.72	3.02	7.87	7.83	0.92	7.86	7.82	0.95

[a]p Values for statistical tests (t tests) of differences in costs between the drugs are as follows: sertraline vs. fluoxetine, p = .31; sertraline vs. paroxetine, p = .26; fluoxetine vs. paroxetine, p = .82. Slight variation between sum of costs and total cost due to rounding. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 5. Depression-Related Health Care Costs During the 12 Months After the Index Diagnosis[a]

	Sertraline			Fluoxetine			Paroxetine		
Cost Variable	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
Total, $	1727	1281	1656	2127	1531	2063	1832	1343	2132
Office visits, $	406	281	458	465	299	592	416	277	458
Hospital, $	123	0	943	107	0	743	103	0	578
SSRI, $	611	406	653	935	601	1032	551	336	655
Other drugs, $	583	269	946	619	251	1142	760	333	1841
Emergency department, $	3	0	34	2	0	28	1	0	13
Laboratory/x-ray, $	1	0	9	0	0	5	0	0	3
Log, total costs	7.10	7.16	0.86	7.29	7.33	0.90	7.13	7.20	0.89

[a]p Values for statistical tests (t tests) of differences in costs between the drugs are as follows: sertraline vs. fluoxetine, p = .0003; sertraline vs. paroxetine, p = .40; fluoxetine vs. paroxetine, p = .01. Slight variation between sum of costs and total cost due to rounding. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

had lower costs than those who initiated fluoxetine or paroxetine therapy. The final row of Table 4 displays log of total costs. The means of logs show lower log costs for sertraline than for the other 2 therapies, which is more similar to the results for median costs than mean costs.

Mean depression-related costs were $1727, $2127, and $1832 for patients who initiated sertraline, fluoxetine, and paroxetine therapy, respectively. Patients who initiated therapy with either sertraline or paroxetine had significantly lower depression-related costs than those who initiated therapy with fluoxetine (p = .0003 and p = .01). Depression-related costs for those who initiated therapy with sertraline versus paroxetine did not differ significantly (p = .40).

Table 6 shows the predicted differences in costs among the 3 SSRIs on the basis of the results of ordinary least squares regressions that predicted the log of total health care costs and of depression-related costs while controlling for other predictors of the cost of care. The coefficients for the independent variables are not shown, but these variables include all variables listed in Tables 2A and 2B. As with the univariate results, the CIs for the differences indicated that total costs did not significantly differ among patients who initiated therapy with the 3 SSRIs. Also as with the univariate results, patients who initiated therapy with either sertraline or paroxetine had significantly lower depression-related costs (p < .05) than those who initiated therapy with fluoxetine ($332 less for sertraline, 95% CI = $125 to $562; $339 less for paroxetine, 95% CI = $144 to $416).

Other explanatory variables that were included in the regressions and found to significantly predict costs (p < .05) were the age of the patient, a diagnosis of single-episode major depression, psychiatric comorbid con-

Table 6. Predicted Difference in Mean Costs Between Therapies: Results From a Multivariable Analysis[a]

	All Costs		Depression-Related Costs	
Drug Comparison	Difference in Means	95% CI	Difference in Means	95% CI
Fluoxetine–Sertraline	410	–41 to 912	332	125 to 562
Paroxetine–Sertraline	141	–316 to 654	–7	–196 to 204
Paroxetine–Fluoxetine	–269	–643 to 128	–339	–416 to –144

[a]Abbreviation: CI = confidence interval.

ditions, the comorbidity index, the costs in the 6 months before the index diagnosis, physician specialty, the number of patients with a diagnosis of major depression in the physicians' practices, and the health plan in which the patient was enrolled.

DISCUSSION

We used data from 6 health plans to evaluate factors associated with duration of SSRI therapy and factors associated with health care costs in the year after the index diagnosis.

The results of our analysis of interruption of therapy indicated that patients who initiated therapy with paroxetine were more likely to discontinue therapy than were patients who initiated therapy with fluoxetine. This finding is not consistent with the sponsor's initial hypothesis.

The finding of greater adherence to fluoxetine was confirmed by a study by Hylan and colleagues,[31] who reported that compared with fluoxetine treatment, the odds ratio for "continuous" therapy was 0.45 (95% CI = 0.33 to 0.62) for patients who began therapy with sertraline and 0.62 (95% CI = 0.40 to 0.94) for those who began therapy with paroxetine. The lengths of therapy in our study also did not substantially differ from those reported by Russell and colleagues,[36] which were as follows: 166.9 days of sertraline for patients who initiated this therapy, with 16.1% of patients switching therapy; 192.6 days of fluoxetine, with 12.4% switching; and 157.0 days of paroxetine, with 21.3% switching ($p = .001$). Other studies[27,43] have also reported differences in therapy duration and rates of switching and augmentation among the different SSRIs.

In our analysis of costs, we found that 1-year total costs did not differ statistically between the treatment groups, but 1-year depression-related costs were significantly lower for patients who initiated therapy with sertraline and paroxetine than for those who initiated therapy with fluoxetine. These findings were generally similar to those of Russell and colleagues.[36] They found that depression-related costs were lower for patients who initiated therapy with sertraline and paroxetine than they were for patients who initiated therapy with fluoxetine, and that total health care costs did not differ among the 3 SSRIs (based on nonparametric statistical tests).[36] Hylan and colleagues,[35] on the other hand, found no significant differences in mental health care costs among patients who initiated therapy with the 3 SSRIs and found only 1 difference in total health care costs: for patients who initiated therapy with sertraline, total 1-year costs were higher than those for patients who initiated therapy with fluoxetine ($p < .05$).

One constant among the studies of costs was the finding that a small number of patients with high costs can dramatically inflate the standard deviation of the mean cost for an SSRI. In our study, the presence of such patients led to a coefficient of variation (standard deviation divided by the mean) of 3.6 for sertraline; in the study by Hylan and colleagues,[35] the presence of these patients led to a coefficient of variation of 2.8 for fluoxetine. These large coefficients of variation, and the fact that they lead to variances that differ in magnitude among the 3 SSRIs, pose problems for the analysis of cost data, possibly even for analysis of the log of costs.[44] This finding may help explain the disagreements that exist in the literature about whether health care and depression-related costs differ among the SSRIs.

A limitation of our observational study, as well as of observational studies in general, is that unobserved characteristics of the patients may lead to biased estimates of the impact of treatment on adherence or cost. This bias results from the fact that the alternative therapies were not selected randomly. An SSRI is selected over an alternative after weighing a number of factors, including the patient's characteristics, because it is believed that that SSRI will yield the best outcome. It is possible, for example, that the factors that lead the physician to believe that fluoxetine is the best option for a particular patient may be the same characteristics that lead to greater adherence independent of SSRI therapy. Because the characteristics observed by the physician are either unavailable to the researcher or are poorly measured, multivariable analysis cannot fully account for this possibility. Without randomization into treatment groups, either through a controlled trial or through a natural experiment, the possibility of biased estimates remains.

Although we could not control for unobserved factors that lead to selection of one therapy over another, we did analyze whether observed characteristics of patients and physicians were associated with treatment. We found that fluoxetine was less likely to be prescribed to older patients, and paroxetine was more likely to be prescribed to patients who experienced other acute psychiatric comorbid conditions. If factors correlated with age, for example, lead to lower adherence, the estimate for adherence to fluoxetine could be biased upward. While this example is speculative, it is important to be mindful of the potential for biased estimates from observational studies.

Several studies have found associations between longer duration of antidepressant therapy and improve-

ment in symptoms,[45] reduction in disabilities,[10] and prevention of relapse.[46–48] In a recent study by Melfi and colleagues,[48] early discontinuation of SSRI therapy as compared with continuous use had a risk ratio of 1.77 ($p < .01$) for the risk of relapse within 2 years of initiating therapy. Thus, 1 hypothesis that derives from our finding of less continuous therapy with paroxetine and sertraline is that patients who initiate therapy with these drugs should be expected to have worse outcomes. However, to the extent that worse outcomes are associated with higher costs, our analysis of treatment costs in the year after the index diagnosis, as well as those of Russell and colleagues,[36] does not appear to support this inference. In these studies, costs for sertraline and paroxetine either could not be distinguished from or were lower than those for fluoxetine.

One possible reason for our and others' failure to observe increased costs for patients who initiated therapy with sertraline and paroxetine is that relapse or recurrence may occur more than 1 year after initiation of therapy. Two studies,[46,49] however, have reported that the probability of relapse or recurrence within 1 year was 37%. We saw no evidence of cost increases that would be associated with the implied differential rates of relapse among the SSRIs.

Our 1-year cost estimates, which ranged between $4224 and $5358 (in 1997 U.S. dollars), and 1-year estimates of depression-related costs, which ranged between $1727 and $2127, fall in the middle of those reported by other studies. Hylan and colleagues[35] reported that costs for the 3 SSRIs ranged between $5598 and $7137 (in 1994 U.S. dollars) and depression-related costs ranged between $3466 and $3613. In a study by Russell and colleagues,[36] costs ranged between $4086 and $4680 (in 1995/1996 U.S. dollars) and depression-related costs ranged between $1203 and $1385. Several factors may explain these differences, including the fact that the patients in some studies were treated in health maintenance organizations whereas those in other studies were treated in the fee-for-service sector and the fact that practice may have changed during the years in which the studies were conducted.

In conclusion, our data indicate that after controlling for relevant covariables, there are no significant differences in total health care costs among the 3 SSRIs, whereas there are significant differences in depression-related costs (with costs of fluoxetine being greater than those of sertraline). Our data also indicate differences in adherence to the 3 SSRIs (with adherence to fluoxetine being longer than to paroxetine). It is possible that the higher depression-related costs of fluoxetine can be attributed to its higher adherence.

Perhaps the most provocative finding of this study is that there was no relationship between continuation of therapy and total health care or depression-related costs. Although those who initiated fluoxetine were less likely to interrupt therapy, this had no impact on total health care costs, and this group actually had higher depression-related costs than the other 2 groups. These findings are in contrast to other data indicating a relationship between treatment failure and higher costs[50] and a relationship between treatment success and better clinical outcome.[48,51] However, they are consistent with other data questioning this relationship.[52] Overall, the heterogeneity of these data underline the importance of investigating the relationship between adherence and outcome/costs in prospective, randomized studies.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft).

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