One-Year Costs of Second-Line Therapies for Depression

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Background: We compared patterns of medical resource utilization and costs among patients receiving a serotonin-norepinephrine reuptake inhibitor (venlafaxine), one of the selective serotonin reuptake inhibitors (SSRIs), one of the tricyclic agents (TCAs), or 1 of 3 other second-line therapies for depression.

Method: Using claims data from a national managed care organization, we identified patients diagnosed with depression (ICD-9-CM criteria) who received second-line antidepressant therapy between 1993 and 1997. Second-line therapy was defined as a switch from the first class of antidepressant therapy observed in the data set within 1 year of a diagnosis of depression to a different class of antidepressant therapy. Patients with psychiatric comorbidities were excluded.

Results: Of 981 patients included in the study, 21% (N = 208) received venlafaxine, 34% (N = 332) received an SSRI, 19% (N = 191) received a TCA, and 25% (N = 250) received other second-line antidepressant therapy. Mean age was 43 years, and 72% of patients were women. Age, prescriber of second-line therapy, and prior 6-month expenditures all differed significantly among the 4 therapy groups. Total, depression-coded, and non–depression-coded 1-year expenditures were, respectively, $6945, $2064, and $4881 for venlafaxine; $7237, $1682, and $5555 for SSRIs; $7925, $1335, and $6590 for TCAs; and $7371, $2222, and $5149 for other antidepressants. In bivariate analyses, compared with TCA-treated patients, venlafaxine- and SSRI-treated patients had significantly higher depression-coded but significantly lower non–depression-coded expenditures. Venlafaxine was associated with significantly higher depression-coded expenditures than SSRIs. However, after adjustment for potential confounding covariables in multivariate analyses, only the difference in depression-coded expenditures between SSRI and TCA therapy remained significant.

Conclusion: After adjustment for confounding patient characteristics, 1-year medical expenditures were generally similar among patients receiving venlafaxine, SSRIs, TCAs, and other second-line therapies for depression. Observed differences in patient characteristics and unadjusted expenditures raise questions as to how different types of patients are selected to receive alternative second-line therapies for depression.

(J Clin Psychiatry 2000;61:290–298)

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Supported by Wyeth-Ayerst Laboratories, Radnor, Pa.

Wyeth-Ayerst Laboratories had no control over the interpretation or presentation of the authors' analyses.

The authors acknowledge the research and editorial assistance of Robert A. Kerr and Vicki L. Watkins.

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Depression is a serious and pervasive disorder associated with total societal costs of approximately $44 billion annually, 27% of which are expenditures on medical services.[1] An estimated 17% of individuals will develop depression sometime during their lifetime.[2] Despite the existence of safe and effective antidepressant therapies, overwhelming evidence suggests that many depressed patients are misdiagnosed or receive inappropriate therapy. This gap in knowledge about the diagnosis and treatment of depression and the provision of adequate mental health services imposes substantial costs on society.[3,4]

The vast majority of antidepressants block reuptake of the neurotransmitters norepinephrine and/or serotonin and fall into 3 principal classes: monoamine oxidase inhibitors (MAOIs), tricyclics (TCAs) and tetracyclics, and selective serotonin reuptake inhibitors (SSRIs). Owing to their favorable tolerability profiles, SSRIs have become the antidepressants of choice.[5] Serotonin-norepinephrine reuptake inhibitors (SNRIs) represent a novel class of antidepressants that potently inhibit norepinephrine and serotonin reuptake and weakly inhibit dopamine reuptake. Venlafaxine, the only SNRI currently available, has demonstrated a relatively benign safety profile,[6] offering dose flexibility and improved tolerability,[7] and has been shown to be effective as a first-line antidepressant and for patients experiencing treatment-resistant depression.[8]

Although 65% to 75% of patients with major depression who receive appropriate doses of an antidepressant for 6 to 8 weeks will experience an excellent treatment response,[9] 20% to 40% of patients may be resistant to or

achieve only a partial response to treatment.[10] Therefore, clinicians often need to prescribe "second-line" therapies. Current strategies to manage treatment-resistant depression include combination therapy or substitution with an alternative antidepressant.

Clinical trials have demonstrated that venlafaxine has a more rapid therapeutic onset of action compared with alternative therapies,[11] a finding that may have significant economic implications.[12] More commonly prescribed as a second-line therapy in current clinical practice, venlafaxine has been shown by recent pharmacoeconomic evaluations to be possibly associated with cost savings compared with SSRIs and TCAs.[13–15] Although multiple studies have demonstrated the economic benefits of SSRIs versus TCAs as first-line therapies for depression,[16–18] the economic implications associated with alternative second-line therapies have yet to be rigorously evaluated. The purpose of this study was to compare medical resource utilization and costs among patients enrolled in a managed care organization (MCO) receiving alternative second-line therapies for depression.

METHOD

Study Design

We performed a retrospective cohort study on patients receiving second-line antidepressants between 1993 and 1997. We obtained patient-level claims and administrative data from 9 health care plans located in the eastern and midwestern United States. All 9 plans function as independent practice associations. The collective membership of these plans is approximately 1.1 million. Claims data contain information related to facility, professional, and pharmacy health services.

Patient Sample

Patients were included if they met all of the following criteria: (1) aged ≥ 19 years; (2) diagnosed with depression*; (3) received at least 2 months of first-line antidepressant therapy consisting of venlafaxine, an SSRI, an MAOI, a TCA, or another antidepressant agent (nefazodone, bupropion, or trazodone) within 1 year of a diagnosis of depression; (4) received second-line therapy consisting of substitution with a different class (venlafaxine, SSRIs, TCAs, MAOIs and other antidepressants) of antidepressant for at least 2 consecutive months; and (5) had claims and administrative data available during 6 months prior and 12 months subsequent to initiating second-line therapy.

Patients were excluded from the study for either of the following reasons: (1) received a diagnosis of a psychiatric comorbid condition in the 6 months before or the 12 months after initiating second-line treatment (ICD-9-CM codes: 295.10–295.30, 295.60, 295.90, schizophrenia–all types; 296.00–296.06, bipolar I disorder–single manic episode; 296.40–296.46, bipolar I disorder–most recent episode manic; 296.60, bipolar I disorder–most recent episode mixed; 301.0, paranoid personality disorder; 294.1, 294.9, dementia; 293.0, 780.09, delirium; 294.09, amnestic disorder) or (2) received care in an intermediate care facility or skilled nursing facility in the 6 months prior to beginning second-line treatment.

Variables

We used submitted charges for medical services as proxies for payer costs. All costs were inflated, by calendar year, to 1997 U.S. dollars using the medical care component of the Consumer Price Index (CPI). We defined a follow-up period for each person as beginning in the calendar month of the first prescription of second-line therapy and lasting until the end of the 12th month after initiation of second-line therapy. Rates of health services utilization and costs associated with overall, depression-coded, and non–depression-coded health care services were calculated for each person's follow-up period. We defined depression-coded claims as those associated with medical encounters at which the health provider recorded an ICD-9-CM diagnosis of depression (using the relaxed ICD-9-CM criteria outlined previously). We also calculated facility, professional, and medication expenditures by treatment group. Using generic drug class codes, pharmacy claims were categorized as antidepressants, sedatives/hypnotics, antianxiety agents, and other medications. Depression-coded medications included antidepressants, sedatives/hypnotics, and antianxiety agents.

To estimate and adjust for severity of illness, we calculated the number of concomitant disease states and medical expenditures incurred during the 6 months prior to initiating second-line therapy. Prior 6-month expenditures have been used in previous economic studies of depression therapies to adjust for underlying differences in comorbidity at the time antidepressant therapy was initiated.[17,18,20]

Statistical Analyses

We compared baseline demographic, clinical, and economic characteristics between treatment groups. We also compared overall, depression-coded, and non–

*Depression diagnosis was indicated by one or more of the following: ICD-9, Clinical Modification (ICD-9-CM)[19] codes 296.20–296.26, major depressive episode–single episode; 296.30–296.36, major depressive disorder–recurrent episode; 296.50–296.56, bipolar disorder–most recent episode depressed. Patients who had a medical encounter at which one or more of these depression diagnosis codes were recorded were classified as having met the "strict" diagnostic criteria for depression. We also included patients who did not meet the strict diagnostic criteria for depression, but who had one or more of the following diagnoses: ICD-9-CM codes, 300.4, neurotic depression–dysthymic disorder; 300.9, adjustment disorder with depressed mood; 296.90, mood disorder not otherwise specified; or 311.0, depression not otherwise specified.

depression-coded expenditures and rates of medical resource utilization between treatment groups using bivariate and multivariate statistical analysis. Bivariate comparisons of patient characteristics, across all 4 types of second-line therapy, were conducted using 1-way analysis of variance (ANOVA) with the Student-Newman-Keuls multiple range test for continuous variables and using contingency table analysis with the chi-square test for categorical variables. Pairwise comparisons of medical resource use were performed using contingency table analysis, and pairwise comparisons of expenditures were performed using ANOVA with the Wilcoxon rank sum test, a nonparametric approach. We did not adjust for multiple comparisons.

We developed a multivariate regression model for each of the 6 dependent expenditure variables: overall, depression-coded, non–depression-coded, facility services, professional services, and medications. The distributions of these variables were skewed, to varying degrees, toward larger expenditure values (i.e., skewed to the right), leading us to consider several approaches to transforming the dependent variables. We conducted exploratory multivariate regression analyses on all 6 dependent variables using 4 alternative specifications of these variables: no transformation, natural logarithm transformation, square root transformation, and weighted least squares transformation, using the inverse of the squared predicted expenditure as the transformation factor. We did not consider other approaches such as the Box-Cox criterion.

We then performed exploratory multivariate analysis with each of the transformed and untransformed expenditure variables as dependent variables and all of the following independent variables included in the models: age, gender, prescriber of second-line therapy, type of second-line therapy, meeting of strict depression diagnostic criteria by patient, prior 6-month expenditures, number of concomitant disease states, and health plan. Prior to performing these exploratory multivariate analyses, we also obtained a correlation matrix of independent variables to identify potential interaction terms for the model, and we generated partial regression leverage plots for each continuous independent variable to assess the need for higher-order (e.g., squared) terms for variables such as age. We did not include interaction or higher-order terms in the exploratory multivariate analyses used to select the preferred transformation factor. However, we did reassess the need for these terms once the final specifications of the dependent variables had been obtained.

Final selection of the specification of the dependent variables was based on goodness of fit of the model (i.e., proportion of variance explained) as well as plots of residuals versus predicted values to assess heteroscedasticity in the residuals. We did not perform tests of heteroscedasticity based on these plots to compare the alternative approaches to transforming the dependent variables. Rather, we relied on visual inspection and comparison of distributions of residuals, by type of transformation, for each dependent variable. On the basis of these criteria, we selected the weighted least squares transformation for depression-coded expenditures and no transformation for the other 5 expenditure variables.

Once we selected the specification of the dependent variables, we performed forward stepwise regression analysis to evaluate the impact of including interaction terms and higher-order terms in each of the 6 models. Our criteria for including these terms in the final models were that including the individual terms had to significantly increase the proportion of variance explained by the model (i.e., the goodness of fit), that the first-order terms had to remain relatively stable (e.g., significant terms did not change signs), and that significant first-order terms did not become nonsignificant in the presence of higher-order or interaction terms. On the basis of these criteria, no interaction term or higher-order term was included in any of the final models. Version 6.10 of the Statistical Applications Software of the SAS Institute (Cary, N.C.) was used to perform all statistical analyses. A p value $\leq .05$ was considered statistically significant.

RESULTS

Descriptive Statistics

Table 1 presents the demographic, clinical, and economic characteristics of the 981 patients who met the eligibility criteria. Twenty-one percent of patients received venlafaxine, 34% received an SSRI, 19% received a TCA, and 25% received another antidepressant as second-line therapy. The mean patient age was 43 years, and 72% of patients in the sample were women. The majority of those receiving venlafaxine, TCA, and other second-line antidepressant therapy had received an SSRI as first-line therapy.

Significant differences were detected between groups in the proportion of patients who met the strict depression diagnosis criteria. Venlafaxine patients and those taking other antidepressants were more likely to have a diagnosis of major depression or bipolar I disorder–most recent episode depressed compared with TCA and SSRI patients. Statistically significant differences also were detected between groups in the prescriber of second-line therapy. Venlafaxine patients and patients taking other antidepressants were more likely to receive second-line therapy from a psychiatrist compared with SSRI and TCA patients.

TCA patients were more likely to have had central nervous system comorbidity during the 6 months prior to initiating second-line therapy. Total medical expenditures during the 6 months prior to commencing second-line therapy were higher among TCA patients compared with patients receiving alternative therapies. The interval between the discontinuation of first-line therapy and

the initiation of second-line therapy was similar between groups. Venlafaxine and SSRI patients remained on continuous second-line therapy longer than those receiving TCA and other antidepressant therapy.

Table 1. Patient Characteristics[a]

Patient Characteristic	All Patients (N = 981)	Second-Line Therapy: Venlafaxine (N = 208)	SSRI (N = 332)	TCA (N = 191)	Other (N = 250)	p Value[b]
Women, %	72	77	73	68	68	.08
Age, mean, y	43	41	44	44	42	.001
First-line therapy, %						
Venlafaxine	2	NA	4	0.5	0.8	.001
SSRI	59	90	NA	90	86	
TCA	29	6	73	NA	13	
MAOI	0.6	0.5	2	0	0	
Other	10	3	21	9	NA	
Prescriber of second-line therapy, %						
Psychiatrist	36	46	27	25	48	.001
Primary care physician	52	44	64	49	45	
Other/unknown	12	9	10	26	7	
Prior 6-month comorbidity, %						
Malignancy	7	7	8	6	6	.77
Central nervous system	12	11	12	18	7	.007
Cardiac/arterial	9	6	12	9	8	.10
Respiratory	10	7	10	12	10	.33
Gastrointestinal	17	15	19	13	18	.25
Renal/genitourinary	8	6	8	9	8	.70
Gynecological	16	20	16	11	18	.10
Arthropathy	21	17	21	26	21	.15
Prior 6-month expenditures, mean, $						
Total	3311	2410	3379	4671	2932	.04
Depression-coded	290	365	109	463	335	.007
Duration of second-line therapy, mean, mo	7.1	7.6	7.8	5.9	6.7	.0001
Meet strict depression diagnosis criteria, %	40	48	34	36	44	.005
Interval between first and second-line therapy, mean, mo	5.2	5.1	5.0	6.0	4.9	.21

[a]Abbreviations: MAOI = monoamine oxidase inhibitor, NA = not applicable, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]Comparisons between treatment groups were made using 1-way analysis of variance for continuous variables. Comparisons between treatment groups were performed with chi-square analysis for categorical variables.

Medical Resource Utilization

Table 2 reports medical resource utilization rates during the year after the initiation of second-line therapy. The likelihood of inpatient hospitalization and the number of hospitalizations among those who were hospitalized were similar between treatment groups. The rate and number of emergency department visits also were similar between groups.

There were no differences between groups in the likelihood of visiting a primary care physician during the year following the initiation of second-line therapy. However, the frequency of office visits to primary care physicians was lower among venlafaxine patients and those taking other antidepressants compared with that for TCA and SSRI patients. Venlafaxine patients and patients taking other antidepressants were more likely to have at least one visit to a psychiatrist during the year following initiation of second-line therapy compared with SSRI and TCA patients. TCA patients were more likely to obtain health services from another medical specialist compared with patients taking alternative second-line therapies.

Venlafaxine patients were less likely to take concomitant antianxiety agents relative to SSRI and TCA patients and patients taking other antidepressants. With the exception of SSRI patients versus patients taking other antidepressants, the rates of concomitant sedative/hypnotic or other medication use were similar between treatment groups.

Medical Expenditures

Bivariate comparisons. Bivariate pairwise comparisons of total 1-year medical expenditures (Table 3) indicated that SSRI patients had significantly lower expenditures compared with TCA patients. Both venlafaxine and SSRI patients had significantly lower facility and professional service expenditures, but higher medication expenditures, than TCA patients. Overall facility, professional, and medication expenditures were similar between venlafaxine and SSRI patients.

One-year expenditures for total depression-coded health services were significantly higher, but expenditures for non–depression-coded services were significantly lower, for patients receiving venlafaxine or an SSRI compared with those for TCA patients. Depression-coded expenditures were significantly higher, but non–depression expenditures were similar, for venlafaxine patients relative to SSRI patients.

Pairwise comparisons between groups indicated that facility expenditures related to inpatient hospital and emergency department services were similar between treatment groups (Table 4), except that outpatient hospital expenditures were significantly higher among TCA patients compared with those for patients receiving alternative antidepressant therapies. Expenditures for professional services provided by primary care physicians were significantly

Table 2. Medical Resource Utilization by Second-Line Therapy: Bivariate Comparisons

Resource[a]	Second-Line Therapy (1) Venlafaxine (N = 208)	(2) SSRI (N = 332)	(3) TCA (N = 191)	(4) Other (N = 250)	p Values for Pairwise Comparisons[b] 1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Facility services										
Inpatient hospital										
Admission rate, %	18.3	13.0	17.3	16.8	.09	.80	.68	.18	.19	.90
No. of admissions, mean	1.3	1.5	1.8	1.4	.85	.40	.98	.52	.87	.41
Outpatient hospital										
Visit rate, %	50.0	48.8	61.3	47.6	.79	.02	.61	.006	.78	.004
No. of visits, mean	2.4	2.8	2.7	2.5	.74	.19	.80	.07	.47	.25
Emergency department										
Visit rate, %	23.6	26.2	21.0	27.6	.49	.53	.33	.18	.71	.11
No. of visits, mean	1.7	1.6	1.9	1.6	.70	.54	.70	.37	.93	.43
Professional services										
Primary care physician										
Visit rate, %	92.0	93.0	94.0	93.0	.69	.47	.58	.68	.84	.83
No. of visits, mean	6.3	7.6	8.0	5.8	.0001	.03	.69	.26	.0001	.007
Psychiatrist										
Visit rate, %	48.0	27.0	29.0	44.0	.001	.001	.38	.64	.001	.002
No. of visits, mean	6.9	5.7	6.3	6.1	.25	.46	.89	.84	.32	.57
Psychologist/social worker										
Visit rate, %	36.0	29.0	25.0	40.0	.10	.02	.44	.32	.009	.001
No. of visits, mean	9.7	7.4	7.1	8.6	.13	.62	.32	.38	.008	.14
Other medical specialist										
Visit rate, %	78.0	78.0	85.0	79.0	.99	.07	.91	.05	.89	.08
No. of visits, mean	6.5	9.2	10.2	7.9	.76	.001	.58	.001	.79	.008
Concomitant medications, %										
Antianxiety agents	29.3	40.7	44.0	40.4	.008	.002	.01	.46	.95	.45
Sedative/hypnotic agents	11.1	13.0	12.6	12.0	.51	.64	.75	.90	.73	.86
Other agents	96.0	98.0	97.0	94.0	.14	.53	.42	.47	.02	.16

[a]Number of admissions/visits refers to the subgroup of patients who had at least one stay/visit.
[b]Pairwise comparisons were performed using 1-way analysis of variance with the Wilcoxon rank sum test for continuous variables and contingency table analysis with chi-square test for categorical variables.

Table 3. One-Year Expenditures by Second-Line Therapy[a]: Bivariate Comparisons

Expenditure Category	Second-Line Therapy, Mean Expenditures (1) Venlafaxine (N = 208)	(2) SSRI (N = 332)	(3) TCA (N = 191)	(4) Other (N = 250)	p Values for Pairwise Comparisons[b] 1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Overall										
Total	$6945	$7237	$7925	$7371	.60	.26	.94	.05	.61	.24
Facility	2668	3112	3393	2911	.84	.05	.96	.01	.81	.04
Professional services	2654	2593	3068	3015	.44	.02	.62	.002	.20	.10
Medications	1623	1532	1465	1445	.59	.07	.45	.02	.18	.30
Depression-coded services										
Total	2064	1682	1335	2222	.004	.0001	.06	.0001	.56	.0001
Facility	690	625	597	1069	.007	.83	.77	.01	.002	.62
Professional services	579	334	347	542	.002	.0001	.54	.03	.0001	.0001
Medications	796	735	391	612	.32	.0001	.0001	.0001	.0002	.0001
Non–depression-coded services										
Total	4881	5555	6590	5149	.60	.001	.66	.001	.94	.003
Facility	1979	2487	2796	1843	.43	.01	.93	.04	.36	.01
Professional services	2075	2260	2720	2473	.98	.002	.85	.001	.85	.006
Medications	827	808	1074	833	.15	.003	.20	.04	.99	.05

[a]Expenditures reported as charges in 1997 U.S. dollars.
[b]Pairwise comparisons were performed using 1-way analysis of variance with the Wilcoxon rank sum test for continuous variables.

Table 4. One-Year Expenditures by Second-Line Therapy[a]: Bivariate Comparisons of Specific Expenditures

Expenditure Category	Second-Line Therapy, Mean Expenditures (1) Venlafaxine (N = 208)	(2) SSRI (N = 332)	(3) TCA (N = 191)	(4) Other (N = 250)	p Values for Pairwise Comparisons[b] 1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Facility expenditures[c]										
Inpatient hospital	$1639	$2021	$2006	$1728	.09	.75	.62	.20	.22	.91
Outpatient hospital	783	859	1081	938	.77	.004	.96	.005	.83	.006
Emergency department	197	208	282	187	.58	.60	.46	.25	.82	.18
Professional expenditures										
Primary care physician	446	550	549	467	.006	.02	.74	.93	.01	.04
Psychiatrist	257	125	158	212	.0001	.0006	.68	.61	.0001	.002
Psychologist/social worker	307	179	159	295	.06	.03	.35	.54	.003	.002
Other medical specialist	1095	1299	1430	1421	.84	.003	.66	.002	.79	.009
Unknown	549	441	773	620	.28	.42	.39	.07	.91	.12
Medications										
Antidepressants	727	631	289	498	.06	.0001	.0001	.0001	.0001	.0001
Antianxiety agents	55	85	88	102	.01	.002	.008	.31	.65	.60
Sedative/hypnotic agents	14	8	13	12	.62	.64	.80	.47	.81	.80
Other agents	827	808	1074	833	.15	.003	.20	.04	.99	.05

[a]Expenditures reported as charges in 1997 U.S. dollars.
[b]Pairwise comparisons were performed using 1-way analysis of variance with the Wilcoxon rank sum test for continuous variables.
[c]Expenditures associated with services provided in free-standing surgicenters are not reported but were included in the calculation of total facility expenditures.

lower, but expenditures for psychiatrist services were significantly higher, among venlafaxine patients compared with those for SSRI and TCA patients. TCA patients incurred significantly higher professional service costs provided by other medical specialists compared with patients receiving venlafaxine or SSRI therapy.

SSRI and venlafaxine patients had higher expenditures associated with antidepressant therapy, and venlafaxine had lower expenditures associated with antianxiety medications, compared with TCA patients. Antianxiety expenditures were lower among venlafaxine patients compared with those for SSRI patients.

Multivariate comparisons. Table 5 presents the multivariate findings for overall, depression-coded, and non–depression-coded 1-year expenditures. After adjustment for potential confounding characteristics, there were no significant differences in depression-coded, non–depression-coded, or overall 1-year expenditures between SSRI and either venlafaxine or other second-line therapy. Only depression-coded expenditures were significantly lower for TCA versus SSRI therapy. Prior 6-month expenditures and number of concomitant disease states were both positively associated with overall, depression-coded, and non–depression-coded expenditures. Psychiatrist versus primary care physician prescriber of second-line therapy was associated with significantly higher depression-coded but significantly lower non–depression-coded expenditures.

Expenditures for facility and professional services, as well as medications, were similar for venlafaxine or TCA versus SSRI therapy (Table 6). Again, prior 6-month expenditures and number of concomitant disease states were positively associated with expenditures.

DISCUSSION

As novel antidepressants are developed, it is critical that the medical community determines those that are the most cost-effective, thereby ensuring that overall costs of depression are minimized. Using medical claims data from an MCO provides a unique opportunity to better understand patterns of prescribing behaviors, health services utilization, and medical expenditures in clinical practice and collect valuable information beyond that which can be obtained in a controlled research setting. The results of this analysis reflect expenditures from the perspective of an MCO during the year after initiation of second-line antidepressant therapy.

Our primary analysis classified patients according to second-line therapy, independent of first-line therapy and subsequent switches to or augmentation with third-line therapy. While randomized clinical trials typically restrict medication switches, our study design focused on all medical expenditures during the year after the initiation of second-line therapy regardless of switching. Patterns of medical resource utilization and expenditures were considered as important consequences of the selection of second-line therapy.

Previous research on patterns of antidepressant use has reported that psychiatrists are more likely to prescribe newer antidepressants (SSRIs vs. TCAs) than primary care physicians and that patients taking newer antidepressants are less likely to have discontinued treatment early.[21] Our findings are consistent with these trends. We observed specialty differences in the prescription of second-line antidepressants and subsequent patterns of health resource utilization among patients taking newer versus

Table 5. Depression-Coded and Non–Depression-Coded Expenditures[a]: Multivariate Analyses

	1-Year Expenditures[b]		
Variable	Depression-Coded[c]	Non–Depression-Coded	Overall
Intercept	$2303†	$2631*	$4591†
Age	0.42	75*	86*
Gender (0 = male, 1 = female)	69	79	283
Prescriber of second-line therapy (0 = primary care physician)			
Psychiatrist	635†	–1387*	–956
Other medical specialist	–64	–760	–640
Second-line therapy (0 = SSRI)			
Venlafaxine	260	309	658
Other	201	266	825
TCA	–374†	417	10
Meet strict depression diagnosis criteria (0 = No, 1 = Yes)[d]	327	–508	–94
Prior 6-month expenditures	0.06*	0.55†	0.64†
No. of concomitant disease states	58†	471*	451*
R^2	0.4540	0.2267	0.2221

[a]All multivariate analyses adjusted for age, gender, prescriber of second-line therapy, second-line therapy, strict depression criteria, health plan, prior 6-month expenditures, and number of concomitant disease states.
[b]Expenditures reported as charges in 1997 U.S. dollars.
[c]Depression-coded costs were modeled using a weighted least squares technique.
[d]Yes = major depressive disorder–single episode, major depressive disorder–recurrent episode, or bipolar I disorder–most recent episode depressed. No = neurotic depression–dysthymic disorder, adjustment disorder with depressed mood, mood disorder not otherwise specified, or depression not otherwise specified.
*p ≤ .05. †p ≤ .001.

Table 6. Facility, Professional, and Medication Expenditures[a]: Multivariate Analyses

	1-Year Expenditures[b]		
Variable	Facility Services	Professional Services	Medications
Intercept	$2563*	$1259*	$769†
Age	37	20	29†
Gender (0 = male, 1 = female)	–7	267	23
Prescriber of second-line therapy (0 = primary care physician)			
Psychiatrist	–784	–451	279*
Other medical specialist	–465	–256	81
Second-line therapy (0 = SSRI)			
Venlafaxine	190	313	155
Other	224	690*	–90
TCA	–172	289	–108
Meet strict depression diagnosis criteria (0 = No, 1 = Yes)[c]	–230	155	–19
Prior 6-month expenditures	0.44†	0.18†	0.02†
Number of concomitant disease states	36	304†	111†
R^2	0.1836	0.1964	0.1680

[a]All multivariate analyses adjusted for age, gender, prescriber of second-line therapy, second-line therapy, strict depression criteria, health plan, prior 6-month expenditures, and number of concomitant disease states.
[b]Expenditures reported as charges in 1997 U.S. dollars.
[c]Yes = major depressive disorder–single episode, major depressive disorder–recurrent episode, or bipolar I disorder–most recent episode depressed. No = neurotic depression–dysthymic disorder, adjustment disorder with depressed mood, mood disorder not otherwise specified, or depression not otherwise specified.
*p ≤ .05. †p ≤ .001.

older classes of antidepressants. Venlafaxine patients were more likely to have received their prescription from a psychiatrist compared with patients receiving alternative therapies. As a likely result, venlafaxine patients had more visits to psychiatrists and fewer visits to primary care physicians and incurred higher psychiatrist expenditures compared with SSRI and TCA patients. In addition, the duration of treatment was longer among venlafaxine and SSRI patients compared with patients receiving TCAs or other antidepressants.

Our evaluation of patterns of medical resource utilization also indicated that patients receiving venlafaxine had significantly lower rates of concomitant use of antianxiety medications compared with patients receiving alternative second-line therapies. Although the detailed results are not described in this article, we performed a logistic regression analysis which indicated that this finding persisted after adjustment for potential confounding patient and provider characteristics. Further investigation of the implications of these data is warranted, especially given recent studies showing that venlafaxine extended release, a new formulation of venlafaxine, is effective in improving anxiety symptoms among patients with generalized anxiety disorder.[22,23]

Most of the significant differences in expenditures among alternative therapies we observed in bivariate analyses became nonsignificant after adjustment for potential confounding characteristics in multivariate analysis. In multivariate analyses, prior 6-month expenditures were positively and significantly associated with each type of expenditure during the follow-up period. This finding suggests that patients who required more intensive management of depression or comorbidities in the 6-month period prior to beginning second-line therapy continued to require more intensive management during the follow-up period, despite the change in therapy. Higher overall prior 6-month expenditures observed among TCA patients compared with SSRI patients may have contributed to the expenditure difference observed in bivariate analyses that was not apparent after controlling for this difference in multivariate analysis. However, depression-coded expenditures were highest among TCA patients during the 6 months prior to second-line therapy. This would have been expected to increase the likelihood of finding higher depression-coded expenditures in the TCA versus venlafaxine and SSRI groups, which would then disappear after adjustment for prior expenditures. Instead, the opposite was true. In bivariate analysis, venlafaxine and SSRI patients had higher depression-coded expenditures, and depression-coded expenditures remained lower among TCA patients compared with SSRI patients in multivariate analysis.

The results from the multivariate analysis showed that the type of prescriber of second-line therapy confounded the association between type of second-line therapy and costs. This relationship was detected when depression-coded and non–depression-coded expenditures were examined separately. One explanation for observed higher depression-coded expenditures among psychiatrists is that primary care physicians were less likely than psychiatrists to code medical encounters as related to depression. Previous studies have reported high rates of miscoding and underreporting of depression among primary care physicians due to uncertainty about diagnosis[24] and due to concerns about not receiving reimbursement for depression-coded services.[25,26]

One possible explanation for the significantly lower depression-coded expenditures among TCA patients in bivariate and multivariate analyses, in addition to lower drug acquisition costs associated with TCAs, is that these patients were not taking TCAs for depression. It has been well documented in the literature that antidepressants, especially the TCAs, are prescribed for multiple nonpsychiatric indications, including pain control, bladder dysfunction, and stress/anxiety.[27] Patients receiving antidepressant therapy for other medical conditions could have been included in this analysis. TCA patients also had higher expenditures related to other medications, including those associated with pain management pharmacotherapy, and were more likely to have had arthropathy comorbidity in the 6 months prior to initiating second-line therapy, a finding that supports this possibility. While controlling for the prescriber of second-line therapy partially addresses this issue, the indication for receiving these antidepressants requires further exploration.

This study has several potential limitations. First, we used submitted claims from a single MCO as a proxy for payer costs. Therefore, expenditures reported in this analysis may represent an overestimate of actual payer costs because payers do not typically reimburse 100% of submitted charges. Generalizability to the depression population as a whole may be limited owing to any unique clinical practice patterns at this particular MCO. Second, we used the medical-care component of the CPI to inflate costs incurred in 1993–1996 to 1997 dollars. If the CPI overestimates the true rate of medical care cost inflation, and if older therapies such as TCAs were used disproportionately earlier in the data window, the present value cost of these therapies could appear higher relative to therapies adopted more recently, simply owing to overinflating the costs of older therapies.

Third, as is often the case in retrospective claims-based analyses, we were unable to control for the potential effects of several unobservable potential confounding factors, including patient and physician preferences. Further, although this retrospective analysis provides an opportunity to examine the impact of second-line therapy on subsequent patterns of resource utilization and costs, the nonrandomized study design remains a source of potential self-selection bias. Given that we did not have detailed clinical data on the severity of depression or on overall patient functional status, we used prior 6-month medical expenditures and number of concomitant disease states to adjust for potential differences between patients receiving alternative classes of second-line therapies. Although these variables were significant predictors of overall, depression-coded, and non–depression-coded expenditures, we may not have accounted for all of the clinical differences or other unobservable confounders between groups in our analysis.

Fourth, we examined medical services use during a restricted window of time, from July 1993 through February 1997. We were limited, therefore, in our ability to determine whether the first and second instances of antidepressant use in our data set actually represented a patient's first- and second-line therapy, respectively. To address this limitation, we attempted to identify a homogenous cohort of patients using well-defined study eligibility criteria and by controlling for medical expenditures incurred during the 6 months prior to initiating second-line therapy.

Finally, to permit more straightforward comparisons between treatment groups, we included only patients receiving substitution therapy as second-line treatment for depression. We did not include patients who received augmentation or combination therapy in the analysis. However, some evidence suggests that switching between antidepressant classes is preferable to augmentation or combination therapy when patients fail initial treatment, particularly with the TCA agents.[28] Substitution with an alternative class of antidepressant decreases the potential for side effects and may enhance patient compliance compared with augmentation or combination therapy.[29]

In spite of these limitations, our findings provide insight about patterns of medical resource and antidepressant utilization and expenditures among patients enrolled in an MCO requiring second-line therapy for depression. We observed differences between groups in the prescriber of antidepressant therapy that had important cost implications. Receipt of second-line therapy from a psychiatrist was associated with significantly higher depression-coded costs and significantly lower non–depression-coded costs. Overall cost differences between TCA and SSRI patients observed in bivariate analysis did not persist after adjustment for potential confounding variables, suggesting that further research should concentrate on the economic implications of provider prescribing behaviors, including antidepressant dosing and patterns of intraclass switching between antidepressant agents.

Drug names: bupropion (Wellbutrin), nefazodone (Serzone), trazodone (Desyrel and others), venlafaxine (Effexor).

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