Course of Antidepressant Treatment with Tricyclic Versus Selective Serotonin Reuptake Inhibitor Agents: A Comparison in Managed Care and Fee-For-Service Environments

Kathleen A. Fairman, MA; Fred Teitelbaum, PhD; Wayne C. Drevets, MD; Gretchen Engquist, PhD; Jerold J. Kreisman, MD; and Marija J. Norusis, PhD

Abstract

We compared course of treatment with tricyclic antidepressant drugs (TCADs) and selective serotonin reuptake inhibitors (SSRIs) to assess interactive effects of antidepressant type with payer type and patient characteristics. A nationwide sampling of adults (n=4,252) from approximately equal numbers of health maintenance organization (HMO) and indemnity enrollees were prescribed no antidepressants for 9 months, and thereafter prescribed a TCAD or SSRI. Using a retrospective analysis of prescription claims, these cohorts of TCAD and SSRI utilizers were followed for 13 to 16 months after their initial antidepressant prescription. Outcome measures included (1) termination of antidepressant treatment before 1 month; and (2) failure to receive at least one therapeutic dose during treatment lasting 3 months or more. Rates of premature termination and subtherapeutic dosing were significantly higher for TCAD-treated than SSRI-treated patients, and for HMO than indemnity enrollees. The interaction of HMO enrollment and TCAD use was associated with particularly high rates. Excluding patients terminating in the first month, the proportions of TCAD and SSRI utilizers remaining in treatment over time were not significantly different. We conclude that SSRIs may provide advantages in treatment adherence and therapeutic dosing, particularly in environments with limited prescriber time. The first month of treatment may be especially critical in determining compliance.

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Deficiencies in antidepressant drug treatment, particularly in primary care settings, have been well documented and are the target of care improvement strategies.[1] Among the problems identified by prior research are premature termination of drug therapy, often after filling only one prescription, and subtherapeutic dosing.[2-5] Because this research was conducted before selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants became widely used, it represents primarily patients treated with tricyclic antidepressant drugs (TCADs). The problems of premature termination and subtherapeutic dosing with TCADs are commonly attributed to the occurrence and/or attempted avoidance of side effects, and to the complexity involved in titrating TCAD dosages to therapeutic levels.[6-10] TCADs' side effects may negatively impact treatment not only for depression, but also for other conditions, including anxiety disorders.[11,12]

Most clinical trials of SSRIs, including fluoxetine, paroxetine, and sertraline, have found them to be as effective as TCADs for outpatients with major depressive disorder, but less likely to cause troublesome side effects and serious adverse effects.[13-20] Additionally, in treatment with SSRIs the starting dose is often the therapeutic dose, and fewer dose adjustments are required than in TCAD treatment.[6,10,13] Consequently, it has been hoped that the use of SSRIs as a "first line" treatment would improve patient outcomes.[6,8,10,21-24] However, these expectations are not universal. Some have argued either that favorable clinical trial results for SSRIs are in part due to methodological flaws, that the limited safety and efficacy data for SSRIs do not support their increasingly widespread use, and/or that these drugs are not sufficiently superior to TCADs to justify their higher cost.[25-28]

Even if there were complete agreement about these clinical trial results, questions would remain about the relative advantages of SSRIs and TCADs in naturalistic treatment settings. Discrepancies between the results of antidepressant clinical trials and actual courses of treatment have been demonstrated, in part because the settings, compliance monitoring techniques, and patients used in these trials are

From: Express Scripts, Inc , Maryland Heights, MO (K.A.F., F.T.), Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA (W.C.D.), Engquist, Pelrine and Powell, Inc., Washington, DC (G.E.), Department of Psychiatry, DePaul Health Center, St. Louis, MO (J.J.K.), and Norusis Statistical Consulting, Highland Park, IL (M.J.N.).

Address correspondence to: Kathleen Fairman, Outcomes Research Manager, Express Scripts, Inc , 1700 North Desert Drive, Tempe, AZ 85281

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not always representative of typical practice.[2,4,26,29-31] Nonetheless, only a few studies have compared SSRIs with TCADs in routine care. These studies documented higher rates of treatment adherence and/or therapeutic dosing for SSRIs than for older antidepressants. However, none of these studies included fee-for-service patients, all were conducted before the two newer SSRIs, paroxetine and sertraline, were fully introduced in the marketplace, and three of five were set in the same health maintenance organization (HMO).[2,32-35]

The primary purpose of this study was to compare SSRIs to TCADs with respect to 2 key measures of the course of antidepressant drug therapy: (1) termination of treatment before 1 month's time; and (2) subtherapeutic dosing. A secondary purpose was to assess interactive effects of antidepressant drug type with payer type and patient characteristics. To address these questions, we analyzed pharmacy claims data from Express Scripts, Inc. (ESI), a pharmacy benefits management company with a large, nationwide, multiple-payer, and demographically diverse population. Because both indemnity (fee-for-service) and HMO enrollees are included in the database, this is the first study to compare the relative advantages of SSRIs and TCADs in care received under different payment arrangements.

··· METHOD ···

Study Population

The study population consisted of adults (age 18 or older) who: (1) were enrolled with ESI clients (indemnity or HMO payers) that had no restrictions on coverage for particular antidepressant products; (2) were continuously eligible to receive prescription benefits through ESI from April 1, 1993 through April 30, 1995; (3) filled at least one antidepressant prescription for a TCAD or an SSRI during the first 3 months of 1994; and (4) filled no antidepressant prescriptions during the last 9 months of 1993. Patients filling any prescriptions for agents in other antidepressant drug classes (eg, trazodone, buproprion) were excluded from the study population. Post hoc sensitivity analyses showed the same study findings when these patients are included. Patients taking more than one antidepressant drug (either concomitantly with other antidepressants or as a result of a switch from one antidepressant to another) were included in order to track realistically the course of antidepressant utilization in actual clinical practice. In post hoc sensitivity analyses of patients using only one antidepressant, study findings are the same, probably in part because the majority (82%) of patients used only one.

More than 1.7 million persons were enrolled during the first 3 months of 1994 with ESI clients (indemnity or HMO payers) that maintained eligibility data for individual patients and that imposed no coverage restrictions on particular antidepressant products. Of that group, 48,982 persons filled a prescription for at least one antidepressant during the first calendar quarter of 1994. Of these, 44,730 were excluded for: (1) failure to meet continuous eligibility criteria (n=12,068); (2) use of antidepressants in the 9-month period prior to the start of the study (n=21,910); (3) use of antidepressants that either had a primary indication other than depression (eg, clomipramine) or were used by a small number of patients (n=152); (4) age less than 18 (n=633); (5) incomplete or erroneous data for one or more claims (n=1,406); (6) information missing from eligibility file (n=28); (7) difficulty in classifying initial treatment because the patient filled prescriptions for more than one antidepressant on the first day of therapy (n=71); (8) use of antidepressants other than TCADs and/or SSRIs (n=744); or (9) combinations of two or more of these reasons (n=7,718). The size of the resulting study population is 4,252.

Study Period

Baseline data were obtained by measuring patterns of drug utilization and cost for each patient for the time period beginning April 1, 1993 and ending on the day before that patient's antidepressant therapy began ("pre"). From the start of antidepressant therapy during the first 3 months of 1994, patients were then followed through April 30, 1995 ("post").

Dependent variables. The first dependent variable was termination of antidepressant treatment before 1 month's time (length of treatment 30 or fewer days). A 1-month marker was selected because prior research has measured treatment adherence in the early part of the therapeutic course[2,7,32,34] and terminations within this very rapid time frame are unlikely to be due to therapeutic response to drug treatment. To calculate the end date of antidepressant treatment, the fill date for the final antidepressant prescription was summed with the days supply figure entered into the claims database by the pharmacist at the time of purchase. The length of treatment was calculated as the difference between the end date and the initial fill date. Gaps in treatment were not taken into account in measuring length, because gaps between antidepressant refills were usually minimal (median 2-3 days) and did not differ in length or frequency by drug type. Since ESI's network pharmacies usually dispense in maximum 30-day supplies, for most patients a termination

at 30 days represents filling only one antidepressant prescription. Because the objective of the analysis was to measure complete cessation of treatment, switches from one antidepressant drug to another were not defined as terminations.

The second dependent variable was failure to receive at least one therapeutic dose, defined according to published dosing standards for depression treatment. In recent years, researchers have cited a number of different dosing standards for antidepressant drugs.[3,5,8,32,34,36] Standards used in the Medical Outcomes Study were chosen to assess therapeutic dosing of TCADs for this study, because they distinguish elderly from nonelderly patients, and because they were designed to be "very conservative" (likely to find that dosing is at a therapeutic level).[25] For SSRIs, *Physician's Desk Reference (PDR)* usual dosage figures for nonelderly and elderly patients were used.[37] The only exception is that the standard for elderly patients taking sertraline was reduced from 50 mg to 25 mg daily because preliminary analyses suggested that the PDR standard classified 13 elderly patients incorrectly. These standards are shown in Appendix 1. To calculate the prescribed daily dose for each prescription, the number of milligrams dispensed (number of tablets times milligrams per tablet) was divided by the number of days supply as reported by the pharmacist on the drug claim.

Patients taking more than one antidepressant drug (either concomitantly or as a result of a switch from one drug to another) were classified as therapeutically dosed if any therapeutic doses were received for any antidepressant drugs. For this analysis, patients were separated into two comparison groups: (1) those who took no SSRIs at any point during the study period; and (2) those who took at least one SSRI. To allow sufficient time for titration to have taken place, these analyses included only those patients who had taken an antidepressant for at least 3 months. Post hoc sensitivity analyses showed that results were the same whether a 3-month or 5-month length of treatment was used as the inclusion criterion.

An additional analysis measured continuation in antidepressant treatment over the course of the 12 months following the initial antidepressant prescription, first for all patients, then for those who continued in treatment for at least 1 month. The purpose of this analysis was to assess the impact of premature termination.

Independent Variables

In addition to antidepressant type, independent variables for this study included patient age on January 1, 1994; gender; type of insurance coverage (HMO or indemnity); and two variables measuring nonantidepressant drug use prior to beginning antidepressant therapy: (1) use of psychotropics and (2) monthly expense for all nonantidepressant drugs. For the analysis of premature termination, an additional independent variable was whether the initial antidepressant dose was therapeutic, using the criteria shown in Appendix 1. Additionally, for claims on which the prescriber's Drug Enforcement Agency number was available, physician specialty data were obtained using the American Medical Association national database. Because this information is complete for only a subset of the patients in the study, it is not presented in detail in this paper. Tertiary amine TCADs (amitriptyline, doxepin, and imipramine) and secondary amine TCADs (desipramine and nortriptyline) were analyzed separately because of their different side effect profiles.[38]

Statistical Methods and Significance Testing

Descriptive and logistic regression analyses were performed using SPSS for Windows NT (Version 7.0).[39] Due to the large study population size, only findings at a significance level of at least $P < .01$ were interpreted.[40]

In descriptive analyses, differences in proportions across different subgroups (for example different age groups) were tested for statistical significance using Pearson chi square. Because the distribution of drug cost was nonnormal due to high-cost outliers, medians were used as the measure of central tendency and nonparametric statistical tests were applied. The non-parametric tests included the two-sample median test and the Mann-Whitney test, which assess equality of medians and distributions, respectively.

Logistic regression analyses of termination and subtherapeutic dosing were performed to assess the effects of multiple independent variables simultaneously. In developing the logistic regression models, different forms of the independent variables were tested (for example, drug expense was assessed on an interval scale, in curvilinear form with the addition of a squared term, and with polychotomous combinations for $0, >$0 to $50, and $50 or more) and the best-fitting form of each variable was selected. Interactions of patient characteristics (age, gender, and drug expense), payer type, and antidepressant type were tested as well. Coefficients were tested using the Wald statistic, and the overall significance of each model was tested using change in -2 times log likelihood (-2LL), which assesses improvement in goodness of fit.

Sensitivity Analyses of Patients with Very Low Doses

A limitation of pharmacy claims data is that they contain no diagnostic information. TCADs are sometimes used to treat patients with nonpsychiatric diagnoses, including chronic pain states, headaches, or diabetic neuropathy. Additionally, both TCADs and SSRIs are sometimes used for psychiatric indications other than depression, such as obsessive-compulsive or panic disorders. Since TCADs for chronic pain, migraines, and diabetic neuropathy are often (although not always) prescribed at a very low dose, patients consistently receiving doses considerably below levels that are therapeutic for depression (eg, imipramine at less than 50 mg per day for a nonelderly patient) were identified and key findings calculated without them. This approach was first used in a 1990 study of California Medicaid claims data to distinguish patients with "major depressive disorder" from those receiving antidepressants for other diagnoses.[8] Although they cannot be construed as establishing diagnosis, sensitivity analyses without the very low dose group do provide a modest test of the proposition that the findings are robust to the inclusion of patients receiving TCADs for nonpsychiatric indications.

For this study's sensitivity analyses, the California Medicaid standards for TCADs were used for nonelderly patients but were adjusted downward for elderly patients, both to be consistent with prior research and to reflect clinically appropriate dosing practices for older patients. Standards for SSRIs were derived from the PDR.[37] These standards are shown in Appendix 1.

Table 1. Profile of Study Population and Factors Associated with SSRI Treatment

	Profile (%)	Percent of Patients Initially SSRI-Treated*	Study Population No.
Age†			
<35 years	18.8	60.2	799
35 to 44	26.6	58.7	1130
45 to 64	39.1	51.3	1662
≥65	15.5	43.0	661
Gender			
Female	68.8	54.0	2925
Male	31.2	52.9	1327
Insurance Type			
HMO	49.1	54.5	2088
Indemnity	50.9	52.8	2164
Prior Psychotropics			
Yes	26.6	52.8	1131
No	73.4	54.0	3121
Prior Monthly Drug Cost‡			
None ($0)	15.0	62.2	637
<$5	12.8	55.1	546
$5 to <$20	23.8	53.0	1010
$20 to <$50	20.5	52.5	870
$50 to <$100	14.2	50.5	604
≥$100	13.8	49.1	585
ALL STUDY PATIENTS	**100.0**	**53.6 (N=2281)**	**4252**

*Patients not initially SSRI-treated were TCAD-treated (N=1971)
†Pearson chi square for association between this variable and initial antidepressant selection (SSRI vs TCAD) is significant at $P < .0001$
‡Average wholesale price for each prescription, summed across claims
SSRI=selective serotonin reuptake inhibitor; HMO=health maintenance organization; TCAD=tricyclic antidepressant drug

··· RESULTS ···

Patient Profiles

Table 1 presents a profile of the study population and of factors associated with initial antidepressant selection. Sixty-nine percent of study patients were women. Although 45% of study patients were younger than age 45, 16% were age 65 or older. Forty-nine percent of patients were enrolled in HMOs, and 51% in indemnity (fee-for-service) insurance. Consistent with previous research documenting high rates of concomitant illness and healthcare utilization among depressed persons,[21,41,42] 49% had incurred drug expenses of at least $20 monthly and 27% had used psychotropic medications other than antidepressants in the 9-12 months prior to starting antidepressant therapy. Physician specialty information was available for 79% of initial antidepressant prescriptions. Of these, 54% were written by nonspecialists, 32% by nonpsychiatric medical specialists, and only 14% by psychiatrists (specialty data not shown in table).

Fifty-four percent of study patients initially were treated with an SSRI, and the remaining 46% with a TCAD. Initial treatment with an SSRI was much more likely for patients who were younger and had

incurred no previous drug expense. Median age and prior monthly drug expense for SSRI-treated patients (44 years and $16, respectively) were lower ($P < .001$) than for TCAD-treated patients (48 years and $21, respectively [medians not shown in table]). Selection of a first line drug type appears unrelated to gender, insurance type, or previous psychotropic use.

The HMO study population contained higher proportions of younger persons and females than the indemnity population (Table 2). However, within age/gender subgroups the prevalence rates for depression treatment, measured as the proportion of enrollees using any antidepressant at any time during the first 3 months of 1994, were similar for HMO and indemnity payers. Although prevalence rates fluctuated somewhat for elderly patients, overall prevalence rates for females and males were approximately equal for the two payer types.

Premature Termination of Treatment

Twenty-six percent of the study population terminated antidepressant treatment before 1 month's time (Table 3). Patient age less than 35 years is associated with higher termination rates for TCAD users, although this effect is statistically significant only for tertiary amine TCADs ($P < .0001$ for HMO and indemnity patients combined, not shown in table). TCAD-treated patients with no drug expenses or with high ($50 or more monthly) expenses prior to beginning antidepressant therapy were less likely to terminate therapy prematurely than those with moderate expense levels ($0 to <$50 monthly), although again this effect is statistically significant only for tertiary amine TCADs. Receipt of an initial dose below therapeutic levels is associated with a higher termination rate only for patients initiating treatment with a tertiary amine TCAD, not for patients treated with secondary-amine TCADs or with SSRIs. Gender and previous psychotropic use are not significantly associated with termination rates for any of the drug types.

Initial antidepressant type and payer type are interactively associated with premature termination of treatment. Overall, 34% of those initiating therapy with a tertiary amine TCAD, 31% of those initiating with a secondary amine TCAD, but just 20% of those initiating with an SSRI, terminated therapy before 1 month's time. HMO enrollees had an overall termination rate of 31%, compared to 22% for indemnity enrollees (not shown in table, $P < .0001$). Notably, this payer type difference is observed only for those initially treated with TCADs, not for those initially treated with SSRIs. Thus, rates are highest among HMO enrollees initially treated with TCADs (42% and 40% for tertiary and secondary amine products, respectively), are lower for indemnity enrollees initially treated with TCADs (27% and 21% for tertiary and secondary amine products, respectively), and are lowest for those treated with SSRIs, irrespective of payer type (22% for HMO and 19% for indemnity enrollees). The younger age of HMO enrollees does not appear to account for these differences. Among those patients younger than age 35 who are initially treated with TCADs, termination rates are high (in excess of 35%) for both payer types. However, for all age groups above 35 years, rates are higher for HMO than indemnity enrollees.

Analysis of rates for individual TCAD products (data not shown) provides further evidence of interactive relationships with payer type. Consistent with clinical trial findings of lower drop-out rates for nor-triptyline than for other tricyclic products,[43] 1-month termination rates

Table 2. Demographic Characteristics and Antidepressant Treatment Prevalence Rates for HMO and Indemnity Populations

	Proportion in Study Population*		Prevalence Rate for Antidepressant Pharmacotherapy†	
	HMO % (N)	INDEMNITY % (N)	HMO %	INDEMNITY %
Males <65 years	27.1 (565)	23.2 (502)	1.6	1.7
Males age ≥65	1.4 (29)	10.7 (231)	2.0	1.2
Females <65	69.5 (1452)	49.5 (1072)	3.9	3.6
Females ≥65	2.0 (42)	16.6 (359)	3.3	4.2
All Males	28.5 (594)	33.9 (733)	1.6	1.5
All Females	71.5 (1494)	66.1 (1431)	3.9	3.7
ALL STUDY PATIENTS	**100.0 (2088)**	**100.0 (2164)**	**2.9**	**2.6**

*Pearson chi squares for study population's age and gender distributions by payer type are significant at P< 00001 (age), P<.001 (gender)
†Represents total number of antidepressant utilizers (not just those meeting study criteria) as a proportion of average enrollment for the first 3 months of 1994. All rates and counts include only payers that maintained member-specific information and that had no coverage restrictions on particular antidepressant products.

for nortriptyline and amitriptyline, respectively, are 19% and 29% ($P < .01$) in indemnity plans. However, in HMOs, nortriptyline andamitriptyline have approxmately equal termination rates (42% and 43%, respectively).

Table 3. Rates* for Key Antidepressant Treatment Events

	Termination Within One Month†			Subtherapeutic Dosing of TCADs‡
	Tertiary Amine TCAD Rate (N)	Secondary Amine TCAD Rate (N)	SSRI Rate (N)	Rate (N)
Insurance Type and Age				
Indemnity	26.5§ (801)	20.9§ (220)	18.6 (1143)	62.2‖ (502)
18 to 34 years	44.6¶ (65)	37.0 (27)	21.6 (185)	72.4 (29)
35 to 44	22.9¶ (109)	18.4 (38)	19.0 (252)	55.7 (61)
45 to 64	25.8¶ (365)	21.0 (81)	16.8 (452)	61.3 (240)
≥65	24.4¶ (262)	16.2 (74)	19.3 (254)	64.0 (172)
HMO	41.6§ (712)	39.9§ (238)	22.1 (1138)	73.8‖ (340)
18 to 34 years	45.2 (166)	38.3 (60)	25.0 (296)	68.9 (74)
35 to 44	44.0 (241)	35.4 (79)	20.9 (411)	68.9 (103)
45 to 64	37.5 (275)	45.5 (88)	20.9 (401)	79.7 (148)
≥65	40.0 (30)	36.4 (11)	26.7 (30)	73.3 (15)
Prior Monthly Drug Cost#				
None ($0)	21.6** (171)	24.3 (70)	18.7 (396)	52.1†† (142)
<$5	36.7** (199)	47.8 (46)	23.6 (301)	59.6†† (104)
$5 to < $20	37.6** (367)	30.6 (108)	22.2 (535)	67.3†† (171)
$20 to < $50	37.7** (305)	33.3 (108)	20.1 (457)	72.3†† (159)
$50 to < $100	29.8** (242)	29.8 (57)	17.4 (305)	73.6†† (129)
≥$100	31.9** (229)	23.2 (69)	19.5 (287)	74.5†† (137)
First Dose Therapeutic‡‡				
Yes	17.5§§ (183)	29.7 (91)	20.2 (2163)	
No	36.3§§ (1293)	31.7 (347)	22.9 (83)	
Gender				
Female	32.3 (1027)	29.8 (319)	19.7 (1579)	67.7 (601)
Male	36.2 (486)	33.1 (139)	21.9 (702)	64.7 (241)
Prior Psychotropics				
Yes	31.0 (403)	23.7 (131)	20.1 (597)	65.1 (218)
No	34.5 (1110)	33.6 (327)	20.5 (1684)	67.5 (624)
ALL STUDY CASES	**33.6‖ ‖(1513)**	**30.8‖ ‖ (458)**	**20.4‖ ‖(2281)**	**66.9 (842)**

*The rate for each of the two key treatment events (termination before 1 month and subtherapeutic dosing) is the proportion of patients in each subgroup of the study population for whom the event occurred. Statistical significance threshold used in the table is $P < .01$.

†Overall 1-month termination rate, all cases: 26.2% (n=4252).

‡Includes patients who took no SSRIs and who took a TCAD for at least 3 months. Excludes patients with missing dose information for any prescription.

§Chi square by insurance type significant at $P < 0001$.

‖Chi square by insurance type significant at $P < .001$.

¶Chi square by age group significant ($P < .01$) only for tertiary amine TCADS.

#Average wholesale price for each prescription, summed across claims.

**Chi square by cost group significant ($P < .01$) only for tertiary amine TCADs.

††Chi square by cost group significant ($P < 001$).

‡‡Based on criteria in Appendix 1. Excludes 92 patients for whom initial dose could not be calculated.

§§Chi square by initial dose level significant ($P < .0001$) only for tertiary amine TCADs.

‖ ‖Chi square by initial drug type significant at $P < 0001$.

Subtherapeutic Dosing

Initially, the analysis of subtherapeutic dosing compared those receiving at least one prescription for an SSRI with those taking no SSRI drugs. For SSRI utilizers, the rate of subtherapeutic dosing was less than 1% overall, and 2% or less for every patient subgroup. For this reason, rates for SSRI utilizers are not shown in Table 3.

Of those patients receiving at least one TCAD for 3 months or more, but taking no SSRIs, 67% were never prescribed a dose that met the therapeutic dosing criteria shown in Appendix 1. Payer type is associated with higher rates of subtherapeutic dosing, with 74% of HMO enrollees and 62% of indemnity enrollees receiving no doses at therapeutic levels. Subtherapeutic dosing rates are associated with higher drug expenses prior to beginning antidepressant therapy, but are not significantly associated with previous psychotropic use, age, or gender.

Logistic Regression Analyses

Table 4 presents exponentiated beta coefficients for logistic regression analyses of each of the two dependent variables. For each independent variable, the coefficient represents the factor by which the odds for each dependent variable (terminating within 1 month or receiving only sub-therapeutic doses) are multiplied when there is a one unit

change in the independent variable. For example, a coefficient of 1.3 represents a 30% increase in odds. Because the independent variables are dummy-coded to represent characteristics (eg, male gender), each coefficient can be described in terms of the change in the odds associated with having a given patient trait. The logistic regression models (Table 4) are statistically significant and have generally acceptable levels of classification accuracy overall (74% for termination and 67% for subtherapeutic dosing), although their accuracy for patient subgroups is limited. Of all the interactions tested (including combinations of patient traits, antidepressant type, and payer type), only the interaction of payer type with antidepressant type (HMO x TCAD) provided a statistically significant improvement to the model fit for the termination equation. None of the tested interactions was significant for the subtherapeutic dosing equation.

Three models of treatment termination are shown, the first (Model #1) without the interaction term (HMO x TCAD) and the term for initially therapeutic dose, the second (Model #2) with the interaction term added, and the third (Model #3) with all terms. All models indicate that age less than 35 years is associated with an approximately 30% increase in the odds of termination. Male gender and previous monthly drug cost of > 0 to and <$50 are associated with increases of approximately 25% and 27%, respectively. Previous psychotropic use is not significantly associated with treatment termination. In Model #1, HMO enrollment and an initial TCAD prescription increase the odds by 51% and 102%, respectively. In Model #2, initial TCAD prescription is again associated with increased odds (54%), and the interaction of HMO x TCAD increases the odds by 63%. In Model #3, with the addition of the term for initial therapeutic dose, neither HMO enrollment or an initial TCAD prescription alone are significant factors. However, the interaction of HMO X TCAD increases the odds of treatment termination by 59%.

The subtherapeutic dosing equation indicates that HMO enrollment and high ($50 or more) previous monthly drug expenses increase the odds of dosing below therapeutic levels by 67% and 77%, respectively. Age, gender, and previous psychotropic use are not significantly associated with this dependent variable.

Relationship Between 1-Month Termination and Subsequent Course

Rates of continuation in treatment during the 12-month period following the initial antidepressant prescription (TCAD or SSRI) are illustrated with cumulative survival curves in Figures 1 and 2. Comparison of Figure 1, which includes all study patients (n=4252), and Figure 2, which includes only

Table 4. Logistic Regression Analyses*† of Key Antidepressant Treatment Events

	Termination Before One Month			Subtherapeutic Dosing of TCADs
	Model #1	Model #2	Model #3	
Age < 35 years‡	1.32¶	1.31¶	1.30¶	1.05
Male gender	1.23¶	1.24¶	1.25¶	0.89
No previous psychotropics	1.07	1.07	1.08	1.36
HMO enrollment	1.51**	1.16	1.17	1.67¶
Prior drug cost >$0 to <$50§	1.27¶	1.27¶	1.27¶	
Prior drug cost ≥$50§				1.77¶
Initial TCAD prescription	2.02**	1.54**	1.02	
HMO x TCAD		1.63#	1.59¶	
Initial dose therapeutic			1.68#	
Model chi square	162.6**	174.1**	190.1**	24.5#
Cases correctly classed‖	74%	74%	74%	67%
Number of cases	4160	4160	4160	842

*Exponentiated beta coefficients. Significance threshold is $P < .01$.

†Interaction terms tested but not significant in any model include: HMO x age < 35; HMO x drug cost; HMO x gender; age < 35 x gender; age < 35 x drug cost; and gender x drug cost. Terms tested but not significant for the termination models include: TCAD x age < 35; TCAD x gender; and TCAD x drug cost.

‡Measures tested for inclusion in the models included age, age with age squared, and polynomial combinations of various age groupings (eg, age ≥ 65).

§Measures tested for inclusion in the models included cost, cost with cost squared, and polynomial combinations of cost > $0, cost $0 to $50 and cost ≥ $50.

‖Accuracy of prediction is low for cases that terminated treatment (2%) and for cases that were not subtherapeutically dosed (0%).

¶Significant at $P < .01$; #Significant at $P < .001$; **Significant at $P < .0001$

those patients continuing in treatment for at least 1 month (n=3138), suggests that the relationship between initial antidepressant selection and remaining in treatment appears to be explained entirely by terminations occurring in the first month. When continuation rates are measured in 3-month intervals (not shown in figure), excluding patients who terminated within 1 month, there are no significant differences by drug type at 3 (85% TCAD vs 87% SSRI), 6 (72% TCAD vs 73% SSRI), 9 (62% both TCAD and SSRI) or 12 (50% both TCAD and SSRI) months.

Sensitivity Analyses

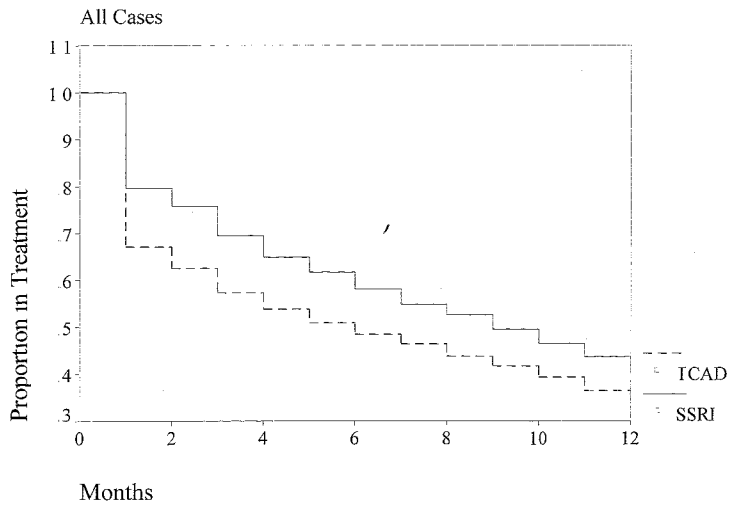
For both of the dependent variables, termination and subtherapeutic dosing, in both descriptive and logistic regression analyses, comparisons by drug types and between payer types produce the same results when analyses are limited to patients who received at least one dose meeting or exceeding the sensitivity analysis thresholds delineated in Appendix 1. Sensitivity analyses of sample selection criteria also suggest robust findings. For example, when patients taking other type antidepressants (eg, trazodone) are included in the calculations, rates of termination at 1 month are 32%, 29%, and 18% for tertiary amine TCADs, secondary amine TCADs, and SSRIs, respectively. Again including these patients, rates of subtherapeutic dosing for patients taking no SSRI drugs are 60% for indemnity and 71% for HMO payers. Similarly, excluding patients taking more than one antidepressant drug, 1-month termination rates are 41%, 40%, and 24% for tertiary amine TCADs, secondary amine TCADs, and SSRIs, respectively, and subtherapeutic dosing rates are 63% for indemnity and 76% for HMO payers. Finally, comparisons of termination rates among drug types produce the same results, whether termination is measured at 1, 2, or 3 months.

··· DISCUSSION ···

Overview of Findings

Three major conclusions are suggested by these findings. First, initial selection of TCADs instead of SSRIs is associated with two indicators of failed or compromised antidepressant treatment—premature termination of therapy and failure to achieve a therapeutic dose. Second, the first month of treatment appears to be particularly important in the relationship between initial antidepressant selection and length of treatment. Among patients whose drug therapy persists past the first month, approximately equal proportions of patients initially treated with TCADs and SSRIs remain in treatment for the subsequent year. Third, although rates of premature termination and subtherapeutic dosing are higher for TCADs than for SSRIs in both HMO and indemnity environments, these differences are particularly large in HMOs.

Figure 1. Continuation in Antidepressant Treatment by Initial Drug Type: All Cases



Methodological Considerations in Interpretation

In interpreting these findings, we first considered the possibility that they were the consequence of the retrospective study design or limitations of the pharmacy claims database. The lack of diagnostic information on pharmacy claims raises a concern that patients who used TCADs for nonpsychiatric indications were responsible for the observed differences between TCADs and SSRIs. Several points counter this possibility. First, the antidepressant utilizers in this study—in particular with respect to the age distribution, the proportion who are female, and the high levels of drug expense—have characteristics consistent with

depression.[1,5,41] Addition-ally, sensitivity analyses excluding patients consistently receiving very low doses produce the same key findings as those observed for the study population as a whole. Additional sensitivity analyses assessing subtherapeutic dosing rates for persons receiving nonantidepressant drugs used to treat migraines, diabetes, or pain found no differences between these subgroups and the rest of the study population. Moreover, a previous comparison of TCADs with SSRIs produced the same results for its whole study population of antidepressant users as for a subgroup of patients with a depression diagnosis.[33] Finally, a 1992 comparison of termination rates for older versus newer antidepressants, using a claims database in which diagnostic information was not available,[2] produced findings similar to those of two later studies restricted to patients with a depression diagnosis.[32,34]

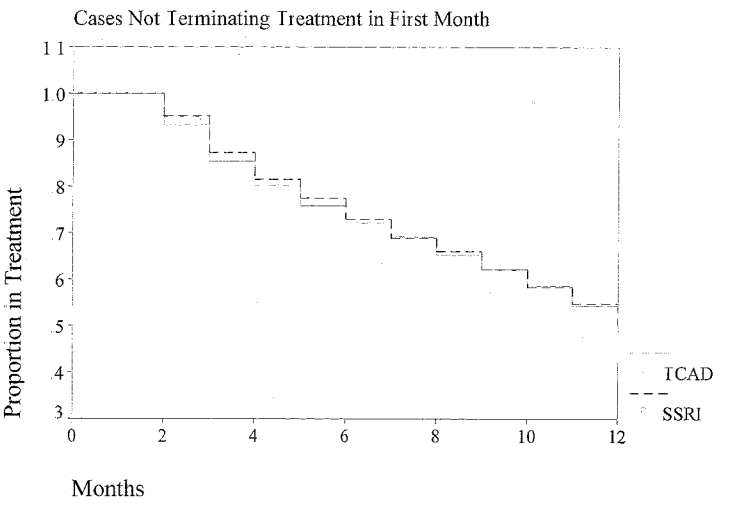
Even if the results of this study were affected by the inclusion of patients receiving treatment for nonpsychiatric indications, this problem would be unlikely to explain the payer differences. The prevalence rates for antidepressant pharmacotherapy are approximately equal for HMO and indemnity payers. For the payer findings to be attributable to use of TCADs for nonpsychiatric indications, HMOs and indemnity plans would have to be using antidepressant drugs in equal proportions overall but in unequal proportions for different diagnostic purposes. Such a use pattern appears unlikely, given the findings of previous research with depressed individuals suggesting that the probability of initiating antidepressant medication is the same in HMO and indemnity plans.[5]

An important limitation of the subtherapeutic dosing analysis is that no measures of plasma levels or of therapeutic response were obtained. It is possible that some of the TCAD-treated patients classified as subtherapeutically dosed were actually slow drug metabolizers and/or responded to low doses of the drugs.[44,45] Mitigating this concern are the conservative dosing thresholds used, which bias results against finding that dosing is subtherapeutic. It has been argued that measuring serum levels of TCADs would produce findings of even lower rates of treatment adequacy.[2] Moreover, this limitation does not appear to explain the payer type difference.

An important question is whether these findings are generalizable to other patients and care settings. Because we excluded patients with antidepressant use in the 9 months prior to the start of the study, the findings generalize only to either new or episodic utilizers, not to patients with chronic depressive disorders. Additionally, although the ESI client base is nationwide, we cannot verify that it is representative of typical care. For example, most of the HMO patients in this study were served by 13 HMOs, owned by three different corporations. The small number of corporations raises the concern that findings are particular only to these organizations. When we examined findings by HMO, key findings were the same, mitigating this concern.

Finally, because claims data are designed for payment, rather than research purposes, the possibility of errors in the claims, for example omissions or keying errors, must be addressed. Pharmacies in ESI's network must submit claims in order to be paid, reducing the likelihood of omissions. It is possible that some patients received prescription drugs from another source, for example, a spouse's insurance. Although no precise data on dual coverage are available, ESI's experience is that use of multiple prescription benefit plans within the same family is rare. Another potential

Figure 2. Continuation in Antidepressant Treatment by Initial Drug Type: Cases Not Terminating in First Month



problem is that drugs received during an inpatient stay would be reflected in the hospital bill rather than in the prescription claims database. However, even if prevalent, this problem is unlikely to affect measurement of the dependent variables used in the study, because the 13-16 month "post" period is much longer than the median length of stay for depression in private hospitals, which is only 15-25 days.[46] Additionally, the calculation of daily dose and treatment length are partly dependent on the days supply figure, which is subject to error because it is keyed in by the dispensing pharmacist. However, most of the antidepressant prescriptions were dispensed for 30 days, consistent with ESI's experience. Generally, although it is possible that some errors or omissions occurred, we can think of no reasons why they would occur more for certain antidepressant types, age groups, or payer types.

Comparison with Previous Research

Two previous observational studies conducted in different HMOs have compared rates of premature termination and subtherapeutic dosing for TCADs as compared to SSRI products. One found that 46% of doxepin users, but only 25% of fluoxetine users, terminated treatment before 30 days, and that rates of subtherapeutic dosing for doxepin and fluoxetine were 74% and 49%, respectively.[34] Another found that 42% of tertiary amine TCAD users and 24% of SSRI users terminated treatment within 45 days. That study found subtherapeutic dosing rates of 13% for SSRIs, 26% for secondary amine TCADs, and 37% for tertiary amine TCADs.[32] An additional retrospective analysis of one HMO's pharmacy claims found that the rate of drop-out after filling only one prescription was 51% for users of amitriptyline, doxepin, or imipramine.[2] Thus, the rates of premature termination and subtherapeutic dosing calculated for HMOs in this study are generally consistent with the findings of previous observational research. Although we are aware of no previous research comparing TCADs with SSRIs in care provided under indemnity payment arrangements, our findings would suggest that higher rates of treatment continuation and lower rates of subtherapeutic dosing for SSRIs are evident for enrollees in both types of insurance.

The unexpected finding of interactive effects of HMO enrollment and TCAD use prompted a review of previous research on the treatment of depression in managed care and fee-for-service environments. Studies conducted in a variety of settings, including one randomized trial in which participants were assigned to different insurance types, have found equal likelihood of receiving mental healthcare, but generally less intensive mental health service utilization, including fewer office visits and/or lower use rates for specialty care, in prepaid than in fee-for-service environments.[47-49] Previous work has also emphasized the importance of provider time and patient education in antidepressant treatment adherence.[2,7,29,50,51] For example, a randomized trial conducted in a population of depressed HMO primary care patients (88% of whom were initially treated with TCADs), found that a program that included longer and more frequent provider visits early in therapy, collaboration between primary care physicians and psychiatrists, monitoring of medication compliance, and patient education about antidepressants and side effects, significantly increased the likelihood of receiving 90 or more days of antidepressant medication at a therapeutic dose.[30] Given the relationship between treatment continuation and intensive provider efforts, a combination of limited provider time and first line use of TCADs, with their higher side effect rates and greater risk for termination, could produce the interactive effects observed in this study. This interpretation is supported by previous research associating prepaid care with possible quality of care problems in the treatment of depression,[5] including the termination of antidepressant medication,[52] although the populations and outcomes measures used in that work are not directly comparable to those used in the present study. It is possible that higher termination rates in HMOs reflect better detection of unnecessary medication use. However, this explanation is inconsistent with the finding of an interaction between TCAD use and HMO enrollment, since there is no reason to believe that TCADs are unnecessarily prescribed any more often than SSRIs.

A recent randomized controlled trial of first line antidepressant treatment in one HMO's primary care clinics[35] compared fluoxetine, imipramine, and desipramine. As with the present study, this trial found that fluoxetine-treated patients were more likely than TCAD-treated patients to continue treatment with the originally dispensed medication and to reach a therapeutic dose. However, in the trial, the TCAD-treated patients were not more likely to drop out of treatment than those prescribed fluoxetine, but were instead more likely to switch to a new antidepressant medication. It is possible that this difference between our findings and those of the trial is attributable to selection bias in our retrospective design—for example, if patients likely to discontinue treatment are also more likely to be prescribed a TCAD initially. Alternatively, as the trial's authors pointed out, the trial's telephone follow-up interviews with patients, which included questions about antidepressant adher-

ence and side effects, may have encouraged treatment continuation. The first of these assessments occurred at 1 month after drug randomization. This latter interpretation is consistent with the view that personal contact with patients early in treatment may increase continuation rates.

This study's finding of higher rates of subtherapeutic dosing for HMO compared with indemnity enrollees may also reflect more limited provider time in the former environment, given the complexity of dosing TCADs. However, the Medical Outcomes Study's comparison of subtherapeutic dosing rates for depressed outpatients in prepaid and fee-for-service care found no differences by payer type.[5] This discrepancy could be attributable to factors unmeasured in this study, including different proportions of specialty use and/or patient race distribution. Both receipt of care from a psychiatrist and white race have been associated with higher rates of adequate depression treatment.[5,32,34] It is also possible that the use of screening measures for depression in the Medical Outcomes study produced a study population that differs from our population of all antidepressant utilizers.

In light of the hypothesis that the findings for TCADs and SSRIs are at least partly due to their distinct side effect profiles, the observation of higher TCAD termination rates for patients under age 35 is intriguing. Also interesting is the finding that, among patients beginning treatment with a tertiary amine TCAD, termination rates were higher for those whose initial dose was below therapeutic minimums. There are a number of possible explanations for these findings. Younger patients may be less tolerant of side effects and generally more willing to question medical treatments. Lower termination rates for patients who initially receive therapeutic doses may reflect better efficacy at the higher dose levels. Specifically, patients maintained at subtherapeutic doses would be expected to experience side effects without therapeutic benefits. It is not possible to resolve these questions using pharmacy claims data alone.

Conclusions

There has been much debate in recent years about which antidepressants should be considered first line treatment. One factor driving this debate, although certainly not the only one, is that SSRIs are more costly than TCADs. While much of this discussion has taken place in relatively theoretical forums such as scientific journals, in practice the outcomes of this discussion are reflected not only in the treatment decisions of individual physicians, but also in the policies of health care payers.[53]

Many clinical and diagnostic factors influence antidepressant selection. This study cannot resolve the debate about first line antidepressant choice, due to important methodological limitations including retrospective design and lack of diagnostic data. However, study findings do suggest that drug treatment decisions and coverage policies should take into account the characteristics not only of the individual patient, but also of the environment in which care takes place. Antidepressant selection may represent, in part, a trade-off of drug acquisition cost against provider time spent in patient education, compliance monitoring, and dose titration. SSRIs' advantages in treatment adherence and ease of dosing may be particularly important in care environments with limited provider time. An additional important implication of this study is that efforts to improve patient compliance may be especially useful in the first month of treatment.

We believe that the questions raised by these findings are important and merit further investigation and discussion. Potentially, first-line antidepressant selection and efforts to improve patient compliance early in the course of therapy could impact not only medical costs, but also quality of care and patient outcome. If confirmed by additional research, our findings have implications for antidepressant selection, patient management, and organizational policies.

Acknowledgments

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Appendix 1. Antidepressant Dosing Standards*

	Minimum Therapeutic Dose		Minimum Dose for Inclusion in Sensitivity Analysis	
	Age 18-60	Age ≥61	Age 18-64	Age≥65
Amitriptyline†	100	75	50	25
Desipramine†	100	75	50	25
Doxepin†	100	75	50	25
Fluoxetine‡	20	10	20	10
Imipramine†	100	75	50	25
Nortriptyline†	75	50	25	25
Paroxetine‡	20	10	20	10
Sertraline‡	50	25	50	25

*Values given in milligrams dispensed per day.
†Therapeutic dose from Wells et al [5] Sensitivity analysis dose modified from McCombs et al [8]
‡Therapeutic dose from *PDR Generics* [37] Sensitivity analysis dose modified from *PDR*.