Economic Outcomes With Antidepressant Pharmacotherapy: A Retrospective Intent-To-Treat Analysis

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Herein we describe a retrospective intent-to-treat evaluation designed to compare the natural course of antidepressant utilization and direct health service expenditures for the treatment of a single episode of major depression among patients enrolled in a multistate network-model health maintenance organization and initially prescribed either a tricyclic antidepressant (amitriptyline or nortriptyline) or the serotonin selective reuptake inhibitor (SSRI) fluoxetine. Patient-level paid-claims data for the period July 1, 1988, through December 31, 1991, were abstracted. During the above time frame, fluoxetine was the only SSRI available in the United States. Patients prescribed amitriptyline were more than three times as likely to require a change in antidepressant pharmacotherapy (OR = 3.27, 95% CI = 2.31 to 5.49), while patients prescribed nortriptyline were nearly four times more likely to change medication (OR = 3.82, 95% CI = 2.74 to 6.83) relative to patients initially prescribed fluoxetine. Consistent with our intent-to-treat design, all accrued health service expenditures were assigned to the pharmacotherapeutic option initially prescribed. Multivariate analyses revealed that initiation of antidepressant pharmacotherapy with amitriptyline resulted in a 25.7% increase in per capita depression-related health service expenditures per year, while initiation of antidepressant pharmacotherapy with nortriptyline resulted in a 28.1% increase in per capita depression-related health service expenditures per year relative to patients initially prescribed fluoxetine. A financial break-even point was achieved at the conclusion of Month 5, at which time all three intent-to-treat cohorts had comparable health service expenditures in total. From a financial perspective, results stemming from this inquiry suggest that the initiation of antidepressant pharmacotherapy with an SSRI is warranted.

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The increasing prevalence of depression and its associated morbidity, mortality, and economic consequences to the health care delivery system and society mandate the selection of both efficacious and effective treatment.[1–10] The American Psychiatric Association and the Agency for Health Care Policy and Research of the United States Department of Health and Human Services have recently issued clinical practice guidelines for the management of major depressive disorders.[11,12] These guidelines stress the importance of improving patients' compliance with prescribed pharmacotherapy and have recommended that pharmacotherapy be modified if patients do not respond adequately to the initially prescribed regimen.

Recent pharmacotherapeutic advances in the treatment of depression have included the development of serotonin selective reuptake inhibitors (SSRIs), thereby providing an alternative to tricyclic antidepressants (TCAs).[13–20] A recent meta-analysis of 42 published randomized clinical trials comparing SSRIs with TCAs discerned a pooled discontinuation rate due to side effects of 14.9% for patients receiving an SSRI and 19% among individuals receiving a TCA ($p \le .01$).[21] In the 7 placebo-controlled studies examined, the pooled discontinuation rate due to side effects for SSRIs was 19.0%, and 27.0% for patients assigned a TCA ($p \le .01$). The authors found no significant difference in discontinuation rates due to insufficient efficacy in either analysis. It was concluded that the risk-benefit calculation

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favored the SSRIs, as there were similar levels of efficacy but significantly higher rates of discontinuation due to side effects with the TCAs.

While findings from randomized clinical trials suggest greater patient tolerability with the SSRIs, and thereby potentially greater regimen adherence, there exist few empirical data regarding the natural history of antidepressant utilization and associated health service expenditures among patients treated in clinical practice (the naturalistic environment).[22,23] Herein we describe a retrospective intent-to-treat evaluation designed to compare the natural course of antidepressant utilization and direct health service expenditures for the treatment of a single episode of major depression among patients enrolled in a multistate network-model health maintenance organization (HMO) and initially prescribed either a TCA (amitriptyline or nortriptyline) or the SSRI fluoxetine.

MATERIALS AND METHODS

Study Design

Cohort assignment stemmed from initial receipt of either amitriptyline, fluoxetine, or nortriptyline for the treatment of a single episode of major depression (DSM-III code 296.2). The attribution of all subsequent health service expenditures emanated from the intent-to-treat design.[24,25] Health service expenditures reflected direct financial outlays made by the HMO (not charges) in 1996 constant dollars.

Data

Information regarding health service utilization was derived from the computer archive of a multistate network-model HMO system serving 700,000 beneficiaries. Patient-level paid-claims data for the period July 1, 1988, through December 31, 1991, were abstracted for patients initiating antidepressant pharmacotherapy with either amitriptyline, fluoxetine, or nortriptyline. During the above time frame, fluoxetine was the only SSRI available in the United States. As outlined in previous research,[26–29] the retrospective archive facilitated the abstraction of data regarding disease-specific health service utilization. Each patient-level file contained extensive information regarding the health services received, including type of service (e.g., hospitalization), date of service, units of service (e.g., days), and ICD-9-CM, and/or DSM-III code. Claims data for paid prescriptions included information indicating the name of the medication, strength, and quantity dispensed. The research protocol was approved by the Center for Health Services Research & Policy of Qual-Med Health Plan of Washington, Inc., Inland Northwest Division.

Selection Criteria

(1) Beneficiaries were aged ≥ 18 but < 65 years. Beneficiaries aged 65 years and older are eligible for health insurance coverage under both the HMO and Medicare (Title XX of the Social Security Act). Therefore, in order to discern actual rather than estimated program expenditures, this research was limited to an investigation of ambulatory patients with a confirmed diagnosis of depression (ICD-9-CM, or DSM-III code 296.2: Major Depression, Single Episode), for whom the multistate network-model HMO provided complete coverage for the utilization of health care services. (2) Patient-level data files contained an ICD-9-CM or DSM-III code of 296.2 as recorded at the time of diagnosis by a primary care physician or psychiatrist and subsequent receipt of amitriptyline, fluoxetine, or nortriptyline within 30 days of said office visit. The HMO commissioned the dispensing of prescription medication in 30-day supplies. HMO beneficiaries were required to contribute a uniform copayment with receipt of each 30-day supply of medication: $5 per prescription for generic compounds (amitriptyline and nortriptyline) and $8 per prescription for brand name compounds (fluoxetine). (3) Patient-level data files contained information for at least 18 months prior to the date on which the initial prescription for amitriptyline, fluoxetine, or nortriptyline was dispensed. (4) Patient-level data files contained at least 12 months of data subsequent to the date on which the initial prescription for amitriptyline, fluoxetine, or nortriptyline was dispensed. (5) Patients were not to have been in receipt of antidepressant pharmacotherapy (i.e., an SSRI or TCA) during the 6 months prior to initiating a regimen of either amitriptyline, fluoxetine, or nortriptyline. (6) Patients were not to have been dispensed medication indicative of psychiatric comorbid conditions (e.g., bipolar disorder, psychosis, schizophrenia), neurologic deficits (e.g., dementia, Parkinson's disease), or a substance abuse disorder (e.g., cocaine addiction) during the 18 months prior to, or post receipt of, the initial prescription for amitriptyline, fluoxetine, or nortriptyline. (7) Patients were not to have utilized an intermediate care or skilled nursing facility during the 18 months prior to, or post receipt of, the initial prescription for amitriptyline, fluoxetine, or nortriptyline.

A total of 550 HMO beneficiaries were found to satisfy the study selection criteria (amitriptyline, N = 211; fluoxetine, N = 180; nortriptyline, N = 159). The date of receipt for the initially prescribed pharmacotherapeutic option to be evaluated was used to partition the patient-level paid-claims data files into pre- and post-time periods. The time periods for analysis were: (1) $Prior_1$: the period 7 to 18 months prior to initiating an antidepressant regimen of interest; (2) $Prior_2$: the period 0 to 6 months prior to initiating an antidepressant regimen of interest; and (3) *Post*: the period 0 to 12 months post receipt of an antidepressant regimen under investigation.

Multivariate Modeling

Comparisons were undertaken between cohorts initiating antidepressant pharmacotherapy with amitriptyline

Table 1. Demographic Characteristics and Utilization of Antidepressant Pharmacotherapy*

Attribute	Amitriptyline (N = 211)	Fluoxetine (N = 180)	Nortriptyline (N = 159)
Age (mean ± SD, y)	38.6 ± 7.4	42.3 ± 8.5	40.5 ± 8.3
Women, %	68%	74%	71%
Diagnosed by psychiatrist, %	17%	23%	15%
Remaining on initial ADP, N (%)	110 (52%)	146 (81%)	75 (47%)
Requiring a change from initial ADP, N (%)	101 (48%)	34 (19%)	84 (53%)
Changed to, N (%)			
TCA	28 (28%)	34 (100%)	39 (46%)
Fluoxetine	73 (72%)		45 (54%)
Requiring ≥ 2 changes from initial ADP, N (%)	14 (7%)	3 (2%)	8 (5%)
Patients obtaining ≥ 180-day supply of ADP, N (%)	109 (52%)	116 (64%)	77 (48%)
Patients with prior diagnosis of major depression, single episode and receipt of ADP, N (%)	23 (11%)	26 (14%)	14 (9%)

*Patients initially prescribed amitriptyline, fluoxetine, or nortriptyline for the treatment of major depression, single-episode (ICD-9-CM or DSM-III Code 296.2). Abbreviations: ADP = antidepressant pharmacotherapy; TCA = tricyclic antidepressant.

versus fluoxetine and nortriptyline versus fluoxetine. The a priori level of significance for all statistical tests was set at $p \leq .05$. Regression analyses (ordinary-least-square and logarithmic transformations) were conducted using the general linear model procedure in SAS[30]; odds ratios and 95% confidence intervals were discerned using the LOGISTIC procedure.[30] All comparisons were adjusted for patient's age, gender, number of concomitant disease-state processes, utilization of health services during the 6 months prior to initiating antidepressant pharmacotherapy, specialty of physician recording a diagnosis of major depression, single episode, at the time a regimen of interest was initiated (primary care or psychiatry), and the presence or absence of a previous diagnosis of major depression, single episode, and receipt of antidepressant pharmacotherapy between 7 and 18 months prior to initiating a pharmacotherapeutic regimen of interest.

RESULTS

Table 1 presents demographic characteristics and utilization sequence of antidepressant pharmacotherapy for HMO beneficiaries initially prescribed either amitriptyline (N = 211), fluoxetine (N = 180), or nortriptyline (N = 159) for the treatment of single episode depression. The majority of subjects were women, with an overall mean age of approximately 40 years. A greater proportion of patients prescribed fluoxetine were diagnosed by a psychiatrist (23% as compared with 17% for amitriptyline and 15% for nortriptyline). Patients initiating antidepressant pharmacotherapy with fluoxetine were far more likely to continue with the original pharmacotherapeutic option (81% as compared with 52% for amitriptyline and 47% for nortriptyline). Adjusted odds ratios revealed patients initially prescribed amitriptyline were over three times more likely to require a change in antidepressant pharmacotherapy (OR = 3.27, 95% CI = 2.31 to 5.49) than were patients initially prescribed fluoxetine; patients initiating antidepressant pharmacotherapy with nortriptyline were nearly four times more likely to require a change in medication (OR = 3.82, 95% CI = 2.74 to 6.83) than were patients initially prescribed fluoxetine. Finally, a greater proportion of patients initially prescribed fluoxetine obtained a 180-day supply or more of antidepressant pharmacotherapy (64% as compared with 52% for amitriptyline and 48% for nortriptyline).

Multivariate models estimating per capita depression-related health service expenditures per year revealed that initiation of antidepressant pharmacotherapy with either amitriptyline or nortriptyline was more expensive relative to initiation with fluoxetine (Table 2). Specifically, initiation with amitriptyline resulted in an increase in expenditures for depression-related physician visits ($44.10; N.S.), psychiatric visits ($51.94; $p \leq .05$), laboratory testing ($1.08; N.S.), general hospitalizations ($174.32; $p \leq .05$), and psychiatric hospitalizations ($164.56; $p \leq .05$), and a decrease in expenditures for antidepressant pharmacotherapy (–$118.26; $p \leq .05$), for a total per capita per year increase in health service utilization of $317.74 ($p \leq .05$) relative to initiation of antidepressant pharmacotherapy with fluoxetine. Logarithmic transformation of the total per capita per year expenditure model yielded the percentage differential in health service utilization for patients initiating with amitriptyline relative to fluoxetine. (In a logarithmic equation, the coefficients of independent dichotomous variables represent the percentage changes in the dependent variable for those observations in which the independent dichotomous variables equal 1 rather than 0.) Results indicated a 25.7% increase in total per capita depression-related health service expenditures per year when initiating antidepressant pharmacotherapy with amitriptyline relative to fluoxetine.

Initiating antidepressant pharmacotherapy with nortriptyline resulted in an increase in expenditures for depression-related physician visits ($47.09; $p \leq .05$), psychiatric visits ($62.33; $p \leq .05$), laboratory testing ($0.46; N.S.), general hospitalizations ($192.87; $p \leq .05$), and psychiatric hospitalizations ($153.18; $p \leq .05$), and a decrease in expenditures for antidepressant pharmacotherapy (–$98.49; $p \leq .05$), for a total per capita per year increase in health service utilization of $357.44 ($p \leq .05$) relative to initiation of antidepressant pharmacotherapy with fluoxetine. Logarithmic transformation revealed there existed a 28.1% increase in total per capita depression-related health service expenditures per year when ini-

Table 2. Regression Analysis: Estimated Per Capita Health Annual Service Expenditures for the Treatment of Major Depression, Single Episode (ICD-9-CM or DSM-III Code 296.2)*

Comparison	Primary Care Physician	Psychiatrist	Laboratory	Hospitalization		Antidepressant Pharmacotherapy	Annual Per Capita Expenditures
				General	Psychiatric		
Amitriptyline vs fluoxetine	$44.10	$51.94[a]	$1.08	$174.32[a]	$164.56[a]	–$118.26[a]	$317.74[a]
Model R^2	0.2383	0.3627	0.0472	0.2234	0.3109	0.4012	0.3149
Nortriptyline vs fluoxetine	$47.09[a]	$62.33[a]	$0.46	$192.87[a]	$153.18[a]	–$98.49[a]	$357.44[a]
Model R^2	0.2720	0.2185	0.0621	0.1838	0.2617	0.4439	0.2817

*1 year after receipt of amitriptyline or nortriptyline relative to fluoxetine as initial antidepressant pharmacotherapy.
[a]$p \leq .05$.

tiating antidepressant pharmacotherapy with nortriptyline relative to fluoxetine.

The allocation of health service expenditures by month (30-day intervals) after initiation of antidepressant pharmacotherapy afforded an examination as to the time period required to arrive at a financial break-even point. Multivariate findings revealed that, by the conclusion of Month 5, all cohorts in the intent-to-treat analysis had comparable health service expenditures in total.

CONCLUSION

We examined paid-claims data from a multistate network-model HMO system in order to discern the natural history of antidepressant utilization and associated health service expenditures 1 year after initiating antidepressant pharmacotherapy with either amitriptyline, fluoxetine, or nortriptyline. Patients initially prescribed amitriptyline were more than three times as likely to require a change in antidepressant pharmacotherapy (OR = 3.27, 95% CI = 2.31 to 5.49), while patients initially prescribed nortriptyline were nearly four times more likely to change medication (OR = 3.82, 95% CI = 2.74 to 6.83) relative to patients initially prescribed fluoxetine. Consistent with our intent-to-treat design, all accrued health service expenditures were assigned to the pharmacotherapeutic option initially prescribed. Multivariate analyses revealed that initiation of antidepressant pharmacotherapy with amitriptyline resulted in a 25.7% increase in per capita depression-related health service expenditures per year, while initiation of antidepressant pharmacotherapy with nortriptyline resulted in a 28.1% increase in per capita depression-related health service expenditures per year relative to patients initially prescribed fluoxetine. A financial break-even point was achieved at the conclusion of Month 5, at which time all three intent-to-treat cohorts had comparable health service expenditures in total.

A recent prospective randomized intent-to-treat analysis discerned comparable economic outcomes at 6 months among cohorts initially prescribed either a TCA (desipramine or imipramine) or the SSRI fluoxetine.[23] Relative to our investigation, the internal validity of the prospective trial was enhanced by both the randomization process and the assessment of mental health status at baseline. Moreover, HMO beneficiaries meeting our study selection criteria reflect a younger population with fewer comorbid disease-state processes than would be found in the general population of depressed patients. The retrospective study herein afforded an evaluation as to the effect of initial antidepressant pharmacotherapy on direct expenditures for depression-related health services. An evaluation as to the effect of antidepressant pharmacotherapy on indirect expenditures at the patient level was infeasible given the retrospective nature of the study design. Therefore, results stemming from this inquiry reflect direct health service expenditures rather than a measure as to the cost-effectiveness of selecting a specific antidepressant as initial pharmacotherapy.

In summary, our analysis reinforces the value of, and disparity between, results obtained from randomized clinical trials designed to discern the efficacy of pharmacotherapy and the natural history of medication utilization and health service expenditures as observed in clinical practice. Taken together, both perspectives (randomized clinical trials and naturalistic inquiry) provide stakeholders with enhanced information for the crafting of pharmaceutical formularies. From a financial perspective, results stemming from this inquiry suggest that the initiation of antidepressant pharmacotherapy with an SSRI is warranted. Finally, evidence from this and previous research indicates that economic evaluations involving pharmacotherapy must extend beyond the procurement cost of medication.[31]

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), nortriptyline (Pamelor and others).

REFERENCES

1. Simon GE, Ormel J, Vonkorff M, et al. Health care costs associated with depressive and anxiety disorders in primary care. Am J Psychiatry 1995; 152:352–357
2. Lane R, McDonald G. Reducing the economic burden of depression. Int Clin Psychopharmacol 1994;9:229–243
3. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distri-

bution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry 1994;151:979–986
4. Johnson J, Weissman M, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. JAMA 1992;267:1478–1483
5. Conti DJ, Burton WN. The economic impact of depression in a workplace. J Occup Med 1994;36(9):983–988
6. Jonsson B, Bebbington PE. What price depression? the cost of depression and the cost-effectiveness of pharmacological treatment. Br J Psychiatry 1994;164:665–673
7. Strum R, Wells KB. How can care for depression become more cost-effective? JAMA 1995;273:51–58
8. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–419
9. Wells KB, Burnam MA. Caring for depression in America: lessons learned from early findings of the Medical Outcomes Study. Psychiatric Medicine 1991;9(4):503–519
10. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines: impact on depression in primary care. JAMA 1995; 273:1026–1031
11. American Psychiatric Association. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993:150(4, suppl):l–26
12. Agency for Health Care Policy and Research. Clinical Practice Guideline: Depression in Primary Care, vol 2: Treatment of Major Depression. Washington, DC: US Government Printing Office; 1993. AHCPR Publication No. 93-0551
13. Gram LF. Fluoxetine. N Engl J Med 1994;331:1354–1361
14. Casey DE. Striking a balance between safety and efficacy: experience with the SSRI sertraline. Int Clin Psychopharmacol 1994;9(3, suppl):5–12
15. Boyer WF, Blumhardt CL. The safety profile of paroxetine. J Clin Psychiatry 1992;53(2, suppl):61–66
16. Nemeroff CB. Evolutionary trends in the pharmacotherapeutic management of depression. J Clin Psychiatry 1994;55(12, suppl):3–15
17. Andrews JM, Nemeroff CB. Contemporary management of depression. Am J Med 1994;97(6, suppl A):24S–32S
18. Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. Drug Saf 1994;10:18–46
19. Leonard BE. Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. Drugs 1992;43:3–10
20. Leonard BE. The comparative pharmacology of new antidepressants. J Clin Psychiatry 1993;54(8, suppl):3–15. Correction 1993;54:491
21. Montgomery SA, Henry J, McDonald G, et al. Selective serotonin reuptake inhibitors: meta analysis of discontinuation rates. Int Clin Psychopharmacol 1994;9:47–53
22. White KL, Williams F, Greenberg BG. The ecology of medical care. N Engl J Med 1961;265:885–892
23. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA 1996;275:1897–1902
24. Simon GE, Wagner EH, VonKorff M. Cost-effectiveness comparisons using real world randomized trials: the case of new antidepressant drugs. J Clin Epidemiol 1995;48:363–373
25. Revicki DA, Luce BR. Methods of pharmacoeconomic evaluation of new medical treatments in psychiatry. Psychopharmacol Bull 1995;31:57–65
26. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. Clin Ther 1994; 16(4):715–730
27. Skaer TL, Sclar DA, Robison LM, et al. Economic valuation of amitriptyline, desipramine, nortriptyline, and sertraline in the management of patients with depression. Curr Ther Res 1995;56(6):556–567
28. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: economic valuation of fluoxetine, paroxetine, and sertraline in a health maintenance organization. J Int Med Res 1995;23(6):395–412
29. Skaer TL, Sclar DA, Robison LM, et al. Antidepressant pharmacotherapy: effect on women's resource utilization within a health maintenance organization. Journal of Applied Therapeutics 1996;1(1):45–52
30. SAS Institute Inc. SAS System Software. Version 6.08. Cary, NC: SAS Institute; 1991
31. Skaer TL. Applying pharmacoeconomic and quality-of-life measures to the formulary management process. Hosp Formul 1993;28(6):577–584