

Evaluation of the Adequacy of Outpatient Antidepressant Treatment

Jeffrey B. Weilburg, M.D.

Kathleen M. O'Leary, B.A.

James B. Meigs, M.D., M.P.H.

John Hennen, Ph.D.

Randall S. Stafford, M.D., Ph.D.

Objective: Most studies evaluating the adequacy of antidepressant treatment have focused on the relatively small segment of the medicated population with a diagnosis of depression. This study assessed the rates and determinants of the adequacy of antidepressant treatment among all outpatients who receive antidepressants. **Methods:** A retrospective analysis was conducted using pharmacy claims made by patients with a primary care physician in a managed care plan at an academic medical center from 1996 through 1999. Adequate antidepressant treatment was defined as prescription of the lowest likely effective dosage of an antidepressant for at least 90 consecutive days. Data for a total of 15,476 records and 1,550 patients were available. **Results:** Overall, 46 percent of the patients receiving antidepressants received minimally adequate treatment. The rates of adequate treatment were significantly higher among patients whose antidepressant prescriptions were written by both primary care physicians and psychiatrists than among patients whose antidepressants were prescribed solely by primary care physicians (61 percent versus 31 percent). Patients who had trials of SSRIs had significantly higher rates of treatment adequacy than those who had trials of tricyclic antidepressants but not SSRIs (51 percent compared with 27 percent) or trials with other antidepressants only (24 percent). **Conclusions:** Pharmacy claims from all patients receiving antidepressants indicate that these drugs are prescribed in ways that are unlikely to be fully effective across the broad spectrum of patients. Adequate antidepressant treatment trials were most likely when psychiatrists collaborated with primary care physicians or other specialists and when SSRIs were used. (*Psychiatric Services* 54:1233–1239, 2003)

Antidepressants can be used to treat mood disorders, such as major depression and dysthymia, as well as anxiety disorders, obsessive-compulsive disorder, and

bulimia. Guidelines exist for treatment of each of these conditions and typically indicate that outcomes are optimized when minimum thresholds for antidepressant dosage and treat-

ment duration are reached or exceeded. The dosage and duration thresholds are similar across the guidelines for mood and anxiety disorders (1–4) and across treatment settings (5,6)—for example, primary care and mental health. A course of treatment involving a dosage or duration below guideline-recommended thresholds is considered inadequate, because most studies (1,7–13), but not all (14–16), have indicated that subthreshold treatment predicts poor outcomes.

Mood and anxiety disorders are highly prevalent (17–20). Recognition of the importance of properly treating these disorders is growing (6–10, 21–23). As a result, antidepressants constitute one of the most frequently prescribed (23,24) and most costly (24,25) classes of medications in many U.S. health care systems. The effectiveness of antidepressant prescribing is a key determinant of outcomes and costs of both mental health and overall health care.

Current data suggest that rates of effective antidepressant prescribing are low in both primary care and psychiatric settings (9,17,18). The low rate in primary care settings is of particular concern, because a majority of patients in the United States who have mood and anxiety disorders receive their mental health care in such settings (19,26). Most currently available studies that showed low rates of effective antidepressant prescribing included only patients with a diagnosis of depression. This approach has limitations, because reliance on the presence of a depression diagnosis on a claims form as a marker of depression

Dr. Weilburg and Ms. O'Leary are affiliated with the department of psychiatry of Massachusetts General Hospital, Wang Ambulatory Care Center, Room 815, 55 Fruit Street, Boston, Massachusetts 02144 (e-mail, jweilburg@partners.org). Dr. Meigs is with the general medical division of Massachusetts General Hospital. Dr. Hennen is with McLean Hospital in Belmont, Massachusetts. Dr. Stafford is with the Institute for Health Policy at Massachusetts General Hospital and with the Stanford Center for Research in Disease Prevention in Palo Alto, California. This paper was presented in part at the American Psychiatric Association's (APA's) Institute on Psychiatric Services held October 9 to 13, 2002, in Chicago and at APA's annual meeting held May 18 to 23, 2003, in Philadelphia.

excludes the large group of patients in primary care settings who do not have this diagnosis recorded (27,28).

Studies that use screening or structured interviews to establish the presence of depression exclude the large segment of primary care patients who refuse to participate in psychiatric research studies (29). Randomized controlled trials of antidepressants typically exclude patients who have comorbid psychiatric or medical conditions. Finally, most previous studies focused on patients who were newly started on antidepressants, thereby excluding patients who were in treatment at the start of data collection.

To overcome such limitations, we analyzed all antidepressant medication claims from patients in one commercial managed care plan at our medical center. This approach introduces its own limitations, because some patients may receive antidepressants for conditions for which guideline concordance is not relevant. Nonetheless, the limits of this broader approach are balanced by the ability to provide information that is useful for improving antidepressant treatment.

Methods

Data

We obtained computerized outpatient pharmacy records from January 1, 1996, to December 31, 1999, for patients who were enrolled in a commercial health maintenance organization and who had a primary care physician based at Massachusetts General Hospital in Boston. The primary care physicians in this plan were distributed across private office settings, the hospital's outpatient departments, and its affiliated community health centers. During the time of data collection, patient copayments varied only by whether a brand or generic medication was prescribed; generic selective serotonin reuptake inhibitors (SSRIs) were not yet available. No formulary restrictions on antidepressant therapy had been imposed, and no depression management program was in operation. During the time of the study, essentially all psychiatrists who were affiliated with the hospital were eligible to see these patients on a fee-for-service basis.

A prescription record was generat-

ed when a patient filled a prescription at any pharmacy. Records included the patient's name, an insurance identification number, the names of the patient's primary care physician and prescribing physician, the date the prescription was filled, the drug name, and the dosage and number of pills. We obtained data from 251,921 pharmacy claims records for analysis. These prescriptions were provided to 12,908 individuals, of whom 76 percent were between the ages of 18 and 65 years and 9 percent were older than 65 years. Of the 79 percent of patients for whom gender was recorded, 63 percent were women.

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We initially identified 18,740 antidepressant prescriptions by drug name (7.4 percent of total prescriptions filled by all claimants in this plan). A total of 14.9 percent of patients in the database received antidepressant prescriptions. After removal of duplicates, corrected records, zero pill count records, and a few records with an incorrect number of pills (zero or negative), data on 16,809 antidepressant prescriptions provided to 1,921 unique patients were available for analysis.

We required that patients whose data were included have at least 180 days of membership in the plan, demonstrated by either policy cover-

age dates or pharmacy fill dates. Excluding the patients with short enrollment periods further reduced the number of antidepressant records. Finally, patients with only a single low-dosage tricyclic antidepressant trial (all prescriptions ≤ 50 mg a day) or only a single low-dosage trazodone trial (all prescriptions ≤ 100 mg a day) were removed. The final number of records available for analysis was 15,476, and the number of patients was 1,550. Each patient received between one and ten individual drug trials, with a total of 2,697 trials. Our primary analysis used patients as the unit of analysis. We conducted additional analyses with each treatment trial as the unit of analysis. The study was approved by Massachusetts General Hospital's institutional review board.

Definition of treatment adequacy

Treatment adequacy was defined as a function of the average daily dosage and cumulative duration of an individual treatment trial, defined to be one or more continuous prescriptions of the same antidepressant. Patients had to reach minimum thresholds for both dosage and duration for adequacy to be obtained. If a gap of more than 120 days between prescriptions occurred, a new trial was considered to have begun. In a few cases, a prescription written before the gap provided a sufficient number of days of medication therapy for a 120-day gap. Such cases were therefore considered as ongoing trials.

Fluoxetine, the most commonly prescribed antidepressant, was selected as a reference, and daily dosage rates were reported as fluoxetine equivalents, as shown in Table 1. If, on average, a given patient had a ratio of total fluoxetine equivalents to days that exceeded a set mean dosage (20 mg a day) for a minimal adequacy period (at least 90 consecutive days), the antidepressant trial for that patient was designated as adequate. We based our calculations on a daily dosage of 18.75 mg, which meant that a patient could miss two doses in a 30-day period and still be considered as receiving adequate treatment. A patient had to reach both dosage and duration thresholds to be considered as receiving adequate treatment.

Because some patients may respond to dosages below the standard dosage, we analyzed trials at a minimum daily dosage of 10 mg fluoxetine equivalents, using 9.375 mg as the actual cutoff. For this subanalysis the equivalent dosages of the other agents were similarly reduced by 50 percent.

Fluoxetine equivalents were chosen for each agent on the basis of manufacturers' guidelines and a consensus of expert opinions (personal communication, Rosenbaum JF, Fava M, Nierenberg AA). Patients with more than one treatment trial were considered to have had adequate treatment if any of their trials met adequacy criteria.

Definition of provider type

Each prescription record listed the patient's prescribing physician and primary care physician. Prescribers were assigned to one of three categories: primary care physicians, psychiatric specialists, and nonpsychiatric specialists, such as cardiologists, which we refer to here as others. Pediatricians were considered to be primary care physicians, and obstetrician-gynecologists were considered to be others. However, if a patient had a specialist listed as his or her primary care physician, we considered the prescriptions written by that physician for that patient to have been written by a primary care physician. For 17 percent of antidepressant records, a specific prescriber could not be identified. Unknown providers were classified as others. If physicians in a single category wrote all prescriptions for a given patient, that patient's antidepressant prescribing was assigned to that category—for example, primary care physician only or psychiatrist only. Otherwise, patients were assigned to a joint prescribing category.

Analysis

For each patient's first antidepressant prescription, we calculated the total fluoxetine equivalent dosage by multiplying the dosage of the antidepressant by the number of pills prescribed. This amount was divided by the amount of time between the first prescription and the first refill to ob-

Table 1

Characteristics of 2,697 antidepressant trials among 1,550 patients in a study of adequacy of antidepressant treatment^a

Generic drug name	Total trials	Adequate trials		Minimum daily dosage for an adequate trial ^b	Drug type
		N	%		
Fluoxetine	571	261	45.7	20 mg	SSRI ^c
Sertraline	493	229	46.5	50 mg	SSRI
Paroxetine	352	89	25.3	20 mg	SSRI
Bupropion	341	94	27.6	150 mg	Other
Trazodone	241	3	1.2	300 mg	Other
Amitriptyline	144	10	6.9	125 mg	Tricyclic
Nortriptyline	91	16	17.6	75 mg	Tricyclic
Citalopram	95	28	29.5	20 mg	SSRI
Venlafaxine	87	41	47.1	75 mg	SSRI
Nefazodone	75	14	18.7	300 mg	Other
Desipramine	49	10	20.4	125 mg	Tricyclic
Doxepin	38	4	10.5	125 mg	Tricyclic
Imipramine	40	12	30	125 mg	Tricyclic
Mirtazapine	39	11	28.2	15 mg	Other
Fluvoxamine	21	3	14.3	150 mg	SSRI
Clomipramine	7	1	14.3	125 mg	Tricyclic

^a Thirteen total trials of amoxapine, isocaboxazid, maprotiline, phenelzine, tranlycypromine, and trimipramine are not included in the table.

^b Adequacy was defined for each patient as at least one trial of an average daily dosage of at least 20 mg fluoxetine equivalents for a period of at least 90 days.

^c Selective serotonin reuptake inhibitor

tain the average daily dosage. This process was repeated for each refill. For each subsequent refill, cumulative dosage and duration were calculated. The last prescription in a trial was used only to indicate the date by which the medication in the previous prescription had been consumed.

Patients who had any 90-day period of an adequate dosage were regarded as having received adequate treatment. This 90-day period could occur at any time during the course of treatment. This approach allowed every refill to be considered as part of the cumulative duration for the previous prescription as well as the start of a new cumulative duration. For the trial-level analysis, any periods for which both dosage and duration were adequate represented an adequate trial. Patients could have more than one adequate trial.

We used SAS software version 6.12 for all analyses. We performed descriptive comparisons of adequacy rates by antidepressant type, with adequacy rates calculated as the number of patients with adequate trials divided by the total number of patients with trials. Least-squares means were used to evaluate overall and pairwise

differences in rates between prescriber types and antidepressant types. We used multivariate logistic regression models to assess statistically significant predictors of adequate antidepressant use. In these models, physician specialty, patient age, gender, and drug class were included as predictors of treatment adequacy at the patient level. We calculated adjusted odds ratios and 95 percent confidence intervals and considered a finding with a two-tailed p value below .05 to be significant.

Results

Of the 1,550 patients, 1,033 (67 percent) were women, 1,477 (95 percent) were aged 20 to 65 years, and 126 (5 percent) were older than 65 years. A total of 821 patients (53 percent) were treated with SSRIs alone, 110 (7 percent) with tricyclic antidepressants alone, and 188 (12 percent) with other antidepressants alone. A total of 431 patients (28 percent) were treated with multiple drug types, either sequentially or concurrently. More patients had prescriptions written solely by psychiatric specialists (430 patients, or 28 percent) than solely by primary care physicians (406 patients, or 26

Table 2

Multivariate predictors of adequacy of antidepressant treatment in a sample of 1,550 patients

Variable	Patients		Adequacy rate		Adjusted	
	N	%	N	%	OR ^a	95% CI
Drug class						
Tricyclic alone or tricyclic and other	142	9.2	45	31.7	1	—
Any selective serotonin reuptake inhibitor	1,220	78.7	627	51.4	1.93	1.32–2.88
Other drug alone	188	12.1	45	23.9	.68	.41–1.14
Physician specialty						
Primary care only	406	26.2	125	30.8	1	—
Psychiatrist only	430	28.7	232	54	2.64	1.97–3.55
Other only	278	17.9	86	30.9	.99	.70–1.39
Primary care and psychiatrist	82	5.3	50	61	3.29	1.99–5.51
Primary care and other	146	9.4	76	52.1	2.33	1.56–3.48
Psychiatrist and other	143	9.2	100	69.9	5.04	3.29–7.81
Primary care, psychiatrist, and other	65	4.2	48	73.9	5.13	2.86–9.61
Age (years)						
Younger than 20	73	4.7	27	37	.59	.33–1.04
20 to 29	242	15.6	104	43	1	—
30 to 39	328	21.1	153	46.7	1.23	.86–1.76
40 to 49	397	25.6	201	50.6	1.55	1.10–2.19
50 to 64	384	24.8	197	51.3	1.6	1.13–2.28
65 or older	126	8.1	35	27.8	.68	.41–1.12
Gender						
Female	1,033	66.6	499	48.3	1	—
Male	517	33.4	218	42.2	.84	.67–1.06
Total	1,550	100	717	46.2		

^a Adjusted odds ratio of the likelihood of antidepressant treatment adequacy, simultaneously adjusted for all variables listed in the table

percent) or solely by other provider types (278 patients, or 18 percent). A total of 436 patients (28 percent) had prescriptions written by multiple prescriber types, including a primary care physician and another type of provider (146 patients, or 9 percent of the total), a psychiatric specialist and another type of provider (143 patients, or 9 percent), a primary care physician and a psychiatric specialist (82 patients, or 5 percent), and all three types (65 patients, or 4 percent). Psychiatrists wrote 49 percent of antidepressant prescriptions (7,529 of 15,476 prescriptions), followed by primary care physicians (28 percent) and all others (23 percent).

Overall adequacy of treatment

We found that 717 (46 percent) of the patients in this sample had adequate treatment. That is, at some time during their use of any antidepressant medication, these patients had treatment sustained for at least 90 days

and during this period had a daily average dosage that met minimum likely effective levels.

Of the 833 patients who did not receive adequate treatment, 289 (35 percent) had trials that included only one prescription. There were 169 patients (20 percent) who had an adequate dosage but not an adequate duration and 158 patients (19 percent) who had an adequate duration but not an adequate dosage. A total of 108 patients (13 percent) met the criteria for adequate dosage and adequate duration, but not concurrently, and 109 patients (13 percent) never met the criteria for adequate dosage or duration.

Treatment adequacy by provider type

Patients who received antidepressant prescriptions from psychiatrists only were more likely to receive adequate treatment (232 of 430 patients, or 54 percent) than patients whose prescrip-

tions were written solely by primary care physicians (125 of 406 patients, or 31 percent) or patients whose prescriptions were written solely by others (86 of 278 patients, or 31 percent) ($p < .001$). When the “other” category was limited to other medical specialists, the rate of adequate treatment was even lower, at 28 percent. The rate of adequate treatment among patients for whom prescriptions were written by primary care physicians alone was lower than that among patients whose primary care physicians wrote prescriptions jointly with other specialists, patients whose primary care physicians wrote prescriptions jointly with psychiatrists, and patients whose primary care physicians wrote prescriptions jointly with both psychiatrists and other provider types (31 percent, 52 percent, 61 percent, and 74 percent, $p < .001$).

The rate of treatment adequacy among patients for whom prescriptions were written by psychiatrists alone tended to be lower than the rate among patients for whom prescriptions were written jointly by psychiatrists and primary care physicians—54 percent (232 of 430 patients) compared with 61 percent (50 of 82 patients); however, this difference was not significant. Among patients whose psychiatrists prescribed jointly with other provider types (100 of 143 patients, or 70 percent, $p < .001$) and among those whose psychiatrists prescribed jointly with both primary care physicians and others (48 of 65 patients, or 74 percent, $p < .003$), the rates of treatment adequacy were higher than when psychiatrists prescribed alone. Our multivariate logistic regression analysis confirmed these patterns of treatment adequacy by prescriber type, as shown in Table 2.

Treatment adequacy varied by the class of medication prescribed. Taken as a group, patients who had trials of SSRIs had higher rates of treatment adequacy than those who had trials of tricyclic antidepressants but no trials of SSRIs (51 percent compared with 32 percent, $p < .001$) or only trials of other antidepressants (24 percent, $p < .001$).

As can be seen in Table 2, patients who received SSRI trials were nearly

twice as likely to have received adequate treatment as patients who had tricyclic antidepressant trials but no SSRI trial. Care by psychiatry was associated with a two-and-a-half-fold increase in odds of an adequate trial than care by a primary care physician. Care by psychiatrists, primary care physicians, and other provider types increased the odds of an adequate trial more than five times compared with care by a primary care physician alone.

To accommodate the possibility that lower antidepressant dosages are adequate for some patients, we conducted an analysis using a minimum effective dosage criterion of 10 mg fluoxetine equivalents. When this dosage was used, the overall adequacy rate increased from 46 percent to 59 percent (918 patients). Treatment adequacy for patients treated solely by primary care physicians increased from 31 percent to 45 percent (183 of 406 patients) and for patients treated solely by psychiatrists increased from 54 percent to 65 percent (279 of 430 patients). Again, observed patterns of adequacy and the statistical significance of contrasts between groups by prescriber type and medication class remained nearly the same as in the main analysis, whereas rates of treatment adequacy were slightly higher.

Discussion and conclusions

In this study we found that between 1996 and 1999 only 46 percent of managed care outpatients who were treated with antidepressants at our academic medical center received adequate antidepressant treatment. The definition of adequacy we used is based on less stringent criteria than those in most guidelines. Unlike guidelines that suggest at least six months of maintenance treatment—that is, continuation of treatment after symptom improvement—we used a period of three months beginning with initiation of treatment. The dosages chosen as minimum thresholds are at the low end of the likely effective range. Many patients require higher dosages to achieve remission. Our definition of treatment adequacy reflects a minimum standard of treatment with antidepressants.

If adequacy had been defined on

the basis of dosages and durations dictated by most guidelines and likely to produce optimal outcomes, the calculated adequacy rates would have been substantially lower. Because low levels of guideline concordance probably predict poor outcomes (5–9,18,30) and because this method is biased toward achievement of adequacy, the low overall adequacy rate shows that antidepressant treatment is suboptimal. In turn, this finding suggests an opportunity for substantial practice improvement.

Our second finding suggests that joint prescribing has an impact on

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treatment adequacy. Katon (15) and others (30,31) have shown that structured collaboration between a psychiatrist and a primary care physician produces significant improvement in rates of adequacy of antidepressant treatment among patients with both mood and anxiety disorders. We also found that joint prescribing was associated with significantly improved treatment adequacy. Although only half of the patients whose antidepressant prescriptions were written solely by a psychiatrist and about a third of those whose prescriptions were written solely by a

primary care physician ever received adequate treatment, two-thirds of patients received an adequate trial under a structure of joint prescribing. We speculate that the communication between psychiatrists and primary care physicians in our health care system was a factor in these higher rates of treatment adequacy. Defining the mechanisms by which such collaborative care improves practice may guide the design of future quality-improvement initiatives.

Previous studies used various thresholds for treatment duration, ranging from two to six months. Some of these studies distinguished between treatment initiation, dosage adjustment, and maintenance phases of treatment. Most previous studies also included only patients who had a diagnosis of depression and included only newly started antidepressant trials. Some previous studies focused on selected antidepressants. Despite the methodologic differences between our study and these previous studies, the rates of treatment adequacy we found are within the range noted in previous studies, especially those that used similar dosage and duration thresholds. Thus under real-world, naturalistic conditions across the full spectrum of antidepressant use, antidepressant adequacy rates and the effectiveness of prescribing are similar in various settings and subsamples of patients, as reported in previous studies. Suboptimal antidepressant prescribing is truly widespread.

Although our approach allows a broad view of antidepressant use, it is inherently limited—without a diagnosis, cases in which there is no link between treatment adequacy and outcomes may be included. Inclusion of such cases may falsely lower the adequacy rate. We addressed this limitation by removing from consideration trials involving only low-dosage tricyclic antidepressants or trazodone, because some of these trials might have been provided for patients with insomnia or chronic pain. In such cases guideline concordance would not be relevant.

Another limitation, resulting from reliance on pharmacy claims data alone, is the absence of traditional

outcome measures, such as number of symptoms, severity of illness, and functional status. However, most previous studies did show a relationship between guideline concordance and clinical outcomes (8). There also is a concern that without a verified diagnosis some patients who are receiving antidepressants do not in fact require treatment. Inclusion of such cases could falsely inflate the rate of inadequate treatment. The rate of false-positive diagnosis of mood or anxiety disorder by primary care physicians has been reported to be low (32). Some patients may experience resolution of mood symptoms shortly after starting antidepressants, but such responses are probably placebo effects (33). Rates of unnecessary antidepressant use or good response to short treatment need to be verified by prospective study but are very likely to be low.

Some authors have raised questions about the relationship between guideline concordance and outcomes for mild depression (14). Such questions represent an important limitation, because patients who are treated by primary care physicians may more often have mild depression or subsyndromal mood symptoms than those treated by psychiatrists. Conclusions about the meaning of the low rate of treatment adequacy among patients whose antidepressants were prescribed by primary care physicians alone must be viewed as tentative until this point is clarified, because the patients treated with antidepressants by primary care physicians may be a different population than those treated by psychiatrists. Furthermore, factors responsible for the significantly higher rate of treatment adequacy among patients whose antidepressants were prescribed by both a primary care physician and a psychiatrist need to be examined before conclusions can be reached.

It has been suggested that some patients with mild depression may respond to relatively low dosages of antidepressants (14). Although treatment adequacy rates improved when the dosage threshold was reduced by 50 percent to 10 mg fluoxetine equivalents, the overall adequacy rate at the reduced threshold remained low,

and adequacy was still significantly higher among patients whose antidepressants were jointly prescribed. This finding suggests that low adequacy was more dependent on a short duration of treatment than on use of low dosages.

Consistent with the findings of other studies (34,35), drug class was associated with adequacy of treatment. Trials involving SSRIs had a significantly higher adequacy rate than trials that did not include SSRIs. SSRIs may be associated with lower rates of side effects and treatment dropout, but they are not associated with significant improvements in efficacy compared with tricyclic antidepressants and other antidepressants (36–38). Adequacy may be influenced by marketing, physician and patient perceptions of safety and social acceptability, relative price, dropout rate, and efficacy. Policy makers may consider differences in treatment adequacy between agents as they seek to increase adherence and optimize clinical outcomes under real-world conditions. Policies favoring the initial prescription of more expensive antidepressant drugs may lead to greater initial adequacy, faster improvements in outcomes, and net overall savings than policies that encourage potentially inadequate use of less expensive drugs.

In conclusion, this analysis of pharmacy claims from all patients receiving antidepressants indicated that these drugs are prescribed in ways that are unlikely to be fully effective across the broad spectrum of patients. Adequate antidepressant treatment trials—associated with the greatest probability of desired outcomes—were most likely when psychiatrists collaborated with primary care physicians and other specialists and when SSRIs were used. Systems that promote collaboration between primary care physicians and psychiatrists and that support the use of SSRIs over tricyclics may achieve greater quality. ♦

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