Prescriber Intent, Off-Label Usage, and Early Discontinuation of Antidepressants: A Retrospective Physician Survey and Data Analysis

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Background: Many patients discontinue antidepressant therapy long before the 6-month minimum duration recommended for the treatment of major depression and many other diagnoses. We explore various possibilities, including prescriber intent and patient diagnosis, to explain some of this early discontinuation.

Method: Patients from a single health maintenance organization who filled at least 1 prescription for an antidepressant during the first 4 months of 2001 and who did not fill an antidepressant prescription in the 6 months prior were identified retrospectively. Prescribers of those patients' antidepressants were surveyed for patient diagnosis and length of intended treatment with antidepressant medication. Actual length of treatment was then obtained from pharmacy data and correlated with survey data and other variables.

Results: Prescriber surveys were returned for 51% (485/951) of the patients identified. Surveys indicated that for 34% of initial antidepressant prescriptions, < 6 months of treatment was intended. Important determinants of the length of antidepressant therapy included prescriber specialty area, number of prescribers, prescriber intent, diagnosis, specific antidepressant used, and concomitant benzodiazepine use.

Conclusions: Prescriber intention to treat many patients with short courses of antidepressants, often for off-label, non–mental health indications, was correlated with early discontinuation and needs further study of both its rationale and efficacy. Although less prevalent, short-term treatment of mental health disorders, including depression, was also intended by psychiatrists and other prescribers. The widespread practice of intended short-term treatment with antidepressants needs to be understood better, since it results in guideline-incompatible, early antidepressant discontinuation.

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Antidepressant use is now an integral and growing part of the pharmaceutical sector in health care delivery. According to statistics derived from the National Ambulatory Medical Care Survey comparing data from 1999 with similar data from 1985, antidepressants accounted for 13.5% of the entire increase in pharmaceutical prescribing.[1] Yet, increasing use (and expense) of antidepressants tells us little, for the real issue is effectiveness. But how might one assess effectiveness in real-world settings as opposed to placebo-controlled trials with very select patients in academic settings?

Others have noted that antidepressant prescription continuation rates may be one way to track effective antidepressant treatment[2] and that almost 50% of patients stop taking their medication as early as 3 months after initiating antidepressant treatment.[3] In a study of 240,604 patients who were given a new prescription for an antidepressant and who had not been on treatment with an antidepressant for at least the prior 6 months, less than 30% continued to take their medication for a full 6 months.[4] A recent study in northwest Italy[5] of all 1,057,053 residents of a catchment area showed that 18,676 patients were prescribed an antidepressant during a 6-month period of time. Nearly 50% of these antidepres-

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sant users filled that prescription (or any other monthly antidepressant prescription) only once or twice.

This early discontinuation of antidepressants conflicts with most guidelines for the treatment of depression. Both the National Committee for Quality Assurance, in its Health Plan Employer Data Information Set criteria,[6] and the Agency for Health Care Policy and Research[7–9] recommend treating depressed patients for a minimum of 6 months. More recent recommendations, such as those of Geddes et al.,[10] conclude from a new meta-analysis of previously published controlled studies of depression treatment that the minimum period for treating depression should be extended further—to at least 1 year of maintenance treatment, given the high risk of recurrence. Several studies document that adequate duration of antidepressant therapy will improve symptoms,[11] prevent relapse,[12] reduce disability,[13] and restore function and work performance[14] in patients with major depression.

Although a 6-month (or more) course of treatment explicitly applies only to the treatment of major depression, most other indications for antidepressants are chronic in nature,[15] and thus 6 months (or more) of treatment may represent a standard for minimum treatment of these conditions as well. These other indications for antidepressants, whether they are clearly within the mental health area (e.g., dysthymia, generalized anxiety disorder, social phobia, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, anorexia nervosa, bulimia, attention deficit disorder, somatoform disorder) or not (e.g., migraine headaches, fibromyalgia, chronic pain), are all known for chronicity and recurrence. Even a cyclical phenomenon such as premenstrual disorder (including premenstrual dysphoric disorder), whether treated only for the 7 to 10 days prior to the onset of menses or continuously, nonetheless requires ongoing prescription refills and chronic treatment with antidepressants. Likewise, perimenopausal hot flashes, bladder dysfunction, colitis, and other such general medical uses are characterized by repetitive episodes over a prolonged time period, with antidepressants being possibly helpful for control of symptoms rather than curative. Only sleep problems and smoking cessation may represent legitimate short-term antidepressant usage (less than 6 months), although recent evidence even casts doubt on short-term antidepressant use for smoking cessation.[16]

Nonetheless, we do not quarrel with the occasional use of antidepressants on a short-term trial basis for off-label indications or symptoms of modest severity. The problem is that so many patients discontinue antidepressant medication well before 6 months. A high volume of antidepressant prescriptions in conjunction with apparently poor adherence is troublesome, but difficult to interpret. Many investigators have assumed that this phenomenon derives primarily from patient resistance due to medication side effects. Yet, studies involving selective serotonin reuptake inhibitors (SSRIs) and other relatively new antidepressants marketed for their tolerability still show much early discontinuation.[17] Maybe part of the answer lies elsewhere. Might there be differential adherence and effectiveness for antidepressants depending on factors usually neglected (or controlled for) in clinical trials? More knowledge about how medication adherence varies with the particular condition being treated, the prescriber(s), and the intent of the prescriber(s) regarding treatment duration might be informative and eventually lead to better antidepressant adherence and cost-effectiveness.

Accordingly, we conducted a survey of practitioners who had written new prescriptions for an antidepressant medication. Claims and pharmacy data provided the names of the prescribers to contact, as well as follow-up data on antidepressant refills and an opportunity to investigate other patient, prescriber, and medication variables for correlations with antidepressant adherence. The setting for this study was a single mid-size, network model health maintenance organization (HMO) in western Massachusetts.

METHOD

The study population consisted of all patients who had filled no antidepressant prescriptions in the prior 6 months and who subsequently filled at least 1 prescription for any type of antidepressant during the first 4 months of 2001. Patients who had used antidepressants in the previous 6 months were excluded in order to identify a population of first-time or episodic antidepressant users and to avoid the inclusion of chronic antidepressant users. The first of the antidepressant prescriptions served as an index date, denoting the start of treatment, and was used to place patients in monthly cohorts (January, February, March, or April). Clinical records for each cohort were then extracted for the 6 months before and the 6 months after the index prescription date. Unlike many prior studies of antidepressant prescription discontinuation, we intentionally did not limit inquiry to patients diagnosed with depression or patients of a particular class of prescribers, such as primary care physicians or psychiatrists.

We developed a survey questionnaire (Appendix 1) designed to elicit more complete diagnostic information from prescribers in order to avoid interpretive problems resulting from incomplete or inaccurate diagnoses that can occur on routine claims forms. The survey contained a list of 37 possible indications placed into 4 major categories, including depression spectrum, anxiety spectrum, schizophrenia spectrum, and other. Each prescriber was asked to check off 1 or more reasons why that patient was prescribed an antidepressant. The provider was also asked to indicate the expected duration of antidepressant therapy: ≤ 1 month, > 1 but < 6 months, or ≥ 6 months.

For administrative reasons, all surveys were sent out as a group between 4 and 8 months following the index prescription. Each survey contained the patient's name, the specific antidepressant prescribed, and the date of the index prescription. An accompanying cover letter from the HMO's medical director explained the study and offered $10 to the provider for each completed survey.

Membership in the HMO provided patients with 30-day supplies of their antidepressant prescriptions from local pharmacies at a typical cost of a $5 or $10 copayment. Patients who were not continuously enrolled in the HMO during the entire 12-month period surrounding an index prescription were excluded. Complete prescription refill records are routinely collected by the HMO's drug benefit manager for all drugs dispensed through the plan and were made available to us for the period of time covering this study. Because it is a network model HMO, all clinical services are billed by procedure on claim forms. Since behavioral health treatment is not subcontracted (i.e., "carved-out") to another organization by this provider, data concerning psychotherapy and other mental health treatments were also available to us on claim forms.

Our principal research strategy consisted of comparing confidential prescriber questionnaire data about patient diagnoses with 12 months of medical claims records available for each patient studied. We chose to obtain diagnoses by way of prescriber questionnaire because of the known unreliability of behavioral health diagnoses available on claim forms.[18]

The questionnaire data also supplied information on the intention of the prescribing physician concerning the duration of treatment (i.e., ≥ 6 months or < 6 months) at the time the initial antidepressant was prescribed. The claims data supplied the actual duration of treatment for each patient. We made the assumption that 4 filled prescriptions for antidepressants over the 6-month study period would be a reasonable (although liberal) marker for 6 months of continuous therapy. We reasoned that patients are often given free samples, both at the time of initial prescription and afterward, and the date of filling of the final prescription may have fallen outside the data collection period. Furthermore, any subsequent antidepressant refill for an index patient, no matter the agent or the prescriber, was attributed to the original medication and prescriber. That procedure avoided the problem of confusing antidepressant or provider change with antidepressant discontinuation.

Senior management of the HMO and its Clinical Care Assessment Committee (a formal committee charged with assessing quality of care chaired by the medical director and including representative network providers and senior clinical managers) approved the study as a routine retrospective quality-of-care audit.

Study-specific, unique patient identifiers were substituted for patients' names and insurance numbers in the data file (prior to data analysis), thereby assuring patient anonymity.

RESULTS

Analytic Sample Characteristics

A total of 951 patients who received an initial prescription for an antidepressant medication through Health New England (Springfield, Mass.) were identified for the period of January through April 2001. The survey group consisted of 485 patients (51%) for whom prescribers had completed survey forms. The 466 patients for whom survey forms were not collected (49%) are referred to as the non-survey group and were analyzed to ascertain that there were no important differences between the survey and non-survey patients.

No statistically significant differences were observed between the survey group and the non-survey group with respect to age, gender, prescriber type, initial antidepressant medication, concurrent use of psychotherapy, or use of benzodiazepine medications (Table 1). Individual psychotherapy in the period following initiation of antidepressant therapy was significantly higher ($p = .043$) among the survey group than the non-survey group; however, we do not regard this difference as likely to affect the overall findings.

Index Diagnosis

Depression or depression plus anxiety was the index diagnosis in 52% of the patients in the survey group. For the survey subgroup with diagnoses other than depression, anxiety, or schizophrenia (178 patients, 37%; Table 2), diagnoses that prompted antidepressant administration in at least 10% of the subgroup were smoking cessation (32%), migraine or other type of headache (13%), chronic pain disorder (13%), and fibromyalgia (12%).

Antidepressant Prescribers by Specialty

Adult primary care physicians (PCPs) were the source of 70% of all antidepressant prescriptions, regardless of whether a patient's survey form was completed. The combined data for all 951 patients (Table 3) indicated that the most common prescribers of antidepressants after PCPs were psychiatrists (15%), obstetricians and gynecologists (4%), pediatricians (3%), and neurologists (3%).

Duration of Treatment

Survey results show that more than 75% of all prescribers for patients with depression, anxiety, or depression plus anxiety intended for their patients to be treated for 6 months or longer (Table 4). For other conditions, the proportion of prescribers intending long-term treatment was lower (44%).

Regardless of index diagnosis or prescriber type, the proportion of patients attaining a long-term treatment

Table 1. Patient Characteristics

Variable	Survey Group (N = 485)	Non-Survey Group (N = 466)	Total (N = 951)	p Value
Age, y				
Mean	42.80	42.39	42.60	.642
Range	6–83	3–84	3–84	
Gender, N (%)				
Female	323 (66.6)	294 (63.1)	617 (64.9)	.258
Male	162 (33.4)	172 (36.9)	334 (35.1)	.258
Prescriber type, N (%)				
Primary care physician	340 (70.1)	327 (70.2)	667 (70.1)	.982
Psychiatrist	72 (14.9)	72 (15.5)	144 (15.1)	.795
Others	73 (15.1)	67 (14.4)	140 (14.7)	.770
Initial antidepressant, N (%)				
SSRI	222 (45.8)	228 (48.9)	450 (47.3)	.331
Tricyclic antidepressant	100 (20.6)	75 (16.1)	175 (18.4)	.072
Bupropion	106 (21.9)	100 (21.5)	206 (21.7)	.882
Trazodone	24 (5.0)	25 (5.4)	49 (5.2)	.772
Other[a]	33 (6.8)	38 (8.2)	71 (7.5)	.429
Index diagnosis, N (%)				
Depression[b]	190 (39.2)	…	…	…
Anxiety[c]	53 (10.9)	…	…	…
Depression plus anxiety[d]	64 (13.2)	…	…	…
Neither[e]	178 (36.7)	…	…	…
Psychotherapy[f]				
Individual, before	0.44	0.46	0.45	.855
Individual, after	0.83	0.56	0.70	.043
Group, before	0.15	0.13	0.14	.824
Group, after	0.17	0.17	0.17	.987
Benzodiazepine use, N (%)	156 (32.2)	129 (27.7)	285 (30.0)	.132

[a]Venlafaxine, nefazodone, mirtazapine.
[b]Depression alone or in combination with any other diagnosis except anxiety.
[c]Anxiety alone or in combination with any other diagnosis except depression.
[d]Depression in combination with anxiety, with or without other diagnoses.
[e]Any diagnosis other than depression or anxiety, including no answer for diagnosis.
[f]Number of hours of therapy before or after index antidepressant prescription.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 2. Index Diagnoses Among Patients Receiving Antidepressants for a Disorder Other Than Depression, Anxiety, or Schizophrenia (N = 178)

Disorder	N	%
Smoking cessation	57	32
Migraine (or other) headaches	24	13
Chronic pain disorder	23	13
Fibromyalgia	21	12
Premenstrual syndrome	12	7
Insomnia (or other sleep problem)	11	6
Perimenopausal hot flashes	8	4
Gastrointestinal disorder	4	2
Anorexia or bulimia	2	1
Bladder dysfunction	2	1
Malaise and fatigue	1	1
Nocturia	1	1
Premature ejaculation	1	1
No diagnosis provided	11	6

Table 3. Antidepressant Prescribers by Specialty[a]

Specialty	N	%
Adult primary care[b]	667	70.1
Psychiatry[c]	144	15.1
All other prescribers	140	14.7
Other prescribers ≥ 1%		
Obstetrics and gynecology	38	4.0
Pediatrics	30	3.2
Neurology	25	2.6

[a]Based on survey and non-survey groups combined (N = 951).
[b]Includes family practice and internal medicine.
[c]Includes adult and child practices.

goal of 6 months (4 or more prescriptions filled in 6 months) was always smaller than the proportion of patients prescribers intended to receive long-term treatment at the time of the index prescription (Table 4, Figures 1 and 2). This shortfall held true even when we linked prescriber intention with prescription refills by specific patient (Table 5).

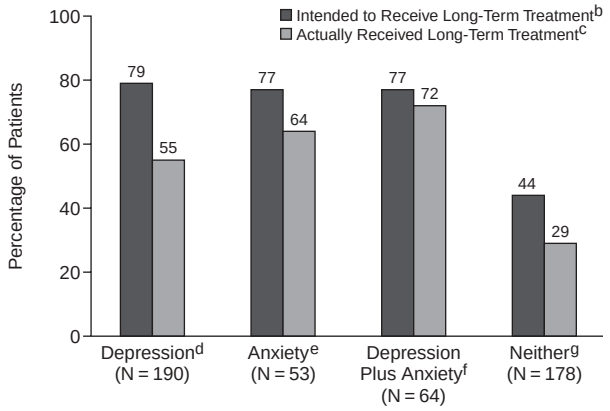
Tables 4 and 5 address the issue of prescriber intention for the length of antidepressant treatment versus the attainment of that goal as measured by prescription refills. Whereas Table 4 shows overall intentions and outcomes, Table 5 links intention and outcome by specific patient. Whichever way one counts, it appears that patients are influenced by prescriber intention for the length of treatment. Psychiatrists most often intend longer courses of antidepressant treatment, and their patients usually follow that recommendation. On the other hand, adult PCPs and other prescribers appear to favor short-term antidepressant treatment, and their patients oblige as well.

Table 4. Duration of Antidepressant Treatment[a]

Variable	Intended Treatment, Survey Group, Duration of Treatment		Actual Treatment: Survey Group, No. of Times Prescription Was Filled		Actual Treatment: Non-Survey Group, No. of Times Prescription Was Filled		Actual Treatment: Combined Groups, No. of Times Prescription Was Filled	
	< 6 mo	≥ 6 mo	< 4	≥ 4	< 4	≥ 4	< 4	≥ 4
Index diagnosis								
Depression[b]	40 (21)	150 (79)	86 (45)	104 (55)	...	…	…	...
Anxiety[c]	12 (23)	41 (77)	19 (36)	34 (64)	...	…	…	...
Depression plus anxiety[d]	15 (23)	49 (77)	18 (28)	46 (72)	...	…	…	...
All other[e]	99 (56)	79 (44)	126 (71)	52 (29)	...	…	…	...
Prescriber type								
Primary care physician	120 (35)	220 (65)	184 (54)	156 (46)	195 (60)	132 (40)	379 (57)	288 (43)
Psychiatrist	17 (24)	55 (76)	20 (28)	52 (72)	31 (43)	41 (57)	51 (35)	93 (65)
Other prescribers	29 (40)	44 (60)	45 (62)	28 (38)	52 (78)	15 (22)	97 (69)	43 (31)

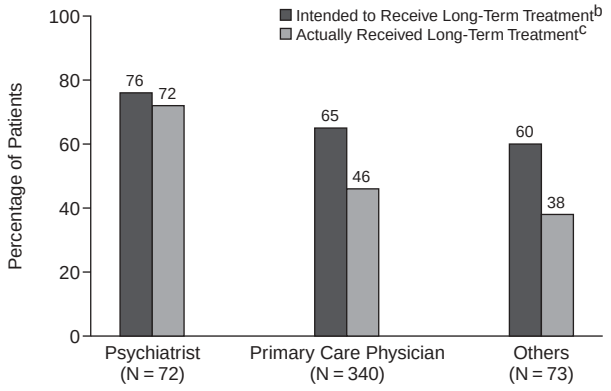
[a]Values shown as N (%).
[b]Depression alone or in combination with any other diagnosis except anxiety.
[c]Anxiety alone or in combination with any other diagnosis except depression.
[d]Depression in combination with anxiety, with or without other diagnoses.
[e]Any diagnosis other than depression or anxiety, including no answer for diagnosis.

Figure 1. Effect of Diagnosis on the Attainment of Long-Term Treatment With an Antidepressant[a]



[a]All groupings are nonoverlapping.
[b]As indicated on completed surveys by the prescriber.
[c]Based on a patient filling at least 4 prescriptions within the 6-month period following the index prescription.
[d]Depression alone or in combination with any other diagnosis except anxiety.
[e]Anxiety alone or in combination with any other diagnosis except depression.
[f]Depression in combination with anxiety, with or without other diagnoses.
[g]Any diagnosis other than depression or anxiety, including no answer for diagnosis.

Figure 2. Effect of Prescriber Class on the Attainment of Long-Term Treatment With an Antidepressant[a]



[a]All groupings are nonoverlapping.
[b]As indicated on completed surveys by the prescriber.
[c]Based on a patient filling at least 4 prescriptions within the 6-month period following the index prescription.

Determinants of Therapy Continuation

The results of multivariate logistic regression analysis expressed in odds ratio (OR) form (Table 6) confirmed observations noted above. In the combined survey group and non-survey group sample, patients of psychiatrists at the time of the index prescription were much more likely than patients receiving index prescriptions from adult PCPs to continue antidepressant medication for at least 6 months (OR = 1.84, p = .008), and patients treated at index by others (nonpsychiatrist, non-PCP) were less likely to do so (OR = 0.59, p = .014). Patients prescribed antidepressants by more than 1 physician were much more likely to continue therapy for 6 months (OR = 4.61, p < .001). Patients for whom SSRIs were prescribed as the initial antidepressant medication were 2 to 4 times (p < .015) more likely to stay on medication treatment than those started on any other type of antidepressant. Patients coprescribed benzodiazepines were also more likely to continue antidepressant treatment for 6 months (OR = 1.85, p < .001).

DISCUSSION

Even in the setting of an HMO that offers good access to mental health care and is supportive of the prescription of the newer, more costly antidepressants as well as

Table 5. Duration of Antidepressant Treatment Linked to Specific Patients

Variable	Duration of Intended Treatment (N)		Treatment/Intent Concordance (N)		Patients for Whom Treatment Outcome Matched Prescriber Intent			
	< 6 mo	≥ 6 mo	< 4 Prescriptions and < 6 mo Intended Treatment	≥ 4 Prescriptions and ≥ 6 mo Intended Treatment	N/N	(%)	N/N	(%)
Index diagnosis								
Depression[a]	40	150	25	89	25/40	(63)	89/150	(59)
Anxiety[b]	12	41	6	28	6/12	(50)	28/41	(68)
Depression plus anxiety[c]	15	49	6	37	6/15	(40)	37/49	(76)
All other[d]	99	79	81	34	81/99	(82)	34/79	(43)
Prescriber type								
Primary care physician	120	220	89	125	89/120	(82)	125/220	(57)
Psychiatrist	17	55	6	41	6/17	(35)	41/55	(75)
Others	29	44	23	22	23/29	(79)	22/44	(50)

[a]Depression alone or in combination with any other diagnosis except anxiety.
[b]Anxiety alone or in combination with any other diagnosis except depression.
[c]Depression in combination with anxiety, with or without other diagnoses.
[d]Any diagnosis other than depression or anxiety, including no answer for diagnosis.

Table 6. Factors Predicting Long-Term Antidepressant Usage[a]

Variable	Survey Group		Non-Survey Group		Combined	
	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p
Male	1.00[b]		1.00[b]		1.00[b]	
Female	1.31	.235	1.13	.592	1.22	.207
Age	0.00	.721	0.00	.049	0.00	.100
Primary care physician	1.00[b]		1.00[b]		1.00[b]	
Psychiatrist	1.98	.049	2.45	.258	1.84	.008
Other prescribers	0.95	.856	0.75	.324	0.59	.014
Multiple prescribers	4.30	.001	4.84	< .001	4.61	< .001
SSRI	1.00[b]		1.00[b]		1.00[b]	
Tricyclic antidepressant	0.50	.027	0.24	< .001	0.32	< .001
Venlafaxine, nefazodone, mirtazapine	0.32	.006	0.55	.117	0.42	.002
Bupropion	0.26	< .001	0.26	< .001	0.23	< .001
Trazodone	0.69	.450	0.34	.023	0.45	.013
Depression	1.00[b]		1.00[b]		1.00[b]	
Depression plus anxiety	1.32	.427	...	...	...	...
Anxiety	1.34	.400	...	...	...	...
Other diagnoses	0.55	.038	...	...	...	...
Psychotherapy before[c]	0.00	.937	–0.02	.228	0.00	.620
Psychotherapy after[c]	0.01	.500	0.01	.273	0.01	.170
No benzodiazepine use	1.00[b]		1.00[b]		1.00[b]	
Benzodiazepine use	1.86	.006	1.78	.016	1.85	< .001

[a]Logistic regression analyses were carried out with a dependent dummy variable set equal to 1, if a patient had received 4 or more antidepressant prescriptions, or zero. Odds ratios are given for the 0-1 binary variables, and coefficient estimates are given for continuous variables in the logistic regression: age, hours of psychotherapy before, and hours of psychotherapy after.
[b]By definition, the reference case is a male patient, with a primary care physician prescribing an index SSRI and all subsequent antidepressant prescriptions from the same prescriber, for depression only, with no benzodiazepine use.
[c]Number of hours of therapy before or after index antidepressant prescription.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

psychotherapy, adherence to antidepressant therapy falls short of that recommended by consensus guidelines for depression or sensible usage for other indications. Our findings reveal that important determinants of continuation of antidepressant therapy include prescriber type, number of prescribers, prescriber intent, diagnosis, the specific antidepressant used, and concomitant benzodiazepine use.

Patient Demographics

Our sample patient population is similar demographically to those of many other published studies of antidepressant treatment. Our results are consistent with the known gender difference in the prevalence of affective illness. Others have also noted the same 2-to-1 female-to-male ratio for depression treatment.[19] Antidepressants were most frequently prescribed for patients in the middle years of life in our sample, which is again consistent with other reports, but may also reflect the predominantly non-Medicare, commercially insured population serviced by Health New England.

Prescriber Characteristics

Our data confirm those from previous studies showing that patients are more likely to continue antidepressant therapy when a psychiatrist has prescribed it.[20] Not reported previously in the literature is the low rate of antidepressant continuation we observed in patients for whom

initial antidepressants were prescribed by others, i.e., nonpsychiatrist/non-PCP prescribers (who wrote as many initial prescriptions for antidepressants as psychiatrists in our study). In previous reports, data concerning this heterogeneous group of prescribers have been combined with data for PCPs treating adults. However, PCPs achieve somewhat better antidepressant adherence rates than these other nonpsychiatrist prescribers. No matter the type of individual prescriber, when multiple prescribers are involved with the same patient, there is a powerful positive effect on patient adherence to antidepressant medication.[21]

Although our sample indicates that psychiatrists wrote 15% of new prescriptions for antidepressants in 2001, data compiled in 1998 from Health New England show that psychiatrists wrote 48% of all (i.e., new and ongoing) antidepressant prescriptions in that year.[22] The relatively high percentage of new and ongoing antidepressant prescriptions written by psychiatrists in 1998 supports our finding from the 2001 data that psychiatrists' patients are more likely to continue antidepressant therapy than are patients of primary care physicians or other medical specialists. Whether this differential patient adherence to antidepressants is simply a function of prescriber type or differences between patients treated (e.g., greater severity, chronicity, comorbidity) by the different provider types is unclear from our analysis.

Prescriber Intent

Our data specifically addressing provider intent show that many providers continue to prescribe antidepressants for less than 6 months, more so for treating non–mental health indications, but also when treating depression or another mental disorder. Psychiatrists are less likely than other prescribers to indicate short-term treatment intentions, but even they often engage in such practice. Even when specifically treating depression, 21% of all prescribers indicate an intended treatment length of less than 6 months (Table 4). This finding could possibly indicate the use of antidepressants for patients with mild cases of depression.

However, studies show that antidepressants are no more effective than placebo in treating mild depression. In the National Institute of Mental Health Treatment of Depression Collaborative Research Program, subjects with mild depression who received imipramine plus clinical management fared no better than those who received clinical management alone.[23] Similar results have been obtained in primary care patients treated with paroxetine.[24] Patients with minor depression showed a high overall remission rate at 11 weeks as measured by the Hamilton Rating Scale for Depression no matter what treatment was employed. In that study, the remission rate for placebo was similar to that for patients treated with paroxetine and those treated with a form of psychotherapy (Problem-Solving Treatment for Primary Care) (65.6%, 60.7%, and 65.5%, respectively).

Mild symptoms and spontaneous early remission may also contribute to a high dropout rate in antidepressant treatment. Among patients entering an antidepressant clinical trial for the treatment of anxiety, patients with a Hamilton Rating Scale for Anxiety (HAM-A) score of 20 or greater (severe anxiety) had a dropout rate of 16% and patients with a HAM-A score of 16 to 19 (moderate anxiety) had a dropout rate of 19%, whereas a HAM-A score of 6 to 15 (mild anxiety) resulted in 54% early discontinuation.[25] Others have noted that the association between mild impairment, quick improvement, and early antidepressant discontinuation occurs in treating depression as well.[26]

A recent article by Fava[27] reminds us that Carroll[28] warned about the inappropriate use of antidepressant drugs almost 2 decades ago: "[We] strongly suspect that many patients who are simply unhappy or dysphoric receive these drugs, with predictable consequences in terms of morbidity from side effects, mortality from overdose, economic waste, and irrational, unproductive clinical management."[28(p169)] Particularly worrisome are new data from as yet unpublished studies, reported first by British drug authorities and then endorsed by the U.S. Food and Drug Administration (FDA), warning that one of the SSRIs, paroxetine, may increase the likelihood of suicide in children and teenagers and that the danger is highest in the first few weeks young patients are taking the drug.[29]

Alternatively, prescribers may empirically know what the scientific literature has failed to demonstrate to date, i.e., that short-term usage of antidepressants works and is cost-effective for some patients, for a variety of indications and diagnoses. In any event, now that we know that the practice of short-term treatment with antidepressants is commonplace (at least in one HMO), it may be important to investigate if the same practice pattern is widespread and if short-term antidepressant treatment is effective as compared with (less expensive and safer) placebo treatment or medical management without use of psychopharmacologic agents.

Diagnoses

Initially, the broad range of index diagnoses captured by our survey might seem surprising, yet in terms of frequency of prescriptions for uses other than depression, our findings are generally supported by the sparse literature available. In our survey, we found that depression and anxiety, alone or in combination, accounted for more than 50% of the diagnoses for which antidepressants were prescribed. However, 14 other indications accounted for 37% of initial prescriptions for antidepressants; these other uses included a mixture of possible depression or anxiety somatic equivalents.

These data parallel the findings of the Practice Partner Research Network, in which 6.3% of a total of 149,327

active patients treated by 389 participating primary physicians received a prescription for an antidepressant in 1996; 40% of those who received an antidepressant were not diagnosed with depression.[30] In another study of 1080 patients who received an SSRI in a network model HMO, 56% of medical claims showed that such treatment targeted non–FDA-approved diagnoses.[31] In addition, previous studies[32,33] show that 13% to 40% of patients treated with antidepressants (for a depressive illness) possibly should not have been treated with these drugs because the patients never fulfilled the criteria for a diagnosis of depression. Not reported by these other studies is our finding that antidepressant prescriptions for indications other than depression and anxiety are characterized by a more pronounced trend for short-term treatment intent and early discontinuation (Tables 4 and 5, Figure 1).

Pharmacotherapy

Our data on the antidepressant medication class confirm previous findings of lower discontinuation rates for SSRIs as compared with older drugs such as tricyclic antidepressants.[34] Interestingly, the newer antidepressants such as venlafaxine, nefazodone, and mirtazapine are associated with discontinuation rates lower than those observed with the tricyclic antidepressants but higher than the traditional SSRIs. Bupropion, another widely used agent, shows even higher rates of early discontinuation, although that finding may be attributable to its short-term use as an aid to smoking cessation. Likewise, it is difficult to meaningfully compare trazodone with the other antidepressants because some trazodone usage may reflect its effectiveness as a sleeping aid rather than its antidepressant activity. In any event, the differential adherence to the different classes of medication reminds us that medication side effects and tolerability vary between agents and that may affect adherence.

Concurrent Psychotherapy

Although we looked for a positive association between psychotherapy and antidepressant continuation, no such finding emerged in our data. Others, however, have found such a link. For example, a study of claims data of 2012 patients with a diagnosis of depression[35] reported a positive effect of concurrent psychotherapy on antidepressant continuation. All forms of psychotherapy, regardless of length, demonstrated this effect. Another study[36] showed that adding psychotherapy to antidepressant treatment resulted in an increase of approximately 11% in the probability of patients receiving at least 6 months of continuous medication treatment.

Concurrent Benzodiazepine Usage (any indication)

Patients treated with a benzodiazepine early in the course of therapy (who were therefore presumed to have manifested symptoms of anxiety at the start of treatment) continued antidepressant therapy longer. Our finding of an odds ratio of 1.85, i.e., almost a doubling of the likelihood of staying on treatment with an antidepressant when a benzodiazepine is coprescribed, is somewhat surprising although in line with the literature. Early coprescription of a benzodiazepine with an antidepressant was recently the subject of a Cochrane Database Systematic Review.[37] Aggregating data from studies involving a total of 679 patients, investigators found that patients in the combination therapy group were less likely to drop out than patients in the antidepressant-only group (relative risk = 0.63). The intention-to-treat analysis (with people dropping out assigned the least favorable outcome) showed that the combination group was more likely to demonstrate improvement in major depression both at 1 week and at 4 weeks. The difference was no longer significant at 6 to 8 weeks.

Study Limitations

As the design of this study is observational, we can only speculate about the direction of causality of the correlations we report.

One finding, that many prescribers often intend patients to stay on treatment with antidepressants for a relatively short period of time (i.e., < 6 months), may have been influenced by a specific feature of our survey, namely that a single check-off item indicated responses to the question of prescriber intent. In retrospect, it would have been useful to have asked for more detailed responses from providers regarding the duration of the intended treatments.

Mailing the questionnaires immediately after initial prescriptions were filled would also have been better than the procedure we utilized for administrative convenience—all the questionnaires were mailed, at the same time, 4 months after the last prescriptions were filled. Although the questionnaire specifically asks about intent at the time of initial prescription, the time delay of 4 to 8 months after the initial prescription not only introduced possible recall problems, but raised the possibility that physicians' "intent" to continue or discontinue therapy reflected post hoc explanations affected by whether patients did in fact complete their course of treatment. Also, since our diagnostic data derive entirely from the prescriber questionnaires, they are subject to the same possible limitations. Nonetheless, it is reassuring that any of the study's imperfections are likely to have affected all prescribers and all patients in a random fashion, increasing the likelihood that the findings of differences and correlations we report are valid.

Finally, we opted for a way of counting refills that ensures that our findings reflect antidepressant discontinuation rather than the switching of antidepressants. However, as we counted any antidepressant refill by any prescriber and attributed such to the initial prescriber and the initial class of antidepressant, our data do not truly compare one antidepressant class versus another or one prescriber class versus another.

CONCLUSIONS

Although treatment guidelines for the use of antidepressants in major depression and (where they exist) in other disorders indicate that at least 6 months of treatment is the minimum standard, our findings document that antidepressant adherence usually falls far short of that goal. There is, however, considerable variability in antidepressant adherence. Important determinants of antidepressant adherence in the first 6 months of treatment include prescriber type, prescriber intent, patient diagnosis, antidepressant class, concomitant benzodiazepine treatment, and whether there are multiple prescribers.

The widespread off-label usage of antidepressants, particularly by nonpsychiatrists, is also noteworthy. We believe that the guideline of a minimum of 6 months of treatment for major depression applies to most off-label use, both for mental health and somatic indications, but that view seems not to be shared by all prescribers. The controversy can only be resolved by controlled trials for each off-label indication for which antidepressants are widely prescribed. Such trials should ideally have a continuation phase to provide clear guidelines for appropriate length of antidepressant treatment. For example, a recent randomized, double-blind trial of paroxetine for the treatment of menopausal hot flashes[38] showed effectiveness, but the trial stopped after 6 weeks of treatment, raising the question of whether the paroxetine was curative and, if not, how long the antidepressant should be continued.

Our most surprising and important finding relates to provider intent. The intention of short-term treatment with antidepressants occurs even for patients with diagnosed anxiety and depressive disorders. Nonpsychiatrist physicians are more likely to intend short-term treatment, but psychiatrists purposefully engage in that practice as well. Furthermore, such provider intent correlates strongly with early patient discontinuation. If early antidepressant discontinuation is often intended and implemented, what might be the reason? Is a trial of antidepressants what many prescribers recommend when a patient has vague complaints, either mental or physical? Unfortunately, prescriber intent of short-term treatment and early patient discontinuation suggest that this strategy is not likely to work, yet is it wrong to try? Is even an infrequent positive response worth the relatively low risk? We do not know the answers to these questions, but asking them is important, especially since the medications involved are so frequently prescribed and are costly.

Finally, if we accept that patient nonadherence to antidepressants is a problem, then to what extent does the problem lie with prescribers rather than (as usually formulated) patients or medication side effects? We need to better answer not only the usual question of what limits patient compliance with intended treatment, but also why a high proportion of intended treatment runs counter to guideline recommendations for minimum length. This phenomenon, not previously focused on in the literature, suggests that provider intent should be included in future studies, not only of antidepressant adherence, but of other medications and treatments as well.

Drug names: bupropion (Wellbutrin and others), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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Appendix 1. Survey Questionnaire

Patient's Name: _____ Patient's HNE ID#: _____

Antidepressant: _____ Date of Initial Pharmacy Fill: _____

Please indicate the length of time you wished for the patient to stay on the antidepressant.
Then kindly check off (or number for more than one indication) the reason(s) for the prescription:

1 month___ > 1 month but less than 6 months___ 6 months or more___

Depression Spectrum Disorders		Anxiety Spectrum Disorders	
Major Depression	_____	Generalized Anxiety Disorder	_____
Single episode	_____	Panic Disorder	
Recurrent	_____	Without agoraphobia	_____
Minor Depression	_____	With agoraphobia	_____
Dysthymia	_____	Social Phobia	_____
Adjustment Disorder (Depressive Symptoms)	_____	Adjustment Disorder (Anxiety Symptoms)	_____
Depression associated with organic mental state (eg Alzheimer's)	_____	Obsessive-Compulsive Disorder	_____
Depression associated with alcoholism or other substance abuse	_____	Post Traumatic Stress Disorder	_____
Seasonal Affective Disorder	_____	Dissociative Disorder	_____
Bipolar Disorder	_____	Attention Deficit Disorder	_____
Borderline Personality Disorder	_____	**Schizophrenia Spectrum Disorders**	
Pathological Mourning	_____	Schizophrenia	_____
Other Disorders		Schizoaffective	_____
Pre-menstrual Syndrome	_____	Brief reactive psychosis	_____
Fibromyalgia	_____	Gastrointestinal Disorder (eg non-specific colitis)	_____
Insomnia (or other sleep problem)	_____	Premature Ejaculation	_____
Migraine (or other) Headaches	_____	Bladder Dysfunction	_____
Chronic Pain Disorder	_____	Smoking Cessation	_____
Impulse Disorder	_____	Nocturia	_____
Malaise and fatigue	_____	Peri-menopausal Hot Flashes	_____
Anorexia or Bulimia	_____		