

Provider and Patient Characteristics Associated With Antidepressant Nonadherence: The Impact of Provider Specialty

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Objective: Given the widespread use of antidepressants in primary care and specialty populations, we sought to examine whether provider specialty and patient demographic and clinical characteristics were associated with nonadherence to antidepressant therapy.

Method: We conducted an observational cohort study of 11,878 patients enrolled in Harvard Pilgrim Health Care who were newly treated with antidepressants between May 2002 and May 2004. Using generalized estimating equations, we examined predictors of 2 types of antidepressant nonadherence: (1) immediate nonadherence: never refilling an antidepressant prescription; and (2) 6-month nonadherence: refilling an antidepressant prescription at least once, but not satisfactorily completing a 6-month treatment episode.

Results: Compared with patients treated by primary care physicians (PCP), being treated by a psychiatrist was associated with significantly lower odds of immediate nonadherence (PCP 18% vs. psychiatrist 13%). Being treated by another type of specialist was associated with significantly higher odds of both immediate (other specialist 23%) and 6-month nonadherence (PCP 53%, psychiatrist 49%, other specialist 62%). Treatment by multiple providers was associated with lower odds of nonadherence than being treated by only 1 provider. Younger patient age and use of pain medication were associated with greater nonadherence.

Conclusion: Rates of both immediate and 6-month nonadherence are high, and clinicians should emphasize the importance of continuing antidepressant treatment for a sufficient duration. Patients whose depression treatment is initiated by nonpsychiatric specialists may benefit from collaborative care models. These strategies may enable providers to better manage the long-term disability associated with their patients' depression.

(*J Clin Psychiatry* 2007;68:867-873)

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For this project, Dr. Bambauer was funded by a Thomas O. Pyle Fellowship at Harvard Medical School and a National Institute of Aging-funded Harvard Initiative in Global Health pilot grant. Dr. Bambauer was funded and Drs. Adams and Soumerai are currently funded by the Harvard Pilgrim Health Care Foundation. Drs. Soumerai and Ross-Degnan are investigators in the HMO Research Network Center for Education and Research in Therapeutics, supported by the Agency for Healthcare Research and Quality.

Presented in abstract form at the 11th annual HMO Research Network Conference; April 4-6, 2005; Santa Fe, N.M.

Drs. Bambauer, Soumerai, Adams, Zhang, and Ross-Degnan report no additional financial affiliations or other relationships relevant to the subject of this article.

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Depression is one of the most common disorders treated by primary care and specialist physicians. While antidepressant therapy is efficacious,¹ treatment nonadherence and early discontinuation rates are high.²⁻⁴ Clinical guidelines recommend continuous use of antidepressant therapy for at least 6 months.⁵ Failure to complete an episode of antidepressant treatment can lead to depression relapse and recurrence⁶⁻⁸ and reduced quality of life.⁹ Alternatively, adherence to antidepressant treatment can improve both depression¹⁰ and overall health outcomes.¹¹

Some researchers have found that provider specialty can influence antidepressant nonadherence rates and quality of care. For example, Robinson et al.¹² recently found that receipt of mental health specialty care was the single greatest predictor of high-quality antidepressant management. Lewis et al.¹³ also found that rates of early antidepressant discontinuation (defined as failure to refill an antidepressant medication within 30 days of the end of the first prescription) were lower among patients treated by psychiatrists. However, contrary to these findings, Dobrez et al.¹⁴ found little impact of initial provider specialty on antidepressant nonadherence rates. Patient

characteristics that have been previously associated with nonadherence to depression treatment include race, presence of comorbid conditions, side effects, provider specialty, and quality of communication between the patient and the prescribing physician.^{6,15} We seek to extend this research in several ways by examining both provider and patient characteristics that are associated with nonadherence to antidepressant therapy in a managed care organization.

This study takes advantage of a large cohort of patients ($N = 11,878$) newly treated with antidepressants during 2002–2004 and examines the combined and concurrent effects of patient comorbidity, age, gender, and provider specialty on rates of nonadherence. It also expands previous research by examining 2 forms of nonadherence: immediate nonadherence (never refilling the antidepressant prescription) and 6-month nonadherence (refilling the antidepressant prescription at least once, but not satisfactorily completing a 6-month treatment episode).

We hypothesized that both patient comorbid conditions and provider specialty could have a significant influence on patient nonadherence to antidepressant treatment. Specifically, we predicted that patients treated by psychiatrists would have lower rates of both types of nonadherence than patients treated by other providers. In addition, we predicted that patients with higher burdens of comorbidity would be more likely to be nonadherent to antidepressant treatment because they might not want to add another medication to their existing potentially complex and expensive treatment regimen.

METHOD

Study Population

The study cohort consisted of Harvard Pilgrim Health Care (HPHC) patients aged 18 and older who began a new episode of antidepressant treatment (defined as more than 100 days without previous antidepressant use) between May 2002 and May 2004 and who were continuously enrolled for at least 6 months before and after the index antidepressant dispensing. Eligible patients filled at least 1 prescription for 1 or more of the following antidepressants: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or venlafaxine. Each patient was followed for a 180-day treatment episode (to approximate a recommended 6 months of treatment⁵). Only the first such episode was included for each patient. Outcomes were based on days of antidepressant dispensed during the episode. Patient provider and enrollment data came from HPHC patient records, and patient prescription data were provided from HPHC's pharmacy benefit manager, MedImpact. This study was reviewed and approved by the HPHC Institutional Review Board.

Measures of Nonadherence

There is no gold standard for measuring nonadherence to medications,¹⁶ and studies may yield conflicting results because they use different populations, different adherence measures, and/or different predictors. National organizations have developed guidelines for the appropriate treatment of depression.¹⁷ The Health Plan Employer Data and Information Set (HEDIS) of the National Committee for Quality Assurance (NCQA) evaluates quality of treatment for depression in managed care organizations.¹⁸ Several studies have considered patients as nonadherent to antidepressant therapy if they fail to refill 4 prescriptions in 6 months.^{19,20}

We categorized patients into nonadherence groups based on prescription refill behavior. First, patients were divided by whether they ever refilled their index antidepressant medication prescription (ever vs. never refill). Next, among those who refilled their index antidepressant medication prescription, patients were considered nonadherent if they had ≥ 52 days without antidepressant treatment during the 180-day episode of treatment, to approximate the HEDIS continuation phase measure.⁵

Predictors

We examined both patient and provider characteristics as potential correlates of antidepressant nonadherence. Patient predictors tested included age, gender, whether the patient was on more than 1 type of antidepressant medication during the treatment episode (of the 7 antidepressants we examined), average copayment per antidepressant refill, type of antidepressant used, and the use of other medications in the 6 months prior to the antidepressant treatment episode. Since we were interested in measuring continuity of medication use, all medications were included in measures of drug use, even if patients switched the type of antidepressant used during the treatment episode. Definitions for the prior use of medications were derived from the chronic disease score.²¹

Provider characteristics tested included whether the patient's prescribing clinician was a psychiatrist (including psychiatrists, child psychiatrists, or geriatric psychiatrists), a primary care physician (including physicians with specialties in internal medicine, family practice, general practice, or geriatric medicine), or a physician with another specialty (such as hematology, neurology, obstetrics, pathology, surgery, etc.) and whether there was more than 1 clinician prescribing antidepressants for a given patient during the treatment episode.

Statistical Analysis

We used generalized estimating equations (GEE)^{22,23} created with PROC GENMOD, from SAS statistical software version 9.1 (SAS Institute Inc., Cary, N.C.), to evaluate patient characteristics predicting antidepressant nonadherence, clustered at the provider level (i.e., by ini-

Table 1. Demographic, Clinical, and Antidepressant Treatment Characteristics of the Study Population by Specialty of Prescribing Physician (N = 11,878)^a

Variable	Primary Care (N = 7982)	Psychiatry (N = 2405)	Other Specialty (N = 1491)
Patient characteristics			
Age, mean (SD), y*	42.6 (11.2)	40.7 (11.5)	41.3 (11.8)
Gender, female*	5368 (67.3)	1439 (59.8)	1194 (80.1)
Chronic disease score categories			
Anxiety*	1865 (23.4)	688 (28.6)	344 (23.1)
Asthma	634 (7.9)	179 (7.4)	101 (6.8)
Bipolar disorder*	3 (< 1.0)	37 (1.5)	2 (< 1.0)
Cardiac disease	214 (2.7)	49 (2.0)	43 (2.9)
Coronary/vascular disease*	135 (1.7)	38 (1.6)	44 (3.0)
Cystic fibrosis	7 (< 1.0)	3 (< 1.0)	3 (< 1.0)
Diabetes*	361 (4.5)	54 (2.3)	42 (2.8)
Epilepsy*	215 (2.7)	184 (7.7)	93 (6.2)
End-stage renal disease*	11 (< 1.0)	2 (< 1.0)	11 (< 1.0)
Gastric acid disorder*	1131 (14.2)	268 (11.1)	224 (15.0)
Glaucoma	23 (< 1.0)	6 (< 1.0)	4 (< 1.0)
Gout	64 (< 1.0)	17 (< 1.0)	5 (< 1.0)
Heart disease*	1018 (12.8)	195 (8.1)	179 (12.0)
Human immunodeficiency virus	24 (< 1.0)	10 (< 1.0)	2 (< 1.0)
Hyperlipidemia*	934 (11.7)	202 (8.4)	132 (8.9)
Hypertension*	1061 (13.3)	223 (9.3)	182 (12.2)
Irritable bowel syndrome	49 (< 1.0)	17 (< 1.0)	9 (< 1.0)
Liver failure	24 (< 1.0)	7 (< 1.0)	10 (< 1.0)
Malignancies	137 (1.7)	42 (1.7)	82 (5.5)
Pain*	1508 (18.9)	361 (15.0)	427 (28.6)
Pain and inflammation*	1216 (15.2)	307 (12.8)	255 (17.1)
Parkinson's disease	12 (< 1.0)	7 (< 1.0)	6 (< 1.0)
Psychotic disease*	144 (1.8)	107 (4.5)	62 (4.2)
Renal disease*	5 (< 1.0)	0 (0.0)	3 (< 1.0)
Rheumatoid arthritis*	607 (7.6)	139 (5.8)	173 (11.6)
Thyroid disorder	561 (7.0)	144 (6.0)	103 (6.9)
Transplant	10 (< 1.0)	7 (< 1.0)	5 (< 1.0)
Tuberculosis	5 (< 1.0)	1 (< 1.0)	1 (< 1.0)
Characteristics of antidepressant treatment episode			
More than 1 prescribing provider*	1228 (15.4)	357 (14.8)	285 (19.1)
More than 1 type of antidepressant used during episode*	707 (8.9)	255 (10.6)	111 (7.4)
Nonadherence variables			
Immediate nonadherence after initial dispensing*	1418 (17.8)	321 (13.4)	341 (22.9)
6-Month nonadherence*	4207 (52.7)	1181 (49.1)	927 (62.2)
Cost sharing			
Copayment per refill during episode, mean (SD), \$	16.41 (6.95)	16.49 (7.39)	16.39 (7.60)
Antidepressant type (first prescription)			
Citalopram*	2039 (25.5)	630 (26.2)	249 (16.7)
Escitalopram*	1259 (15.8)	467 (19.4)	115 (7.7)
Fluoxetine*	723 (9.1)	301 (12.5)	155 (10.4)
Fluvoxamine*	9 (< 1.0)	29 (1.2)	1 (< 1.0)
Paroxetine*	1782 (22.3)	262 (10.9)	327 (21.9)
Sertraline*	1478 (18.5)	402 (16.7)	409 (27.4)
Venlafaxine*	692 (8.7)	314 (13.1)	235 (15.8)

^aData shown as N (%) unless noted otherwise.

* χ^2 test of differences between groups: $p < .05$.

tial provider who prescribed an antidepressant) using an exchangeable covariance structure. We conducted 2 GEE analyses: (1) an analysis of what factors predict whether patients will ever refill their index antidepressant prescription (immediate nonadherence) and (2) among patients who refill at least 1 antidepressant prescription, an analysis of what factors predict whether patients will be adherent according to our modified HEDIS definition of adherence (6-month nonadherence). Our modeling strategy included the following process: we tested which individual patient and provider characteristics predicted non-

adherence and included all characteristics that reached a level of significance of $p \leq .20$ in our adjusted model.

RESULTS

A total of 11,878 patients met study criteria. Of these patients, 2080 (18%) never refilled their initial antidepressant prescription. Of the remaining 9798 patients, 5563 (57%) were adherent (< 52 days without treatment during the first 180 days of treatment) to the antidepressant medication regimen, while 4235 (43%) were nonadherent.

Table 2. Predictors of Antidepressant Nonadherence Among Managed Care Enrollees (2002–2004)

Predictor ^a	Model 1: Immediate Nonadherence				Model 2: 6-Month Nonadherence			
	Unadjusted Results		Adjusted Results		Unadjusted Results		Adjusted Results	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age (reference group = 18–29), y								
30–39	0.88	0.76 to 1.02	0.86	0.74 to 1.01	0.91	0.80 to 1.03	0.90	0.79 to 1.02
40–49	0.92	0.79 to 1.07	0.89	0.77 to 1.04	0.77	0.68 to 0.87	0.78	0.69 to 0.88
50–59	0.99	0.85 to 1.15	0.95	0.81 to 1.11	0.71	0.62 to 0.80	0.74	0.65 to 0.85
60+	1.01	0.80 to 1.27	0.95	0.75 to 1.20	0.71	0.58 to 0.86	0.76	0.62 to 0.94
Antidepressant type (reference group = venlafaxine)								
Citalopram	0.88	0.74 to 1.05	0.90	0.76 to 1.07	1.21	1.03 to 1.41	1.22	1.04 to 1.43
Escitalopram	0.93	0.77 to 1.12	0.97	0.81 to 1.17	1.07	0.90 to 1.27	1.09	0.92 to 1.29
Fluoxetine	0.73	0.59 to 0.91	0.76	0.61 to 0.94	1.57	1.31 to 1.88	1.56	1.30 to 1.87
Fluvoxamine	0.35	0.11 to 1.13	0.42	0.12 to 1.41	0.96	0.50 to 1.84	0.99	0.51 to 1.89
Paroxetine	0.90	0.75 to 1.08	0.87	0.73 to 1.05	1.09	0.93 to 1.28	1.07	0.91 to 1.26
Sertraline	0.78	0.65 to 0.94	0.76	0.64 to 0.92	1.12	0.96 to 1.31	1.08	0.92 to 1.27
Chronic disease score category								
Anxiety	0.90	0.82 to 0.99	0.94	0.86 to 1.04
Asthma	0.86	0.71 to 1.03	0.84	0.70 to 1.02
Diabetes	0.84	0.68 to 1.03	0.97	0.78 to 1.21
Heart disease	0.80	0.71 to 0.91	0.90	0.79 to 1.03
Hyperlipidemia	0.79	0.69 to 0.90	0.91	0.79 to 1.06
Hypertension	0.80	0.71 to 0.91	0.90	0.78 to 1.03
Malignancies	1.19	0.91 to 1.55	1.16	0.88 to 1.52
Pain	1.11	1.00 to 1.25	1.09	0.97 to 1.22	1.14	1.03 to 1.27	1.16	1.04 to 1.29
Thyroid disorder	0.88	0.75 to 1.02	0.92	0.78 to 1.07
Provider type (reference group = primary care)								
Psychiatry	0.70	0.61 to 0.81	0.70	0.61 to 0.80	0.96	0.87 to 1.06	0.93	0.83 to 1.03
Other specialty	1.37	1.20 to 1.57	1.39	1.22 to 1.60	1.41	1.25 to 1.59	1.40	1.24 to 1.59
More than 1 prescribing provider ^b	0.86	0.77 to 0.95	0.83	0.75 to 0.92

^aUnadjusted predictors with $p < .20$ were included in multivariate models; inclusion of age, initial antidepressant type, and provider type categories tested as a group. Chronic disease score categories with less than 1% of the patient population experiencing the disease were excluded. We controlled for gender in adjusted analyses.

^bOnly 1 provider prescribed an antidepressant for those who were immediately nonadherent. Symbol: ... = not a significant univariate (and therefore adjusted) predictor.

Baseline characteristics of the study participants by specialty of the prescribing physician are presented in Table 1. Patients treated by psychiatrists tended to be younger than patients treated by other physicians, and more women were treated by other specialists and primary care providers than psychiatrists. Patients whose treatment was initiated by another specialist were more likely to have more than 1 provider during the treatment episode, while patients treated by psychiatrists were more likely than other patients to use more than 1 type of antidepressant during the treatment episode. There were no significant differences in average copayments per refill among patients treated by any type of provider. Finally, in unadjusted comparisons, patients who were treated by other specialists were most likely to be nonadherent (both by never refilling their index prescription and by becoming nonadherent later in treatment), while patients treated by psychiatrists had the lowest rates of nonadherence.

Results from the GEE models examining odds of nonadherence are presented in Table 2. After adjusting for potential confounders, only provider type and initial antidepressant type were significant predictors of immediate nonadherence. Being treated by a psychiatrist was

associated with significantly lower odds of immediate nonadherence (OR: 0.70, 95% CI: 0.61 to 0.80), while being treated by another specialist was associated with significantly higher odds (OR: 1.39, 95% CI: 1.22 to 1.60) compared with patients treated by primary care physicians. Patients started on the antidepressants fluoxetine or sertraline were less likely to be immediately nonadherent than patients started on any of the other types of antidepressants studied.

In adjusted models, younger age and prior use of pain medication were associated with higher odds of 6-month nonadherence. Once again, being treated for depression by another specialist was associated with an increased risk of nonadherence (OR: 1.40, 95% CI: 1.24 to 1.59) compared with patients treated by primary care physicians, but no differences were seen between primary care physicians and psychiatrists. Treatment by multiple providers during an episode of depression was associated with lower odds of 6-month nonadherence (OR: 0.83, 95% CI: 0.75 to 0.92) than being treated by only 1 provider. Initial treatment with citalopram or fluoxetine during the episode was associated with increased odds of 6-month nonadherence compared with the other antidepressants studied.

DISCUSSION

Our analyses indicate that patients treated by psychiatrists are more likely to refill an initial antidepressant prescription than patients treated by primary care physicians, but once patients are established on therapy (i.e., have filled their antidepressant prescription more than once), rates of nonadherence during the treatment episode do not differ between these specialties. In contrast, patients treated by other specialists (excluding psychiatrists) had higher odds of both immediate and 6-month nonadherence than patients treated by primary care physicians. This finding may in part be explained by the higher likelihood that patients whose depression treatment is initiated by another specialist will see multiple providers during their treatment. Interestingly, patients seen by psychiatrists had the highest rates of switching antidepressants during a treatment episode, which was associated with increased odds of 6-month nonadherence. The higher incidence of switching medication can possibly be explained by the more severe case-mix of patients (seen by psychiatrists) who may require more frequent adjustments to their antidepressant regimens. The results regarding initial antidepressant choice are harder to interpret, and our study was not intended to compare differences in rates of nonadherence by antidepressant type. Further experimental research needs to be conducted to test short- and long-term nonadherence to all types of antidepressants in naturalistic settings.

Our findings are in accordance with previous research indicating that reasons for nonadherence vary as treatment progresses²⁴ and that patients initially treated by psychiatrists are most likely to receive adequate treatment.²⁵ It is troubling that patients treated for depression by other specialists have the highest rates of nonadherence, which could reflect the specialists' lack of experience in or time constraints associated with treating this condition.^{3,26} The relationship between depression and pain is undoubtedly complex²⁷⁻²⁹ and indicates that patients suffering from pain may represent a vulnerable subgroup of patients who seek out other specialists to manage both their pain and emotional distress.

It is also interesting to note that patients seen by multiple providers (16% of the sample) were more likely to be adherent than patients seen by only 1 provider. Most patients in this population were being treated with antidepressants by primary care providers alone. Only 20% of patients were initially prescribed antidepressants by psychiatrists. Several studies have demonstrated the benefits of collaborative or coordinated care among primary care providers and specialty mental health providers.³⁰ We were not able to measure frequency of physician visits in our sample, since we had access to only pharmacy data. However, our results also support existing findings that rates of coordination between primary care physicians

and specialty mental health providers such as psychiatrists are low, particularly in managed care organizations. So while our results suggest that patients treated by multiple providers may be more likely to be adherent, only a small proportion of our sample was seen by multiple providers.³¹

While our analysis has produced several interesting findings, there are some limitations of note. We were unable to measure potential predictors of patient nonadherence to antidepressant therapy that are not identifiable using pharmacy claims data, which exclude patient diagnosis. For example, we could not evaluate patients' attitudes toward antidepressants or concurrent use of psychotherapy, both of which may affect nonadherence.^{32,33} Patient attitudes toward antidepressant therapy and their use of psychotherapy are likely to vary by specialty of the prescribing physician, with patients who see psychiatrists being more predisposed to accept treatment.^{34,35} Patient disposition might explain some of the differences we see between psychiatrists and other physicians. In addition, because we did not have data on physician visits, we could not examine the relationship between visit frequency and nonadherence. We also could not determine if patients had previously taken antidepressants prior to the 100-day washout period used to identify new use of antidepressants, or if patients received a prescription for an antidepressant but never filled it (i.e., they never initiated treatment). Furthermore, by counting all medications equally, patients who used more than 1 type of antidepressant (i.e., switching from one medication to another during the treatment episode) could have appeared to be more adherent than they actually were. However, only 9% of patients in our population switched medications, and switching did not have a significant effect on their rates of adherence.

In addition, our analyses were limited to patients who were prescribed antidepressants by physicians. Therefore, if a patient was being treated for depression by another type of provider, such as a clinical social worker or psychologist, or was being treated without antidepressants, this would not be detected in our data. Thus, we would not be able to identify possible failures in the continuum of care for patients managed by multiple types of providers. Furthermore, patient nonadherence could have reflected inadequate provider prescription behavior or variable instructions to refill the medication for at least 6 months.

It is also worth noting that we examined only newer antidepressant medications (primarily selective serotonin reuptake inhibitors [SSRIs]) because many older antidepressant medications may be used for indications other than depression, and we sought to focus our analyses on patients most likely to be using antidepressants to treat depression. Nonadherence rates with SSRI medications have usually been lower than the rates of nonadherence

among patients taking tricyclic antidepressants,^{14,36,37} suggesting that our estimate of antidepressant nonadherence may actually be lower in this study than in the overall population of patients taking all types of antidepressant medications.

Finally, our data cannot suggest a causal relationship between provider specialty and patient adherence. Rather, we are demonstrating in a large, naturalistic study that patients who initiate antidepressant treatment outside of specialty psychiatry settings may be less likely to be adherent to a recommended regimen of treatment. In addition, because our results are from 1 large insurance plan, they may not be generalizable to all privately insured patients. In a previous study using the same data,³⁸ we examined whether there were any other factors that may have influenced rates of antidepressant adherence during the study period. While there were several attempts to influence antidepressant adherence, none had a significant effect on actual rates of adherence. In addition, the real-world significance of the statistical difference in immediate nonadherence between patients initially treated by psychiatrists compared with primary care physicians may be questioned due to our large sample size. However, this finding remained robust and significant in analyses that adjusted for a large number of other potential confounding variables.

Despite these limitations, our study has several strengths, including the use of a large, longitudinal pharmacy claims database to measure nonadherence.³⁹⁻⁴¹ In addition, we had a large sample size of patients being treated with antidepressants, data on both patient and provider characteristics, an analysis accounting for clustering of patients by provider, controls for comorbidity, and recent data (2002-2004). Furthermore, our measure used gaps in treatment as a way of identifying treatment nonadherence, a method that has both the timeliness and frequency of refilling.⁴² Given the dearth of naturalistic studies examining both patient and provider predictors of antidepressant nonadherence, this study provides several useful insights for targeting approaches to improving nonadherence.

Antidepressant nonadherence remains a challenging problem for managed care organizations. To prevent relapse and recurrence, proper dose and duration of treatment are required.⁴³ All clinicians should be mindful of high rates of both immediate and 6-month nonadherence and provide patients with specific instructions about the importance of continuing antidepressant treatment as prescribed. It may also be useful for nonpsychiatrist physicians who prescribe antidepressants to be reminded about the importance of ongoing treatment and to be trained in how best to follow up with their patients about nonadherence. These providers should also be particularly vigilant about following up with their patients within the first month of treatment to prevent immediate cessation of

therapy and make any necessary changes to the treatment regimen. Developing a consultation and coordination between other providers and psychiatrists might be another way to decrease antidepressant nonadherence among patients seen outside of the specialty mental health sector. Providers of all specialties should be mindful of a possible relationship between antidepressant nonadherence and concurrent or recent pain medication use. By emphasizing these issues, managed care organizations may be better able to reduce the long-term disability associated with their patients' depression.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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