Reasons for Antidepressant Nonadherence Among Veterans Treated in Primary Care Clinics

John C. Fortney, PhD; Jeffrey M. Pyne, MD; Mark J. Edlund, MD, PhD; Tracy Stecker, PhD; Dinesh Mittal, MD; Dean E. Robinson, MD; and Kathy L. Henderson, MD

Objective: To examine the experiences of veterans (mostly middle-aged and elderly men) prescribed antidepressants, specifically with regard to different types of nonadherence, reasons for nonadherence, and side effects.

Method: A mixed-methods analysis of Department of Veterans Affairs primary care patients (N = 395) with depression (9-item depression scale of the Patient Health Questionnaire criteria) enrolled in a randomized collaborative care trial was conducted. Adherence was measured from patient self-report and pharmacy data. Qualitative interviews elicited in-depth information regarding adherence. The study was conducted from April 2003 to September 2005.

Results: The intervention significantly improved self-reported adherence at 6 months (OR = 2.1; 95% CI, 1.0–4.4; $P = .04$) and 12 months (OR = 2.7; 95% CI, 1.4–5.4; $P < .01$), as well as medication possession at 12 months (OR = 1.82; 95% CI, 1.0–3.2; $P = .04$). The most common type of nonadherence at 6 months was discontinuation (12.2%), followed by not taking as prescribed (10.9%) and never took (4.8%). For patients discontinuing their antidepressant in the first 6 months, the most common and important reason was that it was not helping. Only 19.4% of patients with self-reported adherence ≥ 80% responded to treatment by 6 months. Side effects were also a commonly reported reason for discontinuation at 6 months, with 82% reporting experiencing side effects. One-third (31.4%) reported difficulty with sexual activity at 6 months, with 66.1% reporting that it was severe. Qualitative interviews supported the finding that side effects, and generally not feeling like oneself, are important adherence barriers.

Conclusions: In this sample of mostly middle-aged and elderly men with depression, treatment nonresponse and side effects were the rule rather than the exception. These findings suggest that nonadherence may have resulted primarily from patients' negative experiences with antidepressants rather than structural barriers or noncompliant behaviors.

Trial Registration: clinicaltrials.gov Identifier: NCT00105690

J Clin Psychiatry 2011;72(6):827–834

Submitted: *July 13, 2009; accepted December 8, 2009.*
Online ahead of print: *November 16, 2010 (doi:10.4088/JCP.09m05528blu).*
Corresponding author: *John C. Fortney, PhD, VA HSR&D Center for Mental Health Outcomes and Research (152/NLR), Little Rock VA Medical Center, 2200 Fort Roots Dr, North Little Rock, AR 72114 (fortneyjohnc@uams.edu).*

Pharmacotherapy is the most common treatment for depression,[1,2] and an adequate trial of antidepressant treatment improves clinical outcomes.[3,4] Nevertheless, almost half (45.4%) of Americans report that they would not take an antidepressant for depression,[5] and 20%–51% of primary care patients prematurely discontinue antidepressants.[6–13] In a large nationally representative sample, only 27.6% of adults prescribed an antidepressant for depression continued taking it for more than 90 days.[12] Moreover, only 11%–30% of patients consult with the prescribing physician before discontinuing antidepressants.[6,14] Antidepressant adherence is lower than adherence to antihypertensives, antihyperlipidemics, and oral hypoglycemics.[7,15]

Qualitative interviews with patients prescribed antidepressants have identified 4 main concerns: (1) fear of addiction, (2) resistance to viewing depression as a medical illness, (3) concern that antidepressants will prevent feelings of natural sadness, and (4) prior negative experience with antidepressants.[16] Survey data suggest that poor adherence is associated with low perceived need for antidepressants,[17] belief that symptoms will go away on their own,[17] belief that antidepressants are not clinically effective,[18] preference for another type of depression treatment,[14] and not associating depression symptoms with an underlying neurochemical imbalance.[17] Although findings have not been consistent from study to study, many patient characteristics have been identified as significant risk factors for nonadherence, including: younger age,[19–21] male sex,[19,21] minority ethnicity/race,[12,22] lower education and income,[12,13] not married,[6,21,22] poor geographic access to prescribing provider,[18,23] stigma,[20] substance abuse,[13,19,21] and lower depression severity.[17,20,24] Side effects also predict nonadherence.[6,8,14,25,26] Nearly all (90.6%) patients beginning a selective serotonin reuptake inhibitor trial report experiencing at least 1 side effect,[27] half (52%) report 3 or more side effects,[6] and half report experiencing moderate to severe side effects.[6] Among patients discontinuing or switching selective serotonin reuptake inhibitors, 36%–62% report that the primary reason was side effects.[6,8,25]

Adherence is improved if the patient is concurrently receiving psychotherapy,[8,12,28] discusses the risks and benefits of antidepressants with the prescriber,[6,25] and has ≥ 3 depression-related visits to the prescriber.[6,29] In contrast, educational interventions that focus only on the nature and course of depression do not significantly improve adherence.[30] Similarly, the passive monitoring and feedback of antidepressant adherence (from pharmacy records) to prescribers does not significantly improve adherence.[10,31,32]

Collaborative care interventions are designed to improve antidepressant adherence by providing education about the potential risks and benefits of antidepressants and by proactively monitoring adherence and symptoms in order to adjust medications when problems with side effects or nonresponse are detected. Most collaborative care interventions have significantly improved antidepressant adherence,[30,33] although 3 previous trials of collaborative care in the US Department of Veterans Affairs (VA) did not.[34–36] This may be due to the already high adherence rates in the VA (compared to the private sector[19]), resulting from low out-of-pocket costs and mail-out pharmacies.

US Department of Veterans Affairs primary care patients with depression report a preference for, and are more likely to receive, pharmacotherapy compared to psychotherapy.[37] Yet few studies have examined the experiences of middle-aged and elderly men who have been prescribed antidepressants. Consequently, understanding reasons for nonadherence in this population is especially important. Therefore, we conducted a mixed-methods analysis of VA primary care patients enrolled in a randomized pharmacotherapy-focused collaborative care trial[38] to examine types of nonadherence (eg, never took, stopped taking, and not taking as prescribed), reasons for nonadherence, and side effects experienced. We also tested the hypothesis that collaborative care improves antidepressant adherence, as measured from both self-report and administrative pharmacy data.

METHOD

Study Setting and Enrollment Procedures

Details about the intervention and evaluation methods are described in a previous article.[39] The multisite study (clinicaltrials.gov Identifier: NCT00105690) was conducted in 7 small VA Community-Based Outpatient Clinics, which are satellite facilities of "parent" VA Medical Centers in Little Rock, Arkansas; Jackson, Mississippi; and Shreveport, Louisiana, that often lack on-site psychiatrists. The VA Medical Center in Little Rock, Arkansas, served as the coordinating center. The study was approved by the institutional review boards associated with the VA Medical Centers in Little Rock, Arkansas; Jackson, Mississippi; and Shreveport, Louisiana, and it was conducted from April 2003 to September 2005. Veterans with upcoming appointments were screened using the 9-item depression scale of the Patient Health Questionnaire (PHQ-9),[40] with a score ≥ 12 specified as the inclusion criterion. Exclusion criteria included a diagnosis of schizophrenia, current suicidal ideation, recent bereavement, pregnancy, a court-appointed guardian, substance dependence, bipolar disorder, cognitive impairment, or receiving specialty mental health treatment. Current or past use of antidepressants was not an exclusion criterion. Among eligible patients contacted, 91.3% agreed to participate, and 91.9% of those agreeing to participate attended their upcoming appointment and provided written informed consent (N = 395).

Intervention

Patients randomized to the intervention received telemedicine-based collaborative care involving 5 types of providers: (1) Community-Based Outpatient Clinic primary care providers, (2) off-site tele-psychiatrist, (3) off-site depression nurse care manager (RN), (4) off-site clinical pharmacist (PharmD), and (5) off-site psychiatrist. The off-site intervention team focused exclusively on optimizing pharmacotherapy. Nurse care manager telephone encounters with patients included monitoring of symptoms, medication adherence, and side effects. The nurse care manager also followed scripts to address side effects and specific reasons for nonadherence (eg, concerned about addiction).[31] Pharmacist telephone encounters with patients not responding to treatment included medication histories and ongoing side effect management. A psychiatrist supervised the off-site team and provided consultations via interactive video.

Collection of Quantitative Data

At baseline, demographics and depression history were measured using the Depression Outcomes Module.[41,42] Psychiatric comorbidity was measured using the Mini International Neuropsychiatric Interview.[43,44] Health status was measured by the physical health and mental health component scores of the 12-item Short-Form Health Survey for Veterans.[45,46] Social support was measured using the Duke Social Support and Stress Scale.[47,48] Acceptability of antidepressant treatment was measured using an item developed for the Quality Improvement for Depression studies[49,50] (1–definitely acceptable, 2–probably acceptable, 3–probably unacceptable, 4–definitely unacceptable). The Depression Health Beliefs Inventory[51] was used to measure perceptions about depression treatment, including barriers, need, and effectiveness. Follow-up interviews were completed for 91.1% (n = 360) of the study participants at 6 months and 84.8% (n = 335) at 12 months. Depression severity was measured using the 20-item modified subscale of the Hopkins Symptom Checklist,[52,53] and response was measured dichotomously as a 50% improvement in depression severity between baseline and follow-up.

Self-reported adherence was assessed using an instrument specifically designed for the study. Prior to administering the follow-up survey, a study psychiatrist (M.J.E.) examined the patients' VA electronic medical records to determine what antidepressants had been prescribed (or refilled) during the previous 6 months. The most recently prescribed or refilled antidepressant medication was recorded prior to the follow-up interview, and the adherence questions referred to the antidepressant explicitly by name. Research assistants asked all patients with an active prescription if they were currently taking the medication. If patients were currently taking the medication, the interviewers asked how frequently they took the medication in the previous month and if they took the dosage prescribed. Patients were categorized as adherent if they reported taking the full dosage ≥ 80% of the days. This cutoff was chosen to facilitate comparison with other studies.[54–56] Patients who never took, stopped taking, or did not

take the antidepressant as prescribed were asked to choose from a prespecified list of potential reasons and to report the most important reason. Those stopping their medication or not taking as prescribed because of side effects were asked which side effects led to nonadherence. Those still taking their antidepressant medications at follow-up were asked whether they experienced specific side effects in the past 6 months and the severity of those side effects.

Adherence was also measured using medication possession ratios calculated from administrative pharmacy data using similar methods reported in other VA antidepressant adherence studies.[57] The days' supplies of nonconcurrent antidepressant prescription fills were summed to calculate the total cumulative days' supply. For multiple concurrent prescriptions of the same antidepressant, the days' supply of each prescription fill was summed to calculate cumulative days' supply. For multiple concurrent prescriptions of different antidepressants, the days' supply of the earlier prescription was truncated (to account for possible switching). The medication possession ratios during the first and second 6-month follow-up periods were calculated by dividing the cumulative days' supply by 180 days. For consistency with self-reported adherence, patients were classified as having a medication possession ratio ≥ or < 0.8.

Analysis of Quantitative Data

Analyses of adherence were conducted on the subsample of patients with an active antidepressant prescription and not reporting discontinuation due to provider instructions: n = 229 for the 6-month follow-up, and n = 243 for the 12-month follow-up. Descriptive analyses report the type of nonadherence (eg, never took, stopped taking, and not taking as prescribed). Reasons for nonadherence are reported separately for each type of nonadherence. Descriptive analyses of side effects were conducted on the subsample of patients still taking medications at the 6- and 12-month follow-ups (n = 190 and n = 187, respectively). Logistic regression analyses were used to identify risk factors for nonadherence. Independent variables with missing values were imputed using multiple imputation methods. Sampling and attrition weights were calculated to adjust for the potential bias associated with nonparticipation and/or loss to follow-up. Separate regressions were estimated for the analyses of the 6- and 12-month follow-ups. Due to the large number of available casemix variables, only those found to significantly predict the dependent variable at the $P \leq .2$ level in bivariate analyses were included in multivariate analyses. Side effects could not be included as an explanatory variable because side effect questions were only administered to those reporting that nonadherence was due to side effects.

Collection of Qualitative Data

During the 12-month follow-up phone calls, consecutive veterans were asked to participate in qualitative interviews designed to elicit information regarding antidepressant adherence. The open-ended, semistructured key informant telephone interviews were digitally recorded. Interviews were conducted by a psychiatrist (J.P., M.E.) or psychologist (T.S.). To elicit information about adherence, interviewers were given a list of probe questions, including the following: "Some people find it hard to take their medication every day, or stay in treatment. Could you tell me about how this has been for you?"; "What sorts of things help or make it difficult for you to take your medication each day?"; and "How do you decide how often to take your antidepressant medication?" Recruitment for the qualitative interviews continued until saturation was reached (ie, no new information was being learned).

Analysis of Qualitative Data

Each interview was transcribed, coded, and checked for completeness and accuracy. Two coders conducted the content analysis to identify commonly held beliefs about antidepressants. Coding occurred on a line-by-line basis in the text in order to increase the likelihood that each theme would be captured. Themes were identified using multiple coding strategies, including searching the text for main ideas, listening to stories, putting themes together, identifying repetition among respondents, looking for opposite themes, and searching for confirming, as well as disconfirming, evidence of themes. Similar themes were grouped together. To increase confidence that all instances of commonly held themes were identified, coders read the material and marked codes independently. After this initial coding effort, the coders met to compare and discuss themes and reach consensus on coding.

RESULTS

Baseline characteristics of the full sample are presented in Table 1. The substantial disease burden in this sample of middle-aged and elderly men is highlighted by their physical health status (physical health component score), which was 2 standard deviations below the US mean. Most (82.0%) patients met diagnostic criteria for major depressive disorder, and the mean number of prior depression episodes was 3.7. Most (66%) had received prior depression treatment, and 41% were receiving depression treatment when enrolled.

Three-quarters of the sample were prescribed an antidepressant (70.0% [n = 252] during the first 6 months and 77.6% [n = 260] during the second 6 months). Of those prescribed an antidepressant and not reporting discontinuation due to provider instructions (n = 229 at 6 months and n = 243 at 12 months), nearly three-quarters reported taking the full dosage ≥ 80% of the days in the prior month (72.1% at 6 months and 70.8% at 12 months). However, only 48.5% and 46.1% had medication possession ratios ≥ 0.8 during the first and second 6-month periods, respectively. Self-reported adherence ≥ 80% and medication possession ratio ≥ 0.8 were significantly correlated at both 6 months ($\chi^2_1 = 31.4$, $P < .0001$; $\kappa = 0.33$, $P < .0001$) and 12 months ($\chi^2_1 = 49.0$, $P < .0001$; $\kappa = 0.39$, $P < .0001$). Pharmacotherapy outcomes among adherent patients were poor. Only 19.4% of patients with self-reported adherence ≥ 80% responded

Table 1. Baseline Socioeconomic and Clinical Characteristics of Full Sample

Variable	Overall (N = 395)
Sociodemographic	
Age, mean (SD), y	59.2 (12.2)
Sex, %, male	91.7
Race, %	
White	74.7
Black	18.2
Native American	3.0
Other	3.6
Annual household income < $20,000, %	51.7
Married, %	62.3
High school graduate, %	76.0
Employed, %	21.9
Social support (0–1), mean (SD)[a]	0.42 (0.22)
Perceived barriers (0–9), mean (SD)[a]	4.14 (1.87)
Perceived need (0–6), mean (SD)[a]	2.91 (1.45)
Perceived treatment effectiveness (0–2), mean (SD)[a]	1.22 (0.82)
Clinical	
Depression screen score (PHQ-9), mean (SD)	16.4 (3.4)
Depression severity score (HSCL-20), mean (SD)	1.8 (0.7)
Physical health component score (SF-12V), mean (SD)	30.0 (13.0)
Mental health component score (SF-12V), mean (SD)	36.5 (12.3)
Quality of Well-Being score, mean (SD)	0.4 (0.1)
Chronic physical illnesses, mean (SD)	5.5 (2.8)
Family history of depression, %	45.2
Age at depression onset < 18 y, %	17.2
Prior depression episodes, mean (SD)	3.7 (1.8)
Prior depression treatment, %	65.7
Current depression treatment, %	40.9
Antidepressants acceptable, %	79.4
Current major depressive disorder, %	82.0
Current dysthymia, %	4.1
Current panic disorder, %	9.6
Current generalized anxiety disorder, %	50.7
Current posttraumatic stress disorder, %	23.8
Current at-risk drinking, %	12.9

[a]A higher social support score indicates greater levels of perceived support from family members and friends. A higher perceived barriers score indicates a greater number of endorsed barriers to depression treatment. A higher perceived need score indicates greater perceptions about the need for depression treatment. A higher perceived treatment effectiveness score indicates a greater belief in the clinical effectiveness of formal depression treatments such as antidepressants and counseling.
Abbreviations: HSCL-20 = 20-item modified subscale of the Hopkins Symptom Checklist, PHQ-9 = 9-item depression scale of the Patient Health Questionnaire, SF-12V = 12-item Short-Form Health Survey for Veterans.

Table 2. Adherence Regression Results[a]

	Self-Reported Adherence		Medication Possession Ratio	
Variable	6-Month Odds Ratio	12-Month Odds Ratio	Months 1–6 Odds Ratio	Months 6–12 Odds Ratio
Intervention	2.11**	2.72***	1.03	1.82**
Depression severity score (HSCL-20)	0.97**	…	…	…
Age, y	1.04**	…	1.02	1.02
Annual household income < $20,000	1.08	…	0.89	…
Race, white	1.18	0.97	2.79***	2.06**
Sex, male	1.61	…	…	…
Married	1.71	2.04***	…	1.63
Employed	…	…	0.91	…
Social support (0–1)	…	6.60**	…	2.17
Perceived barriers (0–9)	0.91	0.85	0.89	…
Perceived need (0–6)	1.24	0.98	…	…
Perceived treatment effectiveness (0–2)	0.96	1.14	…	…
Antidepressants acceptable (1–4)	0.80	0.51**	0.67	0.59***
Chronic physical illnesses	1.08	1.06	1.10	1.08
Prior depression treatment	…	…	1.04	…
Current depression treatment	2.04	1.19	…	…
Prior depression episodes	1.32***	…	…	…
Family history of depression	1.82	…	…	…
Current major depressive disorder	…	…	0.47	…
Current dysthymia	…	…	…	0.64
Current at-risk drinking	0.43	0.32***	0.60	…

[a]Sample includes patients with an active antidepressant prescription and not reporting antidepressant discontinuation due to provider instructions at the 6- and 12-month follow-ups (n = 229 and n = 243, respectively).
**$P < .05$.
***$P < .01$.
Abbreviation: HSCL-20 = 20-item modified subscale of the Hopkins Symptom Checklist.
Symbol: … = variable not significant in bivariate analysis and excluded from multivariate analysis.

to treatment by 6 months, and only 28.5% responded by 12 months. Likewise, 25.2% of patients with medication possession ratios ≥ 0.8 responded to treatment by 6 months, and 27.7% responded by 12 months.

Table 2 presents the baseline casemix factors that are associated with self-reported adherence and medication possession ratio. As hypothesized, the intervention significantly improved self-reported adherence at both 6 (OR = 2.1; 95% CI, 1.0–4.4; $P = .04$) and 12 (OR = 2.7; 95% CI, 1.4–5.4; $P < .01$) months and medication possession ratio during the second 6-month period (OR = 1.82; 95% CI, 1.0–3.2; $P = .04$). Contrary to our hypothesis, the intervention did not improve medication possession during the first 6-month period (OR = 1.03; 95% CI, 0.6–1.9; $P = .91$). Few casemix factors consistently predicted adherence. Being white was a significant predictor of medication possession ratio at both 6 and 12 months. At 12 months, reporting that antidepressants are acceptable was a significant predictor of both self-reported adherence and medication possession ratio.

Table 3 reports the types of nonadherence and reasons for nonadherence. At 6 months, 28% of patients reported being nonadherent, with 4.8% never taking the antidepressant, 12.2% having stopped taking the antidepressant, and 10.9% not taking the antidepressant as prescribed (eg, taking full dose < 80% of the time). At 12 months, 29.2% of patients reported being nonadherent, with 8.6% never taking the antidepressant, 14.4% having stopped taking the antidepressant, and 6.2% not taking the antidepressant as prescribed. For patients never taking the antidepressant, concerns about side effects was the most common reason and the most important reason reported at both the 6- and 12-month follow-ups. For patients discontinuing their antidepressant, the most common and most important reason reported at 6 months was that the antidepressant was not helping. Side effects were also a commonly reported reason for discontinuation at both follow-ups, and it was the most important reason at 12 months. For those discontinuing because of side effects, the most common side effect reported at 6 months was trouble

Table 3. Self-Reported Reasons for Nonadherence

6-Month Follow-Up,[a] n (%)		12-Month Follow-Up,[b] n (%)	
Total nonadherent	**64 (27.9)**	**Total nonadherent**	**71 (29.2)**
Never took	11 (4.8)	Never took	21 (8.6)
Top five reasons		Top five reasons	
Concerned about side effects	8 (72.7)	Concerned about side effects	10 (47.6)
Should be able to solve problem without antidepressants	8 (72.7)	Afraid antidepressant would make me feel like I wasn't myself	8 (38.1)
Afraid antidepressant would make me feel like I wasn't myself	7 (63.6)	Didn't think antidepressant would help	7 (33.3)
Concerned antidepressants were not safe	7 (63.6)	Didn't think I needed an antidepressant	7 (33.3)
Didn't think antidepressant would help	6 (54.6)	Should be able to solve problem without antidepressants	5 (23.8)
		Concerned antidepressants were not safe	5 (23.8)
Most important reason[a]		Most important reason(s)[b]	
Concerned about side effects	4 (40.0)	Concerned about side effects	4 (23.5)
		Didn't think I needed an antidepressant	4 (23.5)
Stopped taking	28 (12.2)	Stopped taking	35 (14.4)
Top five reasons		Top five reasons	
Antidepressant wasn't helping	13 (46.4)	Should be able to solve problem without antidepressants	19 (54.3)
I was having side effects	12 (42.9)	Antidepressant wasn't helping	15 (42.9)
Antidepressant made me feel like I wasn't myself	9 (32.1)	I was having side effects	15 (42.9)
Should be able to solve problem without antidepressants	8 (28.6)	Antidepressant made me feel like I wasn't myself	15 (42.9)
Not someone who takes antidepressants	8 (28.6)	Didn't need an antidepressant any longer	13 (37.1)
		Concerned antidepressants were not safe	13 (37.1)
Most important reason		Most important reason	
Antidepressant wasn't helping	8 (28.6)	I was having side effects	8 (22.9)
Not taking as prescribed	25 (10.9)	Not taking as prescribed	15 (6.2)
Top five reasons		Top five reasons	
I forgot to take my antidepressants	11 (44.0)	I forgot to take my antidepressants	8 (53.3)
I only take antidepressants on the days I need it	9 (36.0)	I was having side effects	8 (53.3)
Concerned about getting addicted to antidepressants	8 (32.0)	Antidepressant wasn't helping	5 (33.3)
I was having side effects	7 (28.0)	Felt antidepressants were just a crutch	5 (33.3)
Antidepressant wasn't helping	6 (24.0)	Not someone who takes antidepressants	4 (26.7)
Should be able to solve problem without antidepressants	6 (24.0)	Concerned antidepressants were not safe	4 (26.7)
Not someone who takes antidepressants	6 (24.0)		
Forgot to refill prescription	6 (24.0)		
Most important reason		Most important reason(s)	
I forgot to take my antidepressants	6 (24.0)	I forgot to take my antidepressants	3 (20.0)
		I was having side effects	3 (20.0)

[a]Sample includes n = 229 patients with an active antidepressant prescription and not reporting antidepressant discontinuation due to provider instructions at the 6-month follow-up; 1 observation had a missing value for most important reason in never took medication group.
[b]Sample includes n = 243 patients with an active antidepressant prescription and not reporting antidepressant discontinuation due to provider instructions at the 12-month follow-up; 4 observations had missing values for most important reason in never took medication group.

falling asleep (6/12, 50.0%), which was uniformly reported as severe by all (6/6, 100%) patients experiencing this side effect. At 12 months, the most common side effects leading to discontinuation were dizziness or light-headedness (10/15, 71.4%) and dry mouth (10/15, 71.4%), which were reported as severe by 60% (6/10) and 10% (1/10), respectively. For patients not taking antidepressants as prescribed, the most common and the most important reason reported at both follow-ups was forgetfulness.

Among patients still taking antidepressants at the 6-month follow-up, 82% reported experiencing an antidepressant side effect, and 43.6% reported that it was severe (Table 4). At 12 months, 82% reported experiencing a side effect, and 40.6% reported that it was severe. At 6 months, the 3 most common side effects were feeling sleepy in the daytime, dry mouth, and dizziness/light-headedness, although few patients reported these side effects as being severe. One-third (31.4%) of patients reported difficulty with sexual activity at 6 months, and two-thirds (66.1%) of these patients reported that this side effect was severe. At 12 months, the 3 most common side effects were dry mouth, feeling sleepy in the daytime, and difficulty with sexual activity. Again, two-thirds (60.0%) of patients who reported difficulty with sexual activity at 12 months rated it as severe.

Baseline characteristics of subjects participating in the qualitative interviews are presented in Table 5. According to the qualitative interviews, the most commonly reported barrier to taking antidepressants was side effects (40%). Many reported a general weariness about the side effects, such as "I don't like the effects of the medication, so I don't take it." Other negative comments were more specific, such as "I just didn't like the side effects at all. It made me shaky and nervous and neurotic and it upset my stomach" and "It seemed like I wasn't fully awake." Other subjects were

Table 4. Self-Reported Side Effects

	6-Month Follow-Up,[a] n (%)		12-Month Follow-Up,[b] n (%)	
Side Effect	Reported	Severe	Reported	Severe
Any side effect	154 (81.9)	82 (43.6)	153 (81.8)	76 (40.6)
Feeling sleepy in daytime	87 (46.3)	10 (11.5)	75 (40.1)	12 (16.0)
Dry mouth	81 (43.1)	18 (22.2)	92 (49.2)	16 (17.4)
Dizziness or light-headedness	59 (31.4)	7 (11.9)	57 (30.5)	10 (17.5)
Difficulty with sexual activity	59 (31.4)	39 (66.1)	65 (34.8)	39 (60.0)
Feeling anxious or jumpy	54 (28.7)	6 (11.1)	64 (34.2)	10 (15.6)
Trouble falling asleep	50 (26.6)	15 (30.0)	48 (25.6)	20 (41.7)
Constipation or diarrhea	50 (26.6)	10 (20.0)	53 (28.3)	8 (15.1)
Feeling hot or sweaty	49 (26.1)	6 (12.2)	56 (30.0)	7 (12.5)
Weight gain or loss	45 (23.9)	9 (20.0)	53 (28.3)	13 (24.5)
Headaches	44 (23.4)	12 (27.3)	35 (18.7)	10 (28.6)
Muscle stiffness or tightness	39 (20.7)	9 (23.1)	43 (23.0)	10 (23.3)
Blurred vision	36 (19.2)	4 (11.1)	39 (20.9)	5 (12.8)
Nausea	21 (11.2)	4 (19.1)	29 (15.5)	5 (17.2)
Difficulty urinating	15 (8.0)	6 (40.0)	22 (11.8)	2 (9.1)

[a]Sample includes n = 190 patients still taking medications at 6-month follow-up; 2 patients had missing values for side effects. [b]Sample includes n = 187 patients still taking medications at 12-month follow-up.

Table 5. Baseline Socioeconomic and Clinical Characteristics of Subsample Participating in the Qualitative Interviews

Variable	Overall (n = 15)
Sociodemographic	
Age, mean (SD), y	56.2 (11.8)
Sex, %, male	100.0
Race, %	
White	86.7
Black	6.7
Native American	0.0
Other	6.7
Annual household income < $20,000, %	66.7
Married, %	26.7
High school graduate, %	93.3
Employed, %	6.7
Social support (0–1), mean (SD)	0.3 (0.2)
Perceived barriers (0–9), mean (SD)	3.5 (1.9)
Perceived need (0–6), mean (SD)	3.1 (1.4)
Perceived treatment effectiveness (0–2), mean (SD)	1.3 (0.9)
Clinical	
Depression screen score (PHQ-9), mean (SD)	15.9 (3.1)
Depression severity score (HSCL-20), mean (SD)	1.8 (0.7)
Physical health component score (SF-12V), mean (SD)	29.6 (15.6)
Mental health component score (SF-12V), mean (SD)	35.2 (8.4)
Quality of Well-Being score, mean (SD)	0.4 (0.1)
Chronic physical illnesses, mean (SD)	6.6 (2.6)
Family history of depression, %	66.7
Age at depression onset < 18 y, %	26.7
Prior depression episodes, mean (SD)	4.2 (1.6)
Prior depression treatment, %	73.3
Current depression treatment, %	33.3
Antidepressants acceptable, %	93.3
Current major depressive disorder, %	93.3
Current dysthymia, %	6.7
Current panic disorder, %	6.7
Current generalized anxiety disorder, %	50.0
Current posttraumatic stress disorder, %	20.0
Current at-risk drinking, %	6.7

Abbreviations: HSCL-20 = 20-item modified subscale of the Hopkins Symptom Checklist, PHQ-9 = 9-item depression scale of the Patient Health Questionnaire, SF-12V = 12-item Short-Form Health Survey for Veterans.

concerned about addiction: "I'm just afraid I'm going to get addicted" and "They gave me the prescription, so I tried it. I just don't like being drugged." Stigma was a less common, but powerful, barrier. One informant stated, "If you're taking psychiatric meds, they don't want you driving…they don't want you to drive a bus because they don't feel you're responsible for people's lives and then after that…I had gotten a job managing a parking garage and when they found out I was taking psychiatric drugs for that, I lost my job there because they don't want someone in that kind of responsibility...you know, on these drugs, in that kind of a responsibility position."

The qualitative interviews also identified important facilitators for antidepressant adherence. Interestingly, 47% discussed symptoms worsening if they weren't regularly taking their medication: "My life is so much different when I'm on my medication than when I didn't have my medication." In addition, 60% stated that having a regular pill schedule helped them to take their medicine daily. "They have those little things that are marked Monday-Tuesday-Wednesday-Thursday-Friday-Saturday-Sunday and they have Morning-Noon-Evening and bedtime. You put your pills, when you're supposed to take them, in those and then you go through them. You leave them on the counter by your bed and then you get up and that is what you do during the day. It's right there." Another stated, "Well, you know the easiest way, which is a good thing, is it is a nighttime medicine. It's just something you do before going to bed."

DISCUSSION

About three-quarters of veterans prescribed antidepressants reported > 80% adherence, which is consistent with other VA studies (range, 67%–85%).[18,26,58,59] While the collaborative care intervention significantly improved self-reported adherence and medication possession ratios as hypothesized, few baseline casemix factors consistently predicted antidepressant adherence. This is consistent with previous antidepressant adherence studies, which have found that regression models with baseline casemix factors as explanatory variables have poor predictive power (r^2: 3.5%–27.0%).[21,24,26] Lack of predictive power may also have resulted from grouping different types of nonadherence together. In fact, the most important reason for nonadherence differed depending on the type of nonadherence. At 6 months, the most important reason for never taking antidepressants was concern about side effects, the most important reason for discontinuation was that antidepressants were not helping, and the most important reason for not taking antidepressants as prescribed was forgetfulness. Lack of predictive power may have also been due to the large number of relatively uncommon, but powerful, barriers to adherence, such as stigma. The fact that self-reliance (eg, should be able to solve problem without antidepressants, not someone who takes antidepressants, felt antidepressants were just a crutch)

was found to be a relatively common barrier to adherence may reflect the military and rural culture of the sample.

Side effects or concerns about side effects were the most consistently reported reasons for nonadherence, regardless of type of nonadherence. Among those taking antidepressants at follow-up, virtually all reported experiencing a side effect, and almost half reported experiencing a severe side effect. The high prevalence of comorbid anxiety disorders and chronic physical health disorders (in conjunction with the potential for interactions with medications prescribed for these disorders) may have resulted in the relatively high incidence of side effects in our sample. Consistent with the literature, feeling sleepy in the daytime was the most commonly reported side effect.[60] Difficulty with sexual activity was the most commonly reported severe side effect. The prevalence and severity of sexual side effects observed in this sample are much higher than reported in antidepressant product information, but are consistent with a review of published studies.[61] Qualitative interviews supported the finding that side effects, and generally not feeling like oneself, are important adherence barriers.

Collectively, the results of this mixed-methods study confirm the importance of frequently and proactively monitoring adherence and side effects, especially for middle-aged and elderly men with poor physical health. Results also suggest that adherence interventions must be able to address a wide range of problems associated with different types of nonadherence. Importantly, these findings also suggest that the overall benefit of antidepressants may be less than previously thought for middle-aged and elderly men with poor physical health. Only one-quarter of patients taking antidepressants as prescribed responded by 12 months. Moreover, the most commonly reported reasons for discontinuation at 6 months were that the antidepressant was not helping and side effects. For many patients, nonadherence might best be characterized as the outcome of a rational decision, based on their perceptions of the positive and negative clinic effects, rather than as noncompliant behavior. This conclusion is supported by a non-VA study of pharmacotherapy-focused collaborative care that found that the intervention had a significant positive effect on the quality-adjusted life-years of women, but a nonsignificant negative effect on men.[62] Consequently, clinicians may want to encourage middle-aged and elderly men with poor physical health to engage in evidence-based psychotherapies as an alternative or adjunct to pharmacotherapy.

A potential methodological concern is that inclusion was based on screening rather than structured clinical interview, and misdiagnosis may have contributed to poor pharmacotherapy outcomes. Another limitation is that the sample was too small to analyze different types of nonadherence separately. Also, like most other adherence studies, a conceptual weakness was the expectation that baseline casemix factors would predict adherence. While baseline factors may contribute to nonadherence for the few patients who never took their prescribed antidepressant, the vast majority of nonadherence problems resulted from patients' ongoing negative experiences with antidepressants. Future antidepressant adherence studies should be designed to measure these emerging risk factors (eg, side effects, nonresponse) more frequently in order to identify cause and effect relationships with nonadherence.

Author affiliations: US Department of Veterans Affairs (VA) South Central Mental Illness Research, Education, and Clinical Center (MIRECC), Central Arkansas Veterans Healthcare System, North Little Rock (Drs Fortney, Pyne, Mittal, and Henderson); VA Health Services Research and Development (HSR&D), Center for Mental Health and Outcomes Research, Central Arkansas Veterans Healthcare System, North Little Rock (Drs Fortney, Pyne, and Mittal); Department of Psychiatry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock (Drs Fortney, Pyne, Edlund, and Henderson); Psychiatric Research Center, Dartmouth Medical School, Lebanon, New Hampshire, and VA HSR&D, White River Junction Veterans Administration, White River Junction, Vermont (Dr Stecker); Mental Health Service, Overton Brooks VA Medical Center and Department of Psychiatry, School of Medicine, Louisiana State University Health Sciences Center, Shreveport (Dr Robinson); and South Central Veterans Health Care Network, Mental Health Product Line, North Little Rock, Arkansas (Dr Henderson).
Potential conflicts of interest: **Dr Mittal** is an employee of the Central Arkansas Veterans Healthcare System. **Drs Fortney**, **Pyne**, **Edlund**, **Stecker**, **Robinson**, and **Henderson** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.
Funding/support: This research was supported by VA Investigator Initiated Research 00-078-3 grant to Dr Fortney, VA National Provider Identifier 01-006-1 grant to Dr Pyne, the VA HSR&D Center for Mental Health and Outcomes Research, and the VA MIRECC. Drs Pyne and Edlund were supported by VA HSR&D Research Career Awards. Dr Mittal was supported by the VISN 16 South Central Network Research/Career Development Grant Program and VA MIRECC.

REFERENCES

1. Harman JS, Crystal S, Walkup J, et al. Trends in elderly patients' office visits for the treatment of depression according to physician specialty: 1985–1999. *J Behav Health Serv Res*. 2003;30(3):332–341.
2. Olfson M, Marcus SC, Pincus HA. Trends in office-based psychiatric practice. *Am J Psychiatry*. 1999;156(3):451–457.
3. Bosworth HB, Voils CI, Potter GG, et al. The effects of antidepressant medication adherence as well as psychosocial and clinical factors on depression outcome among older adults. *Int J Geriatr Psychiatry*. 2008;23(2):129–134.
4. Fortney J, Rost K, Zhang M, et al. The relationship between quality and outcomes in routine depression care. *Psychiatr Serv*. 2001;52(1):56–62.
5. Croghan TW, Tomlin M, Pescosolido BA, et al. American attitudes toward and willingness to use psychiatric medications. *J Nerv Ment Dis*. 2003;191(3):166–174.
6. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA*. 2002;288(11):1403–1409.
7. van Dijk L, Heerdink ER, Somai D, et al. Patient risk profiles and practice variation in nonadherence to antidepressants, antihypertensives and oral hypoglycemics. *BMC Health Serv Res*. 2007;7(1):51.
8. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2002;36(4):578–584.
9. Peveler R, George C, Kinmonth AL, et al. Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. *BMJ*. 1999;319(7210):612–615.
10. Hoffman L, Enders J, Luo J, et al. Impact of an antidepressant management program on medication adherence. *Am J Manag Care*. 2003;9(1):70–80.
11. Lewis E, Marcus SC, Olfson M, et al. Patients' early discontinuation of antidepressant prescriptions. *Psychiatr Serv*. 2004;55(5):494.
12. Olfson M, Marcus SC, Tedeschi M, et al. Continuity of antidepressant treatment for adults with depression in the United States. *Am J Psychiatry*. 2006;163(1):101–108.
13. Akincigil A, Bowblis JR, Levin C, et al. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Med Care*. 2007;45(4):363–369.
14. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence

to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. *Prim Care Companion J Clin Psychiatry*. 2007;9(2):91–99.
15. Katon W, Cantrell CR, Sokol MC, et al. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. *Arch Intern Med*. 2005;165(21):2497–2503.
16. Givens JL, Datto CJ, Ruckdeschel K, et al. Older patients' aversion to antidepressants. A qualitative study. *J Gen Intern Med*. 2006;21(2):146–151.
17. Aikens JE, Nease DE Jr, Klinkman MS. Explaining patients' beliefs about the necessity and harmfulness of antidepressants. *Ann Fam Med*. 2008;6(1):23–29.
18. Gonzalez J, Williams JW Jr, Noël PH, et al. Adherence to mental health treatment in a primary care clinic. *J Am Board Fam Pract*. 2005;18(2): 87–96.
19. Busch SH, Leslie DL, Rosenheck RA. Comparing the quality of antidepressant pharmacotherapy in the Department of Veterans Affairs and the private sector. *Psychiatric Serv*. 2004;55(12):1386–1391.
20. Sirey JA, Bruce ML, Alexopoulos GS, et al. Stigma as a barrier to recovery: Perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. *Psychiatr Serv*. 2001;52(12): 1615–1620.
21. Busch SH, Leslie D, Rosenheck R. Measuring quality of pharmacotherapy for depression in a national health care system. *Med Care*. 2004;42(6):532–542.
22. Charbonneau A, Rosen AK, Ash AS, et al. Measuring the quality of depression care in a large integrated health system. *Med Care*. 2003;41(5):669–680.
23. Fortney J, Rost K, Zhang M, et al. The impact of geographic accessibility on the intensity and quality of depression treatment. *Med Care*. 1999;37(9):884–893.
24. Brown C, Battista DR, Bruehlman R, et al. Beliefs about antidepressant medications in primary care patients: relationship to self-reported adherence. *Med Care*. 2005;43(12):1203–1207.
25. Lin EHB, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care*. 1995;33(1):67–74.
26. Maidment R, Livingston G, Katona C. Just keep taking the tablets: adherence to antidepressant treatment in older people in primary care. *Int J Geriatr Psychiatry*. 2002;17(8):752–757.
27. Goethe JW, Woolley SB, Cardoni AA, et al. Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. *J Clin Psychopharmacol*. 2007;27(5):451–458.
28. Harman JS, Edlund MJ, Fortney JC. Disparities in the adequacy of depression treatment in the United States. *Psychiatr Serv*. 2004; 55(12):1379–1385.
29. Jones LE, Turvey C, Carney-Doebbeling C. Inadequate follow-up care for depression and its impact on antidepressant treatment duration among veterans with and without diabetes mellitus in the Veterans Health Administration. *Gen Hosp Psychiatry*. 2006;28(6):465–474.
30. Vergouwen ACM, Bakker A, Katon WJ, et al. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry*. 2003;64(12):1415–1420.
31. Simon GE, VonKorff M, Rutter C, et al. Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. *BMJ*. 2000;320(7234):550–554.
32. Bambauer KZ, Adams AS, Zhang F, et al. Physician alerts to increase antidepressant adherence: fax or fiction? *Arch Intern Med*. 2006;166(5): 498–504.
33. Williams JW Jr, Gerrity M, Holsinger T, et al. Systematic review of multifaceted interventions to improve depression care. *Gen Hosp Psychiatry*. 2007;29(2):91–116.
34. Swindle RW, Rao JK, Helmy A, et al. Integrating clinical nurse specialists into the treatment of primary care patients with depression. *Int J Psychiatry Med*. 2003;33(1):17–37.
35. Dobscha SK, Corson K, Hickam DH, et al. Depression decision support in primary care: a cluster randomized trial. *Ann Intern Med*. 2006;145(7):477–487.
36. Hedrick SC, Chaney EF, Felker B, et al. Effectiveness of collaborative care depression treatment in Veterans' Affairs primary care. *J Gen Intern Med*. 2003;18(1):9–16.
37. Dobscha SK, Corson K, Gerrity MS. Depression treatment preferences of VA primary care patients. *Psychosomatics*. 2007;48(6):482–488.
38. Fortney JC, Pyne JM, Edlund MJ, et al. A randomized trial of telemedicine-based collaborative care for depression. *J Gen Intern Med*. 2007;22(8):1086–1093.
39. Fortney JC, Pyne JM, Edlund MJ, et al. Design and implementation of the telemedicine-enhanced antidepressant management study. *Gen Hosp Psychiatry*. 2006;28(1):18–26.
40. Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. *Psychiatr Ann*. 2002;32(9):509–515.
41. Smith GR Jr, Burnam A, Burns BJ, et al. Depression Outcomes Module (DOM). In: American Psychiatric Association, ed. *Handbook of Psychiatric Measures*.Washington, DC: American Psychiatric Association; 2000. 213–215.
42. Kramer TL, Smith GR, D'Arezzo KW, et al. *Depression Outcomes Module*. Little Rock, AR: The Guide to Behavioral Health Outcomes Management Systems; 2000:71–83.
43. Lecrubier Y, Sheehan DV, Weiller E, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *Eur Psychiatry*. 1997;12(5):224–231.
44. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*. 1997;12(5):232–241.
45. Jones D, Kazis L, Lee A, et al. Health status assessments using the Veterans SF-12 and SF-36: methods for evaluating otucomes in the Veterans Health Administration. *J Ambul Care Manage*. 2001;24(3):68–86.
46. Kazis LE, Miller DR, Clark J, et al. Health-related quality of life in patients served by the Department of Veterans Affairs: results from the Veterans Health Study. *Arch Intern Med*. 1998;158(6):626–632.
47. Parkerson GR Jr, Michener JL, Wu LR, et al. Associations among family support, family stress, and personal functional health status. *J Clin Epidemiol*. 1989;42(3):217–229.
48. Parkerson GR Jr, Broadhead WE, Tse CK. Quality of life and functional health of primary care patients. *J Clin Epidemiol*. 1992;45(11):1303–1313.
49. Rost K, Nutting P, Smith J, et al. Improving depression outcomes in community primary care practice: a randomized trial of the quEST intervention. Quality Enhancement by Strategic Teaming. *J Gen Intern Med*. 2001;16(3):143–149.
50. Wells KB, Sherbourne C, Schoenbaum M, et al. Impact of disseminating quality improvement programs for depression in managed primary care: a randomized controlled trial. *JAMA*. 2000;283(2):212–220.
51. Edlund MJ, Fortney JC, Reaves CM, et al. Beliefs about depression and depression treatment among depressed veterans. *Med Care*. 2008;46(6):581–589.
52. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Symptom Checklist (HSCL): a measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry*. 1974;7(0):79–110.
53. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974;19(1):1–15.
54. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–497.
55. Revicki DA, Brown RE, Palmer W, et al. Modelling the cost effectiveness of antidepressant treatment in primary care. *Pharmacoeconomics*. 1995;8(6):524–540.
56. Thompson C, Peveler RC, Stephenson D, et al. Compliance with antidepressant medication in the treatment of major depressive disorder in primary care: a randomized comparison of fluoxetine and a tricyclic antidepressant. *Am J Psychiatry*. 2000;157(3):338–343.
57. Jones LE, Turvey C, Torner JC, et al. Nonadherence to depression treatment guidelines among veterans with diabetes mellitus. *Am J Manag Care*. 2006;12(12):701–710.
58. McCarthy JF, Bambauer KZ, Austin K, et al. Treatment for new episodes of depression. *Psychiatr Serv*. 2007;58(8):1035.
59. Sleath B, Tulsky JA, Peck BM, et al. Provider-patient communication about antidepressants among veterans with mental health conditions. *Am J Geriatr Pharmacother*. 2007;5(1):9–17.
60. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry*. 2004;65(7):959–965.
61. Gregorian RS Jr, Golden KA, Bahce A, et al. Antidepressant-induced sexual dysfunction. *Ann Pharmacother*. 2002;36(10):1577–1589.
62. Pyne JM, Smith J, Fortney J, et al. Cost-effectiveness of a primary care intervention for depressed females. *J Affect Disord*. 2003;74(1):23–32.