Depression: A Modifiable Risk Factor for Poor Outcomes in Fibromyalgia

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Abstract

Background: About 4 out of 10 fibromyalgia patients suffer from depression. The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend using antidepressants to treat fibromyalgia. **Objective:** To determine predictors of improved outcomes following a multicomponent treatment program. **Design:** We designed this longitudinal treatment outcome study to evaluate the prevalence of depression symptoms in patients diagnosed with fibromyalgia at a tertiary care facility, and the impact of depression on functional outcomes after completing a multicomponent fibromyalgia treatment program. **Setting:** Tertiary care center. **Patients:** This study included 411 adult patients with fibromyalgia who completed a multicomponent treatment program for fibromyalgia. Expert physicians performed comprehensive evaluations following American College of Rheumatology (ACR) criteria to confirm fibromyalgia before referral to the program. **Intervention:** An intensive outpatient multicomponent treatment program consisting of 16 hours of cognitive behavioral strategies served as the intervention. **Measurements:** Functional status was assessed using the Fibromyalgia Impact Questionnaire Revised (FIQR). Depression was evaluated with the Center for Epidemiologic Study of Depression (CES-D) measure. Measures were administered prior to participation in the program and approximately 5 months following completion of the program. **Results:** The cohort had a high prevalence of depressive symptoms (73.2% had depression at admission). Higher depression scores at baseline predicted poorer outcomes following multi-component treatment. Effectively treated depression resulted in improved functioning at follow-up. **Limitations:** Findings limited to tertiary care center cohort of fibromyalgia patients. Patients did not undergo a structured clinical diagnostic interview to diagnose depression. **Conclusions:** The current data links depression to poorer outcomes in patients with fibromyalgia. Depression is an important modifiable factor in the management of fibromyalgia. Guidelines should reflect the importance of assessing and effectively treating depression at the time of diagnosis of fibromyalgia, to improve functional outcomes.
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Keywords

Introduction

Widespread pain and stiffness for at least 3 months are characteristic findings of fibromyalgia.[1] After osteoarthritis, fibromyalgia is the second most common rheumatological disorder that occurs in 1% to 5% of the general population.[2-4] Approximately 80% of patients are female; the frequency in

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the general population tends to increase through middle age and then declines in frequency among the elderly.[3,5,6] Fibromyalgia accounts for 15% of outpatient rheumatology visits and 5% of all general medicine visits.[7,8] Patients' quality of life is affected negatively, and these patients are often high utilizers of medical care.[9-11] Patients with fibromyalgia are heterogeneous, and vary in disease presentation, symptom severity, functional impairment, and overall quality of life.[1] Fibromyalgia is associated with somatic pain conditions including irritable bowel syndrome (IBS), chronic headaches and migraine, temporomandibular disorders, sleep disorders, rheumatic diseases, and psychiatric conditions such as mood disorders and depression.[12-17] Depression has been a controversial issue in the conceptualization and treatment of fibromyalgia, and the 2 disorders are linked in important ways. Fibromyalgia patients have 3 times the rate of depression compared to those without fibromyalgia.[18] Greater than 50% of patients with fibromyalgia have lifetime depression.[7] There is a significant overlap in symptoms resulting in theories that posit fibromyalgia is merely a depressive equivalent or an affective syndrome disorder due to shared symptom presentation.[19] Additionally, fibromyalgia symptoms improving with certain antidepressants, raises the possibility of shared pathophysiology.[9] Fibromyalgia and depression have been found to have a bidirectional temporal relationship, with 1 illness increasing the risk of developing another.[20,21] It is also known that individuals with persistent pain are more likely to meet diagnostic criteria for depression compared to those without pain[22] and the risk for developing depression is higher for individuals with multiple pain sites.[23]

The impact of depression on the treatment of fibromyalgia has been unclear. Antidepressants improve pain, mood, sleep, and quality of life in fibromyalgia patients.[7] Despite the availability of Food and Drug Administration (FDA)-approved medications, including antidepressants for the treatment of fibromyalgia, the vast majority of patients receive inadequate treatment.[24-27] Adherence to pharmacological treatment amongst patients with fibromyalgia is also poor, with poor medication tolerance as a potential contributor.[25] The lack of effectiveness of antidepressants may also be why fibromyalgia patients report difficulty tolerating medications or require dose adjustment to notice an improvement.[26] Many patients report feeling misunderstood by health care professionals when clinicians suggest or prescribe antidepressants, and fear being blamed for their symptoms or their symptoms being dismissed as psychological.[25,28,29] Fibromyalgia can be potentially frustrating and challenging for health care providers to manage, particularly when comorbid with major depression.[1]

As we previously reported, a multicomponent fibromyalgia treatment program can successfully improve both depression and functioning.[25] What is not known is whether baseline depression impacts treatment outcomes for patients with fibromyalgia. In the present study we assessed the prevalence of depression symptoms in a well-defined sample of patients with fibromyalgia and determined the impact of depression on treatment outcomes following participation in a multicomponent fibromyalgia treatment program.

Methods

Participants

Subjects (n = 411) were recruited from a 2-day intensive Fibromyalgia Treatment Program at a tertiary medical center from August 2015 to November 2018. All study subjects signed informed consent at enrollment and baseline assessment and were followed for an average of 5 months post-treatment. All study procedures were reviewed and approved by the Institutional Review Board (IRB#19-000495).

Inclusion criteria included the diagnosis of fibromyalgia using the American College of Rheumatology (ACR) criteria.[10,30,31] Exclusion criteria included: active suicidal ideation, evidence of psychosis, and inability to physically take part in the 2-day program. Demographic and clinical data collected prior to enrollment and participation in the Fibromyalgia Treatment Program are described in Table 1.

Procedure

Subjects were assessed at baseline using the Fibromyalgia Impact Questionnaire-Revised (FIQR) and the Center for Epidemiologic Studies of Depression Scale (CES-D). Expert clinicians also conducted a chart review to abstract information related to medication use, including antidepressants and opioids. Follow-up data were collected with mailed surveys post-treatment and approximately 5 months following completion of the treatment program.

Measures

The FIQR is a validated, widely used measure of functional impairment among fibromyalgia patients. Its psychometric properties have been described.[32] The FIQR includes 3 domains: function, overall impact, and symptoms. It also assesses pain, work limitations, and fatigue. About 21 items are scored on a scale of 0 to 10, higher scores reflecting more significant functional impairment. Scores of 60 or higher indicate severe functional impairment.

The Center for Epidemiologic Studies of Depression Scale (CES-D) is a self-reported measure of depressive symptoms[33] that encompasses 20 items with scores ranging from 0 to 60. Higher scores reflect a higher level of depressive symptoms, and scores of 20 and above reflect the clinical threshold for depression.[34] Psychometric properties of the CES-D have been described elsewhere.[33]

Table 1. Demographics.

Variables	N	Overall (N=411)
Age at survey (years)		
Mean (SD)	411	54.7 (13.9)
Range		22.5-85.6
Gender		
Female	411	371 (90.3%)
Male		40 (9.7%)
Race		
White	411	372 (90.5%)
Black or African American		16 (3.9%)
Other		23 (5.6%)
Ethnicity		
Hispanic or Latino	410	34 (8.3%)
Not Hispanic or Latino		368 (89.8%)
Other		8 (2.0%)
Marital status		
Married/domestic partnership	410	300 (73.2%)
Single/divorced/widowed		110 (26.8%)
Duration of symptoms		
Less than 1 year	411	20 (4.9%)
1-2 years		81 (19.7%)
3-5 years		109 (26.5%)
Greater than 5 years		201 (48.9%)
Time since diagnosis (months)		
Mean (SD)	411	48.1 (79.6)
Range		0.0-480.0
FDA approved medicines at admission	411	124 (30.2%)
Opioids at admission	411	107 (26.0%)
Antidepressants at admission	411	232 (56.4%)
SSRI	411	122 (29.7%)
SNRI	411	83 (20.2%)
TCA	411	21 (5.1%)
Psychological variables at intake		
FIQR		
Mean (SD)	411	59.1 (18.1)
Range		0.0-94.7
CES-D		
Mean (SD)	411	25.3 (9.8)
Range		0.0-52.0
Met clinical threshold for depression (CESD ≥ 20)	411	301 (73.2%)
Met severe threshold for functional impairment (FIQR ≥ 60)	411	214 (52.1%)

Treatment Program

The Fibromyalgia Treatment Program is a 16-hour, group-based multicomponent program based on cognitive behavioral therapy (CBT), which is facilitated by health psychologists and nursing staff. Evidence-based strategies to target central sensitization syndrome (CSS), are provided to decrease pain and fatigue, improve non-restorative sleep, and decrease the cognitive symptoms associated with fibromyalgia. The treatment program groups consist of 12 to 15 patients and their family members, and the program is provided over 2 days. Patients with fibromyalgia that present to the 2-day treatment program have had symptoms for many years without effective treatment. The patients present as skeptical and have often received the message from healthcare providers that their symptoms are "not real" and are not amenable to treatment. Evidence for the role of central sensitization in the progression of their symptoms lays the groundwork for the development of a structured treatment plan to address their symptoms.

Statistical Analysis

Demographic and clinical data were described with the mean, standard deviation, and range for the continuous variables and with the number and percentage of patients for the categorical variables. Differences in baseline and follow-up measures of functional impairment (FIQR) and depression (CES-D) were analyzed with a paired *t*-test for continuous variables and a McNemar test for categorical variables. Predictors of severe functional impairment at follow-up (FIQR ≥ 60), including age, gender, duration of symptoms, time since diagnosis, FDA medication at admission, and depression, were analyzed with univariate logistic regression models where odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Further, patients were split into 4 groups: depressed and on antidepressant, not depressed and on antidepressant, depressed and not on antidepressant, and not depressed and not on antidepressant. Depressed was defined as a CES-D score of 20 or higher. Both depressed and antidepressant status measures were based at admission. These 4 groups were compared for depression and functional impairment measures at baseline and at follow-up using a one-way ANOVA. To evaluate the significant differences between the 4 groups, pairwise comparisons with Bonferroni correction were performed. Analyses were conducted using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria), and a *P*-value of <.05 was considered statistically significant.

Results

Demographics and Clinical Data

The demographics of the sample are described in Table 1. The average age of the patients in the sample was 54.7 years with a range of 22 to 85 years of age. Most of the sample was White (90.5%) and female (90.3%). Most participants were married or had a domestic partner (73.2%). The average time since receiving a fibromyalgia diagnosis was over 4 years and approximately 50% of patients had symptoms of fibromyalgia for over 5 years at the time of treatment.

At admission to the program, approximately 30% of the study population were taking an FDA-approved medication for the treatment of fibromyalgia that included Pregabalin,

Table 2. Comparison of Functioning and Depression Scores at Admission vs Follow-Up.

	Admission (N = 411)	Follow-up (N = 411)	*P*-value
FIQR			
Mean (SD)	59.1 (18.1)	46.2 (21.3)	<.001
Range	0.0-94.7	0.0-98.0	
CES-D			
Mean (SD)	25.3 (9.8)	21.4 (9.8)	<.001
Range	0.0-52.0	0.0-56.0	
Met clinical threshold for depression (CES-D ≥ 20)	301 (73.2%)	235 (57.2%)	<.001
Met severe threshold for functional impairment (FIQR ≥ 60)	214 (52.1%)	117 (28.5%)	<.001

Abbreviations: CES-D, Center for Epidemiologic Study of Depression; FIQR, Fibromyalgia Impact Questionnaire Revised.
P-values result from a paired *t*-test for continuous variables and a McNemar test for categorical variables.

Table 3. Predictors of Severe Functional Impairment at Follow-Up (FIQR ≥ 60).

	OR (95% CI)	*P*-value
Age at survey (years)	1.00 (0.98, 1.01)	.66
Gender: Male	1.24 (0.60, 2.45)	.55
Duration of symptoms (1-2 years)	0.87 (0.31, 2.71)	.80
Duration of symptoms (3-5 years)	0.85 (0.31, 2.58)	.75
Duration of symptoms (greater than 5 years)	0.99 (0.38, 2.92)	.99
Time since diagnosis (months)	1.00 (1.00, 1.00)	.40
FDA approved mediciness at admission	1.16 (0.73, 1.84)	.52
CES-D at admission[a]	1.99 (1.57, 2.57)	<.001

Abbreviations: CES-D, Center for Epidemiologic Study of Depression; CI, confidence interval; OR, odds ratio.
[a]ORs for CES-D at admission are estimated on a 10-unit increase.
P-values result from unadjusted logistic regression models.

Duloxetine, and Milnacipran, 26% were using opioids, and 56.4% were taking at least 1 antidepressant. Table 1 shows the number of patients taking selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), and tricyclic antidepressant (TCA).

The results of the paired *t*-test and McNemar test are reported in Table 2. Depression (measured by CES-D) and functional impairment (measured by FIQR) significantly improved following the treatment program (CES-D: Mean 25 vs 21, *P* < .001; FIQR: Mean 59 vs 46, *P* < .001). Categorical outcomes were also significantly improved by the treatment program (*P* < .001).

Logistic Regression results are described in Table 3. Using follow-up functional status (FIQR ≥ 60) as the dependent variable, relevant predictors (age, gender, duration of symptoms, time since diagnosis, use of FDA-approved medication for fibromyalgia, and baseline depression) were analyzed. Of these factors, baseline depression was the only significant predictor, where for a 10-unit increase in CES-D score, patients were twice as likely to report severe functional impairment at follow-up (OR = 1.99, *P* < .001).

Table 4 shows admission scores for FIQR and CES-D for the following 4 patient groups: Fibromyalgia patients who were depressed at admission and on an antidepressant (n = 178), fibromyalgia patients who were depressed at admission and not on an antidepressant (n = 123), fibromyalgia patients who were not depressed at admission and on an antidepressant (n = 54), and fibromyalgia patients who were not depressed at admission and not on an antidepressant (n = 56). Significant differences in functional status at admission were observed between depressed and nondepressed patients (*P* < .001). Table 5 shows depressed patients were more functionally impaired than patients without depression at follow-up. There was no difference in results by multivariate model adjusting for baseline factors (Supplemental Table 1).

Discussion

Our study was designed to determine predictors of severe functional impairment following completion of a multicomponent treatment program. Interestingly, the severity of depression at admission to the program was the sole predictor of poor functioning following treatment. We propose that effective treatment of depression prior to non-pharmacologic management of fibromyalgia is likely to improve long-term outcomes.

Previous research has found significant improvement in functioning of fibromyalgia patients who complete a multicomponent treatment program[25] but the timing of assessment and individual response to treatment programs has been variable. Redondo et al[35] noted improvement in strategies to cope with pain, improvement in functional capacity in patients receiving physical exercise-based therapy, improvement in physical activity of the vertebral column only in patients receiving cognitive-behavioral therapy, but no differences in anxiety, depression, and self-efficacy in either group, with return to baseline values in both groups

Table 4. Comparisons Between Patient Groups at Admission.

Measure	N	Depressed and on antidepressant, N=178	Depressed and on no antidepressant, N=123	Not depressed and on antidepressant, N=54	Not depressed and on no antidepressant, N=56	*P*-value
FIQR at admission						
Mean (SD)	411	66.0 (15.8)	60.8 (16.2)	47.2 (15.5)	44.8 (18.0)	<.001
Range		29.3-94.7	11.0-91.0	0.0-81.0	0.0-71.0	
CES-D at admission						
Mean (SD)	411	30.7 (7.2)	28.2 (6.8)	15.0 (3.8)	12.0 (5.3)	<.001
Range		20.0-52.0	20.0-51.0	3.0-19.0	0.0-19.0	

Abbreviations: CES-D, Center for Epidemiologic Study of Depression; FIQR, Fibromyalgia Impact Questionnaire Revised; PCS, Pain Catastrophizing Score.
Pairwise comparisons with Bonferroni correction were conducted. All differences between the groups were statistically significant at the .05 level expect the following: Not depressed and on antidepressant vs. Not depressed and on no antidepressant (FIQR, CES-D).
P-values result from a one-way ANOVA model. Depressed is defined as CES-D at admission ≥20.

Table 5. Comparisons Between Patient Groups at Follow-Up.

Measure	N	Depressed and on antidepressant, N=178	Depressed and on no antidepressant, N=123	Not depressed and on antidepressant, N=54	Not depressed and on no antidepressant, N=56	*P*-value
FIQR at follow-up						
Mean (SD)	411	50.2 (21.1)	45.4 (22.7)	39.7 (19.7)	41.2 (18.1)	.002
Range		0.0-96.8	5.5-98.0	5.0-86.8	4.0-81.3	
CES-D at follow-up						
Mean (SD)	411	23.6 (9.8)	22.7 (9.7)	16.9 (8.0)	15.8 (7.9)	<.001
Range		0.0-56.0	0.0-47.0	2.0-40.0	1.0-35.0	

Abbreviations: CES-D, Center for Epidemiologic Study of Depression; FIQR, Fibromyalgia Impact Questionnaire Revised; PCS, Pain Catastrophizing.
Pairwise comparisons with Bonferroni correction were conducted. All differences between the groups were statistically significant at the .05 level expect the following: Not depressed and on antidepressant vs. Not depressed and on no antidepressant (FIQR, CES-D), Depressed and on antidepressant vs. Depressed and on no antidepressant (FIQR, CES-D), Depressed and on no antidepressant vs. Not depressed and on no antidepressant (FIQR), and Depressed and on no antidepressant vs. Not depressed and on antidepressant (FIQR).
P-values result from a one-way ANOVA model. Depressed is defined as CES-D at admission ≥20.

after 1 year of follow-up. A prospective, randomized, controlled trial by Saral et al[36] noted intensity of pain, severity of fatigue, number of tender points, and pressure pain threshold decreased significantly in long-term and short-term intervention groups, and physical components of quality of life improved significantly in both groups, but there was no significant difference between intervention groups and the control group in terms of quality of sleep, severity of depression symptoms, mental components of quality of life, and no difference between efficacies of the 2 treatment groups compared to control group.

We noted a high prevalence of depression (73%) in this tertiary sample of fibromyalgia patients. This is a much higher rate of depression compared to other studies that show a co-occurrence rate of fibromyalgia and depression of 40%.[37] Statistically significant improvement in overall functioning and severity of depressive symptoms were observed following the program, but 57% of patients continued to report clinically significant depression symptoms at 5-month follow-up (mean CES-D score of 21.4).

Interestingly, of the patients who were depressed at admission, 33% were already taking an antidepressant which was not effective. Another 30% of patients who were depressed at admission were not on an antidepressant. These 2 groups of depressed patients had the poorest outcomes as measured by level of functioning on the Fibromyalgia Impact Questionnaire assessed at 5-month follow-up (*P* < .001).

Genetic predisposing factors have been well studied for fibromyalgia and depression and increase the risk of developing depression in response to a precipitating event.[38] A polymorphism in the serotonin transporter (5-HTT) gene, involved in major depressive disorder (MDD), has also been implicated in fibromyalgia.[39] The "kindling hypothesis" (because of an abnormal pattern of information processing, each episode of depression increases the likelihood of a new episode of depression that is less influenced by environmental adversity) has been suggested as a mechanism that occurs in MDD which shares similarity to central sensitization implicated

in fibromyalgia.[17] Central sensitization and kindling may share neurobiological bases such as neuroplastic changes and alterations in gene expression.[40] In this subset of patients who do not respond to FDA-approved antidepressants and have fibromyalgia, genetic factors may predict outcomes. Alternate antidepressants and non-pharmacologic management of depression may be warranted prior to enrolling in a multicomponent treatment program to manage fibromyalgia.

In our study, approximately 27% of the fibromyalgia patients were not depressed upon admission to the program. Half of these patients (54/110) were on antidepressants and were considered to be effectively treated. The other half of the non-depressed patients (56/110) were not taking an antidepressant. There were no differences between these 2 groups. The non-depressed groups together and alone were linked to significantly improved outcomes in functioning when assessed on average 5 months after treatment. It appears that effectively treated depression is equally predictive of improved functioning in the absence of depression upon admission. Depression is a modifiable risk factor in the treatment of fibromyalgia. Additionally, our study showed 56.4% of patients were on antidepressants on admission, 73.2% were depressed, scoring over the threshold for depression on the CES-D of 20. Of the 3 FDA-approved medications for fibromyalgia, 2 are anti-depressants (Duloxetine and Milnacipran). In this study, being on 1 of the 3 FDA-approved medications was shown not to be effective in improving functional status at follow-up. Numerous studies have shown the efficacy of antidepressants in treating fibromyalgia.[9] However, most currently available therapies (including Pregabalin, Duloxetine, Milnacipran among others) for fibromyalgia are not supported by high quality evidence.[41] SNRIs improve both chronic pain and depression, but the effects are independent of each other: improvement in mood is a direct effect of SNRIs, being independent of pain relief.[42]

Lee and Song[43] performed a meta-analysis of 9 randomized controlled trials, 5140 individuals, comparing the efficacy and tolerability of the 3 FDA-approved drugs and concluded Duloxetine was superior to Milnacipran and Pregabalin for pain improvement. Häuser et al[44] conducted a meta-analysis of randomized controlled trials comparing Duloxetine, Pregabalin, and Milnacipran in terms of efficacy and harm, and noted Duloxetine was superior to Pregabalin in improving depressive symptoms in patients with fibromyalgia. However, 2 other randomized controlled trials differed from these findings: Gilron et al[45] conducted a crossover randomized, double-blind trial of placebo, Pregabalin, Duloxetine, and the combination of Pregabalin and Duloxetine, and reported insignificant differences between Duloxetine and Pregabalin in depression improvement, despite Duloxetine showing higher pain improvement than Pregabalin. In 2022, Bidari et al performed a randomized clinical trial to compare Duloxetine and Pregabalin for the treatment of pain and depression in Iranian women with fibromyalgia from 2016 to 2017. Similarly, to Gilron et al[45] and Bidari et al[46] this study did not find a significant difference in mental health or quality of life improvement between Duloxetine and Pregabalin and reported the superiority of Duloxetine in pain improvement.

Guidelines should delineate the steps to effectively treat depression in fibromyalgia patients, increasing the chances of functional improvement in this population of patients. Structured screening and measured and stepped care for depression in fibromyalgia patients is likely to improve health-related quality of life. Educating patients about comorbid depression without attribution of somatic symptoms, to mood or anxiety (psychiatric) illness, may improve acceptance of treatment with antidepressants.

There are several limitations of this study. The study site is a tertiary care center and hence the findings from this cohort of fibromyalgia patients can be generalized only to similar settings (patients may have more severe symptoms than in the general population). Also, even though the study used CES-D which is a valid screening tool to identify patients with depression, the patients did not undergo a structured clinical diagnostic interview (formal depression testing evaluation) to confirm the diagnosis of depression. There are also limitations in statistical analyses as we did not control for certain variables such as illegal substance use, sleep disorders, symptoms of fatigue, and cognitive issues that affect the veracity of the information. We have not accounted for change in antidepressant status from baseline to follow-up. The strengths of our study include the large population sample, the consistent use of ACR criteria for the diagnosis of patients with fibromyalgia, and independent evaluation of patients diagnosed with fibromyalgia by other criteria to confirm or negate diagnosis, improving the validity of the fibromyalgia diagnosis.

This study has implications for fibromyalgia treatment when depression is present as a comorbid condition. Proactive identification with validated screening tools and treatment of depression as a part of comprehensive fibromyalgia programs may improve outcomes. Further study with a large cohort of fibromyalgia patients in a randomized controlled trial, to study the impact of depression and its treatment on fibromyalgia outcomes is essential to confirm the differences in outcomes noted in our study, and to determine differences in efficacy and tolerability of various SSRIs, SNRIs, and TCAs. Additionally, future research should study the dosing of specific antidepressants for management of pain, as well as mood disorders. Given the impact of both fibromyalgia and depression on individuals' quality of life, diagnosing and effectively treating depression is likely to improve individual response to non-pharmacologic management of fibromyalgia.

Conclusions

Depression is a modifiable factor that can have a significant effect on fibromyalgia treatment outcomes. The preponderance of evidence suggests that depression in fibromyalgia can be effectively treated. There is a high prevalence of depression in patients diagnosed with fibromyalgia. This study shows that depression is associated with poorer outcomes in this population and has a significant deleterious impact on functioning.

Antidepressants have been found to be effective in the treatment of fibromyalgia. However, many patients with fibromyalgia do not receive these medications for a variety of reasons including noncompliance, patient refusal, and the lack of clear guidelines for physicians in addressing depression in this population. Guidelines should reflect the importance of assessing and effectively treating depression at the time of diagnosis of fibromyalgia to achieve optimal outcomes.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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