

# Management of Fibromyalgia and Comorbid Psychiatric Disorders

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According to the American College of Rheumatology, fibromyalgia is widespread pain of at least 3 months' duration in combination with pain at 11 or more of 18 specific tender point sites on the body. Many individuals with fibromyalgia also have comorbid psychiatric disorders, which can present diagnostic dilemmas and require additional treatment considerations to optimize patient outcomes. Fibromyalgia has been found to be strongly associated with depressive and anxiety symptoms, a personal or family history of depression, and accompanying antidepressant treatment. Psychiatric comorbidities negatively impact the severity and course of fibromyalgia. Pharmacotherapy can be employed to control fibromyalgia and comorbid mood and anxiety disorders. Additionally, nonpharmacologic therapies for fibromyalgia and comorbid psychiatric disorders include cognitive-behavioral therapy and aerobic exercise. The efficacy of pharmacologic and nonpharmacologic treatments is examined in this article, as well as the diagnostic difficulties that comorbid disorders present.

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**F**ibromyalgia is a chronic pain disorder that is defined by the American College of Rheumatology as widespread pain lasting at least 3 months in combination with pain at 11 or more of 18 specific tender point sites on the body.<sup>1</sup> Studies<sup>2–6</sup> in both community and clinical groups suggest that fibromyalgia is strongly associated with depressive and anxiety symptoms, a personal or family history of depression, and accompanying antidepressant treatment.

Several possible pathophysiologic links may exist between mood and anxiety disorders and fibromyalgia.<sup>7</sup> Because fibromyalgia and mood disorders coaggregate in families, common heritable factors have been suggested.<sup>3,7</sup> Another possible way these disorders may be linked is through dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis. For example, chronic stress may induce proinflammatory cytokine expression in the brain, and cyto-

kines, in turn, may contribute to symptoms of both depression and pain enhancement. Cytokines might cause depressive symptoms through modulation of the HPA axis—for example, through glucocorticoid resistance—or they may cause downregulation of the synthesis of serotonin; both of these effects might contribute to the development of depression and enhanced pain perception.<sup>8–10</sup> In addition, evidence suggests that central monoamines are involved in mood regulation and descending pain pathways,<sup>11–13</sup> making it possible that an individual with abnormalities in monoamine neurotransmission may be at risk for the development of mood or anxiety disorders and some chronic pain conditions.

## PREVALENCE, IMPACT, AND DIAGNOSIS OF FIBROMYALGIA AND COMORBID PSYCHIATRIC DISORDERS

Psychiatric symptoms are often comorbid with fibromyalgia. A study<sup>4</sup> of a community sample of adults with fibromyalgia (N = 74) showed that depressive and anxiety symptoms were common and frequently severe. About one third of these individuals reported major current problems with depression or anxiety, and a strong positive association was found between depressive and anxiety symptoms. Furthermore, in a recent study<sup>5</sup> using a U.S. health insurance database, 33,176 patients with fibromyalgia were compared with an identical number of patients without fibromyalgia. The study showed that patients with fibromyalgia were much more likely to have comorbid sleep disorders and depressive and anxiety disorders than individuals without fibromyalgia. The odds ratios (ORs)

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**Table 1. Lifetime Prevalence of Selected Psychiatric Disorders in Patients With Fibromyalgia or Rheumatoid Arthritis<sup>a</sup>**

Psychiatric Disorder	Hudson et al. <sup>3</sup>		Walker et al. <sup>6</sup>		Arnold et al. <sup>7,14</sup>	
	FM, % (N = 31)	RA, % (N = 14)	FM, % (N = 36)	RA, % (N = 33)	FM, % (N = 78)	RA, % (N = 40)
Major depressive disorder	71	14	86	31	62	28
Bipolar I disorder	0	0	NA	NA	1	0
Bipolar II disorder	0	0	NA	NA	12	0
Any anxiety disorder	26	0	NA	NA	60	25
Panic disorder	23	0	47	12	28	8
Posttraumatic stress disorder	NA	NA	NA	NA	23	5
Generalized anxiety disorder	NA	NA	33	15	5	8
Social phobia	NA	NA	NA	NA	21	5
Obsessive-compulsive disorder	6	0	14	0	6	0

<sup>a</sup>Data from Hudson et al.,<sup>3</sup> Walker et al.,<sup>6</sup> and Arnold et al.<sup>7,14</sup>

Abbreviations: FM = fibromyalgia, RA = rheumatoid arthritis, NA = not assessed.

for depression, anxiety, and sleep disorders in patients with fibromyalgia compared with those without fibromyalgia were 4.9, 4.3, and 6.1, respectively.

Arnold et al.,<sup>7,14</sup> Hudson et al.,<sup>3</sup> and Walker et al.<sup>6</sup> examined the lifetime prevalence of comorbid psychiatric disorders in patients with fibromyalgia compared with patients with rheumatoid arthritis, another chronic pain condition. The studies<sup>3,6,7,14</sup> demonstrated that the patients with fibromyalgia were more likely than those with rheumatoid arthritis to have comorbid major mood disorders and anxiety disorders (Table 1).

Arnold et al.<sup>7</sup> also evaluated subjects with fibromyalgia or rheumatoid arthritis and their first-degree relatives aged 18 years or older. The OR for the presence of fibromyalgia among family members of individuals with fibromyalgia was 8.5 (95% CI = 2.8 to 26.0,  $p = .0002$ ), which provides evidence of the familiarity of fibromyalgia. Fibromyalgia was also found to coaggregate significantly with major mood disorders (major depressive disorder, bipolar disorder; OR = 1.8, 95% CI = 1.1 to 2.9,  $p = .013$ ). The coaggregation findings suggest that fibromyalgia shares some familial factor or set of factors with mood disorders.<sup>7</sup>

### Impact of Psychiatric Symptoms on Fibromyalgia

The presence of psychiatric symptoms has a profound impact on the severity and course of fibromyalgia. In an incidence study,<sup>15</sup> self-assessed depression was a prognostic factor for the development of fibromyalgia over time in a cohort of women. In addition, high levels of depression and anxiety in patients with fibromyalgia were found to be associated with more physical symptoms and poorer functioning than pain controls.<sup>4</sup> Furthermore, the number of reported medical symptoms in patients with fibromyalgia has been positively associated with current and past depressive and anxiety disorders.<sup>6</sup> Mood and anxiety disorders are associated with functional disability in patients with fibromyalgia,<sup>6,16</sup> and psychological disturbance is a predictor of persistence of pain associated with fibromyal-

gia.<sup>17</sup> Therefore, when treating patients with fibromyalgia, clinicians should identify and address psychiatric comorbidity to improve patients' long-term outcomes.

### Diagnostic Recommendations

The clinical presentation of fibromyalgia is heterogeneous. Although only widespread pain and tenderness are included in the American College of Rheumatology criteria for fibromyalgia,<sup>1</sup> researchers have identified several other symptom domains that commonly occur in patients with fibromyalgia. For example, in the study<sup>1</sup> that established the American College of Rheumatology criteria, 73% to 85% of patients with fibromyalgia reported fatigue; sleep disturbance, including both nonrestorative sleep and insomnia; and morning stiffness. Paresthesias, headache, and anxiety were experienced by 45% to 67% of patients. Irritable bowel syndrome was present in 22% to 36% of patients.<sup>1</sup> Other commonly reported symptoms include cognitive problems such as trouble concentrating, forgetfulness, and disorganized thinking.<sup>18</sup> Recently, a group of fibromyalgia researchers<sup>18</sup> identified the most common symptoms associated with fibromyalgia that were rated by patients and clinicians as having a substantial impact on patients. These symptom domains included pain, fatigue, quality of life, sleep disturbance, cognitive problems, stiffness, depression, tenderness, and anxiety.

To help clinicians identify fibromyalgia in the psychiatric setting, Pope and Hudson<sup>19</sup> developed alternative criteria to those of the American College of Rheumatology<sup>1</sup> (Table 2). This structured interview was designed to be similar to the Structured Clinical Interview for DSM-IV Axis I Disorders.<sup>20</sup> The criteria<sup>19</sup> require patients to have widespread, chronic pain of at least 3 months' duration as defined by the American College of Rheumatology.<sup>1</sup> However, the interview allows the clinician to either conduct the American College of Rheumatology criteria<sup>1</sup> tender point examination to identify fibromyalgia or document at least 4 of the 6 symptoms shown in Table 2.<sup>19</sup> The final criterion is that the clinician should rule out other systemic

**Table 2. Criteria for Fibromyalgia<sup>a</sup>**

American College of Rheumatology Criteria for Fibromyalgia <sup>1</sup>	Pope and Hudson Criteria for Fibromyalgia <sup>19</sup>
Widespread pain $\geq$ 3 months' duration Pain at $\geq$ 11 of 18 tender points	Widespread pain $\geq$ 3 months' duration Pain at $\geq$ 11 of 18 tender points <b>or</b> $\geq$ 4 of 6 of the following symptoms: Generalized fatigue Headaches Sleep disturbance Neuropsychiatric complaints Numbness or tingling sensations Irritable bowel symptoms

<sup>a</sup>Based on Wolfe et al.<sup>1</sup> and Pope and Hudson.<sup>19</sup>

conditions that might be contributing to the patient's symptoms.

## PHARMACOTHERAPY FOR FIBROMYALGIA AND COMORBID MOOD AND ANXIETY DISORDERS

### Treating Fibromyalgia and Comorbid Major Depressive Disorder

Treatment of fibromyalgia also often includes the use of antidepressant medications. One rationale behind the use of antidepressant pharmacotherapy is the evidence of high lifetime rates of mood and anxiety symptoms and disorders in patients with fibromyalgia.<sup>3,6,14</sup> Tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) may also reduce pain independent of their antidepressant actions as a result of their serotonin- and norepinephrine-mediated effects on the descending pain-inhibitory pathways in the brain and spinal cord.<sup>21</sup> TCAs and SNRIs that have effects on both serotonin and norepinephrine may have more consistent benefits than other types of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), in their relief of persistent pain associated with multiple chronic pain conditions, including fibromyalgia.<sup>21</sup> Duloxetine,<sup>22,23</sup> venlafaxine,<sup>24</sup> and milnacipran<sup>25</sup> are selective dual-reuptake inhibitors that reduce pain associated with fibromyalgia independent of their effect on depression. Mirtazapine may also be effective in patients with fibromyalgia and depression, but controlled trials of this medication in the treatment of fibromyalgia are needed.<sup>26</sup>

Patients with fibromyalgia should be evaluated for current or lifetime comorbid mood disorders. In general, if a patient has a history of major depressive disorder, a TCA or SNRI may be preferable to an SSRI.<sup>14,27</sup> The clinician should titrate antidepressant medications to an adequate therapeutic dose for an adequate duration—at least 6 to 8 weeks—to allow for a response. If a patient does not respond to an antidepressant, the clinician should consider a switch to a different antidepressant. Another strategy is to add an augmenting agent to the antidepressant. One such combination of medications that has been studied is that of an SSRI and a TCA.<sup>28</sup> This study found both fluoxetine and amitriptyline to be effective for patients with fibro-

myalgia, but the combination was more effective than either drug as a monotherapy. However, awareness of drug interactions is important because some SSRIs and SNRIs elevate TCA levels. Another strategy that has been found to be effective in the clinical setting for the treatment of fibromyalgia is the combination of an antidepressant and an anticonvulsant medication such as gabapentin or pregabalin.<sup>29</sup> Pregabalin is currently the only U.S. Food and Drug Administration–approved treatment for fibromyalgia.<sup>30</sup> However, more study is needed to assess the efficacy of combination pharmacotherapy in patients with fibromyalgia and in patients with fibromyalgia and comorbid mood and anxiety disorders.

### Treating Fibromyalgia and Comorbid Anxiety Disorders

In patients who present with a history of comorbid anxiety disorders and fibromyalgia, antidepressants are also potentially effective in relieving both the anxiety symptoms and the painful symptoms associated with fibromyalgia, especially the antidepressants that are efficacious for treating anxiety disorders. Another pharmacotherapeutic option is pregabalin, which has anxiolytic properties and has been studied as a treatment for generalized anxiety disorder (GAD).<sup>31,32</sup> Gabapentin has a similar mechanism of action as pregabalin and may also be effective in treating comorbid anxiety disorders, including panic disorder<sup>33</sup> and social phobia.<sup>34</sup> In a study<sup>35</sup> of patients with fibromyalgia, gabapentin was also effective for the treatment of pain.

### Treating Fibromyalgia and Comorbid Bipolar Disorder

In patients with comorbid bipolar disorder and fibromyalgia, the treatment options may be more limited because very little study of bipolar disorder in patients with fibromyalgia exists. If antidepressants are used to manage the pain associated with fibromyalgia, they should only be used in combination with mood stabilizers to prevent patients from switching into mania or from having instability of mood.<sup>14</sup> Patients with bipolar II disorder, however, may respond to low doses of antidepressant monotherapy, but must be observed carefully for any development of mood instability.<sup>14</sup> Gabapentin and pregabalin are alternatives to

antidepressants in the treatment of comorbid bipolar disorder and fibromyalgia, but should be used in combination with well-established mood stabilizers.

### Treating Fibromyalgia and Comorbid Insomnia

Sleep disturbances and unrefreshing sleep are common in patients with fibromyalgia. Several options for the treatment of insomnia associated with fibromyalgia have been studied. One option is to use a sedating agent at bedtime. The nonbenzodiazepine sedatives—for example, zolpidem<sup>36</sup> and zopiclone<sup>37</sup>—have been studied in fibromyalgia and showed benefits for sleep and daytime energy but not for pain. Therefore, they have limited usefulness as monotherapy in patients with fibromyalgia. The long-term use of sedating agents for fibromyalgia-related insomnia has not been studied.

Alternatives to nonbenzodiazepine sedatives are sedating antidepressants, such as TCAs. For example, amitriptyline at a dose of 25 mg to 50 mg at bedtime has been effective for the treatment of insomnia in patients with fibromyalgia.<sup>38</sup> Another option for the management of insomnia is the use of pharmacotherapies such as gabapentin or pregabalin, which have sedative and pain relieving effects and have demonstrated an improvement in sleep quality in patients with fibromyalgia and enhanced slow-wave sleep in healthy adults.<sup>35,39–41</sup>

## NONPHARMACOLOGIC THERAPIES FOR FIBROMYALGIA AND COMORBID MOOD AND ANXIETY DISORDERS

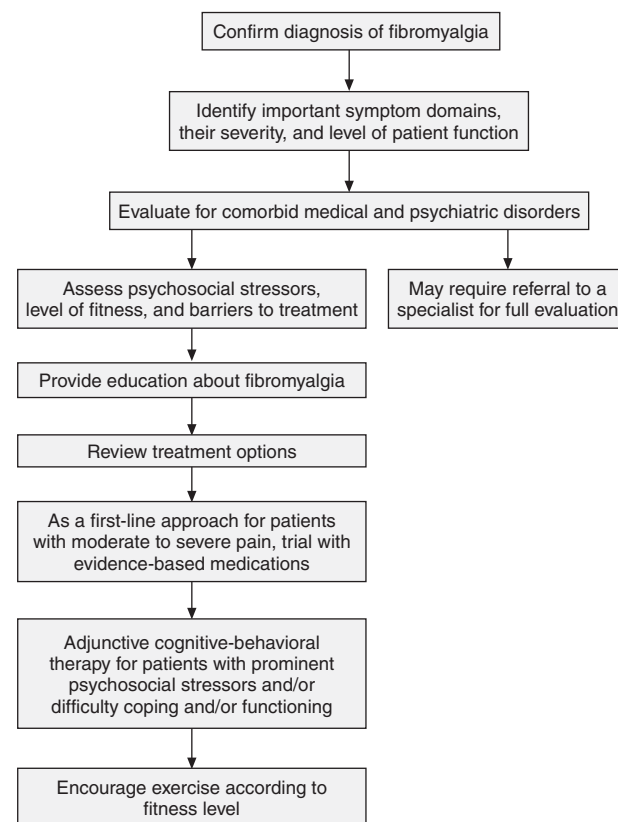
Nonpharmacologic treatments for fibromyalgia with comorbid psychiatric disorders include cognitive-behavioral therapy (CBT), education, and aerobic exercise. Nonpharmacologic treatments may be employed in order to increase a patient's general health and to achieve greater efficacy with pharmacotherapy.

### Cognitive-Behavioral Therapy and Psychoeducation for Comorbid Mood and Anxiety Disorders

Cognitive-behavioral therapy has demonstrated positive effects on patients' ability to cope with the pain associated with fibromyalgia; however, group education provided similar results.<sup>42,43</sup> These results suggest that education itself can be therapeutic. In another study<sup>44</sup> of CBT for fibromyalgia, 6 CBT sessions were added to standard medical care and the CBT sessions improved patients' physical functioning.

Cognitive-behavioral therapy is also effective for mood and anxiety disorders. Meta-analyses<sup>45</sup> have demonstrated the superiority of CBT compared with placebo controls for unipolar depression, for which there have been over 75 clinical trials since 1977.<sup>45</sup> Evidence also supports the efficacy of CBT in GAD,<sup>46</sup> panic disorder,<sup>47</sup> social phobia,<sup>48</sup> obsessive-compulsive disorder,<sup>49</sup> and posttraumatic stress

Figure 1. Stepwise Treatment for Fibromyalgia<sup>a</sup>



<sup>a</sup>Adapted with permission from Arnold.<sup>29</sup>

disorder.<sup>50</sup> Because these conditions tend to co-occur with fibromyalgia, CBT may be a viable treatment option for patients living with fibromyalgia.

### Aerobic Exercise for Comorbid Depressive Disorders

Aerobic exercise treatment is beneficial to patients with fibromyalgia. In a review<sup>51</sup> and its follow-up,<sup>52</sup> studies of aerobic exercise revealed improvements in patients' well-being, physical functioning, and tenderness.

Aerobic exercise has also been recommended as treatment for depression. One study<sup>53</sup> found aerobic exercise at a public health recommended dose to be an effective treatment for mild to moderate major depression. The total energy expenditure needed to have an effect on depression was 17.5 kcal/kg per week, or approximately 30 minutes of moderately intensive physical activity 3 to 5 days per week.

## STEPWISE TREATMENT PLAN FOR FIBROMYALGIA AND COMORBID PSYCHIATRIC CONDITIONS

The high prevalence of comorbid mood and anxiety disorders in patients with fibromyalgia can present diagnostic dilemmas as well as require additional pharmacologic and

nonpharmacologic treatments. To optimize patient outcomes, a stepwise treatment plan for fibromyalgia and common comorbidities has been developed (Figure 1).<sup>29</sup> Once a diagnosis of fibromyalgia is confirmed and any comorbidities have been identified, a clinician may begin treatment with evidence-based medications. Next, the clinician should implement nonpharmacologic treatments such as CBT and exercise.

## CONCLUSION

Fibromyalgia accompanied by comorbid psychiatric disorders can be difficult to diagnose and manage. Clinicians must take a thorough patient and family history, paying particular notice to reports of mood and anxiety disorders. Psychiatric disorders comorbid with fibromyalgia are prevalent and negatively impact the course of fibromyalgia. Using medications to treat fibromyalgia and comorbid psychiatric disorders as well as incorporating appropriate nonpharmacologic therapies should help optimize patients' overall outcomes.

**Drug names:** duloxetine (Cymbalta), fluoxetine (Prozac and others), gabapentin (Neurontin and others), mirtazapine (Remeron and others), pregabalin (Lyrica), venlafaxine (Effexor and others), zolpidem (Ambien and others), zopiclone (Lunesta).

**Disclosure of off-label usage:** The author has determined that, to the best of her knowledge, duloxetine, fluoxetine, mirtazapine, venlafaxine, zolpidem, zopiclone, and milnacipran are not approved by the U.S. Food and Drug Administration for the treatment of fibromyalgia; gabapentin is not approved for the treatment of fibromyalgia, panic disorder, social phobia, insomnia, and bipolar disorder; pregabalin is not approved for the treatment of generalized anxiety disorder, bipolar disorder, and insomnia; and amitriptyline is not approved for the treatment of fibromyalgia and insomnia.

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