Antidepressant Treatment of Fibromyalgia

A Meta-Analysis and Review

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Fibromyalgia is a common musculoskeletal pain disorder associated with mood disorders. Antidepressants, particularly tricyclics, are commonly recommended treatments. Randomized, controlled trials of antidepressants for treatment of fibromyalgia were reviewed by methodology, results, and potential predictors of response. Twenty-one controlled trials, 16 involving tricyclic agents, were identified; 9 of these 16 studies were suitable for meta-analysis. Effect sizes were calculated for measurements of physician and patient overall assessment, pain, stiffness, tenderness, fatigue, and sleep quality. Compared with placebo, tricyclic agents were associated with effect sizes that were substantially larger than zero for all measurements. The largest improvement was associated with measures of sleep quality; the most modest improvement was found in measures of stiffness and tenderness. Further studies are needed utilizing randomized, double-blind, placebo-controlled, parallel designs with antidepressants administered at therapeutic dose ranges, using standardized criteria for fibromyalgia and systematically assessed for co-occurring psychiatric illness.

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Fibromyalgia is a common musculoskeletal pain disorder of unknown etiology, characterized by widespread pain and muscle tenderness and often accompanied by fatigue, sleep disturbance, and depressed mood.\(^1,2\) With an estimated lifetime prevalence of approximately 2% in community samples,\(^3\) fibromyalgia is at least twice as common as rheumatoid arthritis and constitutes a significant public health problem.\(^4\) Although a number of pharmacologic treatments have been studied in patients with fibromyalgia, the majority of studies have examined antidepressant agents.\(^4–6\) The rationale for treating this musculoskeletal disorder with antidepressant medications is based on a number of lines of evidence.

The initial impetus for examining tricyclic antidepressants as potential treatments for fibromyalgia\(^4,5\) was based on the identification of the alpha-delta NREM sleep abnormality in polysomnographic studies of patients with the disorder.\(^7\) This sleep abnormality consisted of an inappropriate intrusion of alpha waves (normally seen during wakefulness or REM sleep in sleep electroencephalograms [EEG]) into deep sleep (characterized by delta waves on sleep EEG).\(^7\) The alpha-delta NREM sleep abnormality was postulated to be associated with the chronic musculoskeletal pain and fatigue characteristic of the syndrome and, in turn, to be mediated by an abnormality in central serotonergic neurotransmission.\(^8\) This hypothesis was supported by the experimental induction of a diffuse pain condition similar to fibromyalgia following the administration of...
of $p$-chlorophenylalanine (PCPA), a centrally acting serotonin synthesis inhibitor. Thus, tertiary amine tricyclics, with higher ratios of serotonin/norepinephrine reuptake inhibition than secondary amine agents, became the initial candidate antidepressants for the treatment of fibromyalgia.

Further evidence for examining antidepressants in the treatment of fibromyalgia has come from studies of psychiatric phenomenology and personal and family history of psychiatric disorders in individuals with fibromyalgia. Phenomenologic studies in patients with fibromyalgia found elevated rates of depressive symptoms. Conversely, elevated rates of myalgia and musculoskeletal pain were reported in patients with major depression. Most, but not all, studies that examined lifetime prevalence rates of psychiatric disorders in patients with fibromyalgia found elevated rates of major depression. Furthermore, studies of family history of psychiatric illness in patients with fibromyalgia found elevated rates of major depression in their first-degree relatives.

Another rationale for studying antidepressants in the treatment of fibromyalgia is based on studies of tricyclics in chronic pain syndromes. In these studies, tricyclics were found to potentiate the effects of analgesics in a variety of conditions, including rheumatoid arthritis and neuropathic pain, and have also been reported to be the primary treatments for a variety of painful conditions. In most studies, analgesic response was not associated with the presence or absence of co-occurring depression or depressive symptoms.

Studies of fibromyalgia treatment have found that medications, including antidepressants and cyclobenzaprine, cardiovascular fitness training, and cognitive-behavioral and behavioral therapies may be helpful to patients with fibromyalgia. To our knowledge, however, there has been no published meta-analysis of antidepressant treatment of fibromyalgia.

We report a systematic review of all studies of antidepressant treatment of fibromyalgia and a meta-analysis of controlled trials of tricyclic agents. We address the efficacy of antidepressants in the treatment of fibromyalgia; whether specific subgroups of patients with fibromyalgia may be particularly responsive to treatment with these agents; and what issues remain to be addressed in further research.

**METHODS**

All randomized controlled trials of antidepressant treatment of fibromyalgia were identified by a Paperchase search that was augmented by reference cross-check. Twenty-one controlled trials, most involving tricyclics (16), were identified. Because tricyclic agents were the most common antidepressant medications studied, all 16 studies of tricyclics were reviewed for suitability for meta-analysis. Fourteen of the trials involving tricyclics compared improvement with tricyclic treatment to a placebo group (parallel group trials) or a placebo period (crossover trials). Those trials that did not have a placebo control could not be used to calculate standard effect size measures, which define treatment effects relative to a control. Five of the remaining studies did not report sufficient statistical data for effect size computations (i.e., means and standard deviations for continuous outcomes, proportions for binary outcomes). Our meta-analysis is based on the nine remaining studies. Although this total sample of studies is small, each study reported more than one effect size. Multiple effect estimates from the studies occurred in three ways: more than one treatment condition was compared on a single outcome measure; treatment conditions were compared on multiple outcome measures; and/or measurements were taken at multiple time points. We included seven outcome measures most commonly used in the studies. These measures included the patients’ self-ratings of pain, stiffness, fatigue, and sleep; the patient and the physician global assessment of improvement; and tenderness as measured by tender points. Where repeated measures were taken or multiple treatments were compared, a mean effect size was calculated.

Studies of the tricyclic agents that were not included in the meta-analysis and studies of other antidepressants were also reviewed, and the study designs and outcomes of these studies were summarized.

**RESULTS**

**Review of Studies of Tricyclic Agents Included in the Meta-Analysis**

The nine studies of tricyclic agents suitable for meta-analysis (Table 1) included two double-blind, placebo-controlled, parallel-group acute treatment trials that examined the efficacy of amitriptyline and dothiepin, respectively. In the first study, 70 patients with fibromyalgia diagnosed according to the criteria of Smythe were randomized to amitriptyline, titrated to 50 mg/day for the last 5 weeks of a 9-week trial, or placebo. In the second study, 60 patients who met the criteria of Campbell et
TABLE 1. The observed effect sizes for seven outcomes in nine controlled studies of tricyclic medications in the treatment of fibromyalgia

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Effective N*</th>
<th>Dosage, mg/day</th>
<th>Duration, weeks</th>
<th>Patient Global</th>
<th>Physician Global</th>
<th>Pain</th>
<th>Fatigue</th>
<th>Sleep</th>
<th>Tenderness</th>
<th>Stiffness</th>
<th>Study Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carette</td>
<td>AMI v PB</td>
<td>31</td>
<td>AMI 50</td>
<td>7</td>
<td>0.58</td>
<td>0.58</td>
<td>0.635</td>
<td>NA</td>
<td>0.70</td>
<td>0.27</td>
<td>0.30</td>
<td>Where repeated measures were taken or multiple treatments were compared, a mean effect size is reported. *Study completers. **Only the results of amitriptyline alone were included in the meta-analysis. NA not assessed; AMI = amitriptyline; PB = placebo; DTP = dothiepin; CBP = cyclobenzaprine; CMI = chlomipramine; MPL = maprotiline; FLX = fluoxetine.</td>
</tr>
<tr>
<td>Caruso</td>
<td>DTP v PB</td>
<td>33</td>
<td>DTP 75</td>
<td>8</td>
<td>0.76</td>
<td>1.32</td>
<td>0.45</td>
<td>NA</td>
<td>0.63</td>
<td>NA</td>
<td>0.25</td>
<td>In particular, cyclobenzaprine appears to affect both noradrenergic and serotonergic neurotransmission in the central nervous system.49-53 In the first study,40 120 patients meeting the criteria of Campbell et al.47 were randomized to cyclobenzaprine (10–40 mg/day) or placebo for 12 weeks. In the second study,41 40 female patients with fibromyalgia as determined by the investigators were randomized to cyclobenzaprine (10–40 mg/day) or placebo for 6 weeks.</td>
</tr>
<tr>
<td>Bennett</td>
<td>CBP v PB</td>
<td>40</td>
<td>CBP 10-40</td>
<td>12</td>
<td>NA</td>
<td>0.44</td>
<td>0.42</td>
<td>0.10</td>
<td>0.31</td>
<td>0.59</td>
<td>0.10</td>
<td>Another placebo-controlled parallel group trial included in the meta-analysis was a study of 208 patients meeting ACR criteria1 for fibromyalgia who were randomized to amitriptyline titrated to 50 mg/day, cyclobenzaprine titrated to 30 mg/day, or placebo for up to 26 weeks.37 Outcome was assessed according to criteria proposed by Simms et al.,43 which best distinguished patients treated with amitriptyline from placebo in a prior study.30 These criteria included physician global assessment score, patient-rated sleep score, and tender-point score.</td>
</tr>
<tr>
<td>Quimby</td>
<td>CBP v PB</td>
<td>41</td>
<td>CBP 10-40</td>
<td>6</td>
<td>0.98</td>
<td>0.98</td>
<td>0.75</td>
<td>0.31</td>
<td>1.19</td>
<td>0.77</td>
<td>0.34</td>
<td>The remaining placebo-controlled trials of tricyclic agents in the treatment of fibromyalgia that were included in the meta-analysis were conducted with crossover designs.32,38,39,42 One placebo-controlled, double-blind study assessed the efficacy of amitriptyline.38 In this study, 22 patients with ACR criteria fibromyalgia received amitriptyline (25 mg/day) or placebo for 8 weeks followed by immediate crossover for 8 more weeks. Another crossover study assessed the efficacy of cyclobenzaprine,42 in which nine patients with fibromyalgia by Campbell et al.47 criteria were randomized to treatment with cyclobenzaprine (20–40 mg/day) or placebo for 4 weeks followed by a 2-week washout and subsequent 4-week crossover. Bibolotti et al.32 conducted a randomized trial in which 37 patients received chlomipramine (75 mg/day), maprotiline (75 mg/ day), or placebo for 3-week intervals without intervening washout periods. Fibromyalgia was diagnosed according to criteria generated by the authors and patients were required to have a score of ≥7 on the Hamilton Depression Rating Scale (Ham-D) at baseline. The mean Ham-D at baseline was 23.5, suggesting that most patients were experiencing depressive symptoms of moderate-to-marked</td>
</tr>
<tr>
<td>Carette</td>
<td>AMI v CBP v PB</td>
<td>37</td>
<td>(AMI) 50</td>
<td>8</td>
<td>0.27</td>
<td>0.44</td>
<td>0.45</td>
<td>0.64</td>
<td>0.53</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reynolds</td>
<td>CBP v PB</td>
<td>42</td>
<td>CBP 20-40</td>
<td>4</td>
<td>NA</td>
<td>0.17</td>
<td>0.55</td>
<td>0.37</td>
<td>0.73</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bibliotti</td>
<td>CML v MLI v PB</td>
<td>32</td>
<td>CML 75</td>
<td>6</td>
<td>0.68</td>
<td>0.68</td>
<td>0.22</td>
<td>0.61</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Where repeated measures were taken or multiple treatments were compared, a mean effect size is reported. *Study completers. **Only the results of amitriptyline alone were included in the meta-analysis. NA not assessed; AMI = amitriptyline; PB = placebo; DTP = dothiepin; CBP = cyclobenzaprine; CMI = chlomipramine; MPL = maprotiline; FLX = fluoxetine; GBL = global.
severity. Because of high dropout and noncompliance rates, data were analyzed only for the initial randomization (Weeks 0–3). The final study to be included in the meta-analysis was another multicompartment, double-blind, crossover study,39 in which 19 patients with fibromyalgia by ACR criteria received four, 6-week trials of fluoxetine (20 mg/day), amitriptyline (25 mg/day), combination amitriptyline (25 mg/day) and fluoxetine (20 mg/day), or placebo. However, only the results of amitriptyline alone were included in the meta-analysis.

**Effect Sizes**

For all effects, Cohen’s measure of effect size was used.54 This measure is defined as the difference between the treatment and control group means, divided by the pooled within-group standard deviation. In the case of ordinal outcomes, counts in categories of moderate and marked improvement were collapsed into a single “improved” category, and the effect size was computed as if the variable were binary. The relevant means are actually differences from pretrial to the time of the outcome measurement. However, the standard deviation of these differences was usually not reported. Instead, the standard deviation at baseline was the only measure of variability available in most cases. Because the standard deviation of the difference score depends on the correlation of the pre- and posttreatment measures, which was rarely available in published reports, the standard deviation at baseline was used. The likely effect of this compromise is to deflate the true size of the effect (assuming a positive correlation between multiple measures on the same individual), and as a result, our estimates of effect may tend to be conservative.

Table 1 summarizes the observed effect sizes for seven outcomes in the nine trials that were suitable for meta-analysis. Figure 1 is a histogram of the observed effect sizes (including all multiple effect sizes from the same study). It appears that effect size is approximately normally distributed, with a mean treatment effect of almost one-half (0.44) of a standard deviation. Under the widely used guidelines of Cohen,54 an effect of this magnitude would be classified as “medium,” and would be recognized clinically. The histogram also suggests that the treatment effect is approximately normally distributed. This distribution is very nearly symmetrical, as supported by the similarity of the median, unweighted mean, and weighted (by number of study completers) mean.

The observed effects are shown by type of outcome as a box plot in Figure 2. The dark line in each box marks the median, the width of the box corresponds to the interquartile range, and the “whiskers” mark the 5th and 95th percentiles. Observations lying beyond the 5th and 95th percentiles are indicated by diamond-shaped markers. These descriptive displays suggest moderate improvement in patient and physician global assessment, pain, and sleep, and more modest improvement in fatigue, tenderness, and stiffness.

To determine the precision of the effect estimates while accounting for the dependence of effect sizes from the same study, we used the mixed model framework developed by Kalaian and Raudenbush.55 Each effect size was weighted by the number of study completers. This model incorporates the hierarchical structure of the data (multiple effect size estimates nested with each study) by treating each study as a random effect. The mixed model approach is also suitable for unbalanced data (different number of effect sizes per study) and takes advantage of the correlation between outcome measures. The latter approach results in confidence intervals that are shorter (i.e., more precise) than if each outcome were treated in a separate analysis. We estimated the effect size for each type of outcome separately to determine what type of improvement contributed to the overall effect. The parameter estimates for this model are shown in Table 2.

It is typical in meta-analysis to test for homogeneity of effect sizes before proceeding to search for possible effect moderators. Unfortunately, the usual tests for this purpose are not valid for correlated effect sizes. In any case, heterogeneity of effect sizes may be due to either real variability in population effects, differences in methodological quality, or both. The interpretation of a significant heterogeneity test, therefore, is open to question even for independent effect size estimates.56 More complicated models were unable to detect significant variation due to type of tricyclic, treatment duration, or dose. The latter was expressed as a percentage of a usual therapeutic antidepressant doses to equate dosage across treatments. Given the low power to detect these effects, these findings should not be taken as evidence that these effects do not exist.

**Summary of Other Controlled Tricyclic Studies**

Studies of tricyclic agents that could not be included in the analysis included a placebo-controlled, parallel-group, acute treatment trial,30 in which 62 patients meeting the criteria of Yunus et al.57 were randomized to combinations of amitriptyline (25 mg/day) and naproxen (500 mg bid), amitriptyline (25 mg/day) and placebo, placebo...
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FIGURE 1. Histogram of 102 observed effect sizes from nine controlled studies of tricyclic medication treatment of fibromyalgia

- Median Effect Size = 0.44
- Unweighted Mean Effect Size = 0.46
- Weighted Mean Effect Size = 0.43

FIGURE 2. Box plot of effect size by type of outcome measure in nine controlled studies of tricyclic medication treatment of fibromyalgia
and naproxen (500 mg bid), and placebo with placebo for 6 weeks. Patients in both amitriptyline arms displayed significantly greater improvement in pain, sleep, fatigue, tender-point score, and patient and physician global assessment. The combination of amitriptyline and naproxen was not significantly better than amitriptyline plus placebo; however, the sample size limited the ability of this study to detect such a difference if one existed.

Four other studies were conducted with crossover designs. The first study of this design compared amitriptyline (10 mg/day Week 1, 25 mg/day Week 2), temazepam (15 mg/day Week 1, 30 mg/day Week 2), and placebo in a double-blind trial consisting of three consecutive 2-week treatment intervals separated by 2-week washout periods. Ten patients who met criteria for fibromyalgia derived by the investigators and who had the NREM alpha-delta sleep anomaly on screening polysomnography were randomized. Amitriptyline produced significant improvement in severity and number of tender points, but the results of this study were limited by the small sample size and brief duration of treatment. In another study, 34 36 patients with fibromyalgia according to the criteria of Smythe and Moldofsky58 received amitriptyline or placebo for 4 weeks followed by a 2-week washout and subsequent crossover. Amitriptyline was titrated at 10 mg/day for Week 1, 25 mg/day for Week 2, and 50 mg/day for Weeks 3 and 4. Treatment with amitriptyline was associated with significant improvement in pain, tender-point sensitivity, and patient global assessment compared with placebo. In the third study, Simms et al.43 analyzed their data from an unpublished double-blind, placebo-controlled trial of 24 patients who met Yunus et al.57 criteria for fibromyalgia randomized to cyclobenzaprine (10–20 mg/day) or placebo, each for 4 weeks separated by a 2-week washout. According to response criteria developed by the authors as part of this study, 30% of cyclobenzaprine-treated patients responded. The response rate to placebo treatment was not presented. Finally, Jaeschke et al.36 reported on the results of 23 double-blind, randomized multiple crossover (N-of-1) trials using amitriptyline (5–50 mg/day) or placebo for intervals ranging from 3 to 12 weeks in patients with fibromyalgia diagnosed clinically. The authors estimated that, overall, 25% of patients responded significantly to amitriptyline.

Of the two controlled trials that did not use a placebo group, the first64 compared the combination of fluoxetine (20 mg/day) and cyclobenzaprine (10 mg/day) with cyclobenzaprine alone in a parallel group 12-week trial involving 21 women with fibromyalgia by ACR criteria. In the second study,45 two doses (10 mg/day and 30 mg/day, respectively) of cyclobenzaprine were compared in a crossover study lasting 15 days separated by a 15-day washout involving 40 patients with fibromyalgia by Yunus et al.57 criteria. Although patients in treatment groups in both studies displayed significant reductions in most outcome measures from baseline to endpoint, the contribution of placebo response could not be assessed in either trial.

### Controlled Studies of Selective Serotonin Reuptake Inhibitors

Two randomized controlled trials have examined the selective serotonin reuptake inhibitor (SSRI) antidepressants, fluoxetine and citalopram, respectively, in the treatment of patients with fibromyalgia. In the first study, 59 42 women with fibromyalgia by ACR criteria were randomized to fluoxetine (20 mg/day) or placebo for a 6-week acute treatment trial. At the end of 6 weeks, there were no significant differences between the two groups. The results of this study were limited by a very high (57%) placebo dropout rate, insufficient sample size, brief trial duration, and restriction of fluoxetine dose to 20 mg/day.

In the second study, 60 43 patients with fibromyalgia by ACR criteria were randomized to citalopram (20 mg/day) or placebo for 4 weeks. Patients who did not display a marked improvement by 4 weeks (17/19 on citalopram, all placebo-treated patients) received citalopram (40 mg/day) or placebo for the last 4 weeks of the trial. At the end of 8 weeks, there were no significant differences in efficacy measures between the two groups. However, citalopram (40 mg/day) appears to be a more optimal antidepressant dose61 and a 4-week trial at this dose is of insufficient duration to detect possible therapeutic effect. Moreover, although both studies used psychometric rating scales to measure the severity of depressive symptoms at entry into

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**TABLE 2. Model-estimated mean effect sizes for each outcome measure in nine controlled studies of tricyclic medication treatment of fibromyalgia**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Effect Size Estimate</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient global</td>
<td>0.506</td>
<td>0.097</td>
</tr>
<tr>
<td>Physician global</td>
<td>0.636</td>
<td>0.091</td>
</tr>
<tr>
<td>Pain</td>
<td>0.565</td>
<td>0.084</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.521</td>
<td>0.092</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.690</td>
<td>0.088</td>
</tr>
<tr>
<td>Tenderness</td>
<td>0.358</td>
<td>0.084</td>
</tr>
<tr>
<td>Stiffness</td>
<td>0.301</td>
<td>0.109</td>
</tr>
<tr>
<td>Study variance</td>
<td>0.026</td>
<td>0.019</td>
</tr>
<tr>
<td>Residual variance</td>
<td>3.388</td>
<td>0.511</td>
</tr>
</tbody>
</table>
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the trial, neither study determined whether patients met criteria for a current or past history of major depression.

Other Antidepressant Trials

Three other controlled trials have examined medications with putative antidepressant properties in the treatment of patients with fibromyalgia. Alprazolam, a triazolobenzodiazepine with antidepressant effects conferred by its triazolo moiety (0.5–3.0 mg/day), was compared with ibuprofen (600 mg qid), the combination, or placebo in 78 patients with fibromyalgia by the criteria of Russell et al. in an 8-week trial. At the conclusion of the study, there were no significant differences in improvement between the four treatment groups.

Two controlled trials assessed the efficacy of S-adenosylmethionine (SAMe), a medication with putative antidepressant activity. In the first study, 17 patients with fibromyalgia by investigator-derived criteria received SAMe (200 mg/day im) or placebo for 21 days in a crossover design, separated by a 2-week washout. Baseline Ham-D scores correlated with the number of trigger points and painful anatomic sites. Treatment with SAMe was associated with significant reductions in the number of trigger points, painful anatomic sites, and Ham-D scores compared with placebo. In the second study, 44 patients with fibromyalgia by criteria of Yunus et al. were randomized to SAMe (800 mg/day) or placebo for 6 weeks in a double-blind, parallel-design trial. Treatment with SAMe was associated with significant improvement in pain, fatigue, morning stiffness, and global improvement compared with placebo. There was no significant difference between SAMe and placebo in reduction of tender-point number.

Predictors of Antidepressant Treatment Response

A number of studies have attempted to identify clinical features that might be associated with antidepressant response. These attempts have focused mainly on polysomnographically identified sleep abnormalities, in particular the NREM alpha-delta anomaly, and severity of depressive symptoms as measured by various psychometric rating scales at baseline. Neither study that assessed for the presence of the NREM alpha-delta sleep anomaly found it to be predictive of antidepressant treatment response. Similarly, although nine studies used changes in validated rating scales for depressive symptoms (e.g., Beck Depression Inventory, Ham-D) as potential predictors of fibromyalgia antidepressant response, in none of these studies was such an association evident. However, psychometric rating scales do not allow for the diagnosis of a past or current episode of depression. Furthermore, some symptoms of depression and fibromyalgia overlap (e.g., sleep disturbance, fatigue), and changes in depression rating scores may be confounded by improvement in these nonspecific symptoms. The potential relevance of a current or past history of major depressive disorder as a predictor of antidepressant response is supported by the results of a recent study that did, indeed, find an association between such a history and response to venlafaxine.

DISCUSSION

The meta-analysis of nine placebo-controlled trials of tricyclic agents, including tertiary amine tricyclic antidepressants and cyclobenzaprine, in the treatment of fibromyalgia showed that the overall effect of these agents was moderate. The largest effect was found in measures of sleep quality, whereas the most modest changes were noted in measures of tenderness and stiffness. Thus, the most consistently observed improvement in these studies may have been attributed, in part, to the sedative properties of these agents. The seven other studies of tricyclics that could not be included in the meta-analysis because they lacked a placebo control group or sufficient statistical data for effect size computations had results that were consistent with the findings of the meta-analysis. Significant clinical response to tricyclic agents was observed in 25%–37% of patients with fibromyalgia and the overall degree of efficacy was modest in most studies.

There were important limitations to the tricyclic studies. First, no studies examined higher or standard therapeutic doses of tricyclics effective in the treatment of depression. Similarly, no studies obtained plasma concentrations of tricyclics that would be useful in determining compliance and whether the low doses used were producing plasma concentrations within the therapeutic range for depression, at least in some patients. The need for monitoring of tricyclic plasma concentrations is especially relevant to the studies that reported greater efficacy for combined amitriptyline and fluoxetine and combined cyclobenzaprine and fluoxetine. The findings of greater efficacy with combined treatment was limited by the probable pharmacokinetic interaction between fluoxetine and tricyclics, an interaction that typically elevates tricyclic plasma levels substantially. Considering the possible as-
sociation between mood disorder and fibromyalgia, it may be that standard antidepressant doses of tricyclics with documented therapeutic plasma concentrations are needed to obtain more than moderate improvement. Furthermore, secondary amine tricyclics (e.g., desipramine, nortriptyline), which have fewer side effects than tertiary amines, have not been examined in controlled trials in patients with fibromyalgia, but would likely be better tolerated.

Second, six studies were <4 weeks in duration. Studies lasting at least 6 weeks are required to detect significant improvement if these agents are ameliorating fibromyalgia in any way related to their antidepressant mechanism. Virtually no data are available regarding the intermediate and long-term efficacy of tricyclics in the treatment of fibromyalgia. In the only study extending to 26 weeks, neither amitriptyline nor cyclobenzaprine exerted significantly greater efficacy than placebo.

Third, despite evidence of elevated prevalence rates of depression in patients with fibromyalgia and the possible prognostic significance of past or current depression, no controlled study systemically evaluated patients for a diagnosis of a mood disorder. Only five studies administered standardized psychometric instruments to measure depressive symptoms, but these are not adequate to establish diagnoses.

Last, interpretation of the results of at least four studies was limited by small sample sizes and over half of all studies employed a crossover design. The frequent and noticeable side effects associated with tertiary amine tricyclics may have affected the blindedness of these trials upon switch to or from placebo. In addition, two studies omitted washout intervals that may have produced discontinuation syndromes after abrupt cessation of tricyclics, contributing to insomnia and myalgias during placebo treatment and reducing placebo response rates.

From the available studies, the overall response of patients with fibromyalgia to treatment with nontricyclic antidepressants has not been compelling. However, the two trials that examined SSRIs were limited by relatively small sample sizes and use of only low doses or brief duration of treatment at higher doses. Although the efficacy of alprazolam was not significantly greater than placebo, the antidepressant activity of this agent may not be robust in general. Finally, although studies of SAMe were promising, this agent is not licensed for clinical use in the United States, and its efficacy as an antidepressant has not been definitively established.

Clinical Recommendations

Although the data are limited, preliminary recommendations about the pharmacological treatment of fibromyalgia can be made. There is some evidence that patients with a history of mood and anxiety disorders may be more responsive to antidepressant treatment of fibromyalgia. Thus, a trial of any antidepressant using therapeutic doses and adequate duration of treatment should be considered for these patients. The tricyclic agents have been most well studied in patients with fibromyalgia. Although the studies have focused mostly on the tertiary amine tricyclics, secondary amine agents may be just as effective and better tolerated, allowing for titration to higher doses. Doses at the therapeutic level for the treatment of depression should be attempted if the patient does not respond to, but otherwise tolerates, lower doses.

Further Research Issues

Because there is promising, though modest, overall efficacy of most antidepressants in the treatment of fibromyalgia but significant methodologic limitations in many of the available studies, a number of design issues are worth considering for future studies. First, double-blind, placebo-controlled, parallel-group studies of sufficient sample size and adequate duration are needed. Candidate agents include tricyclic agents (including secondary amines) administered at therapeutic antidepressant doses and confirmed by measurement of serum concentrations, dose ranging studies of newer (e.g., SSRIs, venlafaxine, bupropion, nefazodone, and mirtazapine) as well as older (e.g., trazodone) antidepressants that have different pharmacologic mechanisms. Ideally, study populations meeting standardized (e.g., ACR) criteria for fibromyalgia and assessed for history of mood disorder using standardized structured interviews (e.g., SCID-IV) should be recruited for study. The use of standardized, operationally defined outcome measures of improvement would enhance the comparative value of treatment trials in fibromyalgia. Actual impact on level of functioning and quality of life should also be included in outcome measures. Finally, studies designed to extend beyond acute treatment are needed to establish the efficacy of antidepressants as maintenance treatment for this chronic musculoskeletal disorder.
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References

17. Stoeckle JD, Davidson GE: Bodily complaints and other symptoms of depressive reaction. JAMA 1962; 180:134–139


