A RANDOMIZED, CONTROLLED TRIAL OF AMITRIPTYLINE AND NAPROXEN IN THE TREATMENT OF PATIENTS WITH FIBROMYALGIA

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Sixty-two patients with fibromyalgia were randomly assigned to receive 25 mg of amitriptyline at night, 500 mg of naproxen twice daily, both amitriptyline and naproxen, or placebo in a 6-week, double-blind trial. Amitriptyline was associated with significant improvement in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Patients taking the combined naproxen–amitriptyline regimen experienced minor, but not significant, improvement in pain when compared with patients who took amitriptyline alone. Amitriptyline, or amitriptyline and naproxen, is an effective therapeutic regimen for patients with fibromyalgia.

Fibromyalgia, also termed fibrositis, is a controversial, chronic, painful musculoskeletal syndrome. Although this condition was described in the 1800s, and the term fibrositis was first used in 1904 (1–4), until recently, there have been no controlled studies of the clinical manifestations or treatment of this disorder (5). During the past 5 years, a number of reports, including reports of some controlled studies from rheumatic disease units, have noted that there are consistent clinical manifestations in patients with fibromyalgia (6–14). These reports have proposed that specific diagnostic criteria be utilized in clinical studies of this condition. Furthermore, they have concluded that fibromyalgia is a common, chronic, painful syndrome with uniform signs and symptoms (6–14).

Although the etiology of fibromyalgia is not known, many investigators believe that sleep disturbances may contribute to the chronic pain, fatigue, and stiffness that are characteristic of this disorder (5,15–17). Anecdotal reports and reports of uncontrolled studies have described the efficacy of antiinflammatory or sleep medications in fibromyalgia patients (5,6,18). We report the findings of an initial placebo-controlled study of an antiinflammatory agent, naproxen, and a low-dose, tricyclic medication, amitriptyline, in 62 patients with fibromyalgia.

PATIENTS AND METHODS

Patients who agreed to participate in this study met the proposed clinical criteria for fibromyalgia, modified from those reported by Yunus et al (6): generalized aches and pain or prominent stiffness involving 3 or more anatomic sites for at least 3 months; absence of underlying causes, e.g., direct or repetitive trauma or systemic disease; at least 6 typical and consistent moderately or severely tender points; and at least 3 of the following: modulation of symptoms by physical activity, weather, anxiety, or stress, poor sleep, general fatigue or tiredness, anxiety, chronic headache, irritable bowel syndrome, or subjective swelling and numbness (Table 1).

Patients were excluded from participating in the study if they had a history of peptic ulcer disease or cardiac arrhythmias, or if they were taking medications that could

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Table 1. Entry and exclusion criteria for the fibromyalgia treatment study

Generalized aches, pain, and stiffness involving 3 or more anatomic sites for at least 3 months
Absence of underlying causes (e.g., generalized illness)
At least 6 characteristic and consistent tender points
At least 3 of the following:
Modulation of symptoms by activity, weather, anxiety, or stress
Poor sleep
General fatigue
Anxiety
Chronic headaches
Subjective swelling and numbness
Irritable bowel syndrome
A score ≥4 on either the initial pain or global assessment analog scale
Reasons for exclusion
History of peptic ulcer disease
Cardiac arrhythmia
Inability to be withdrawn from analgesic, antiinflammatory, or central nervous system–active medications

not be stopped (Table 1). Only 2 patients who were asked to participate in the trial were excluded from the study because they refused to discontinue their current medications, which were amitriptyline and piroxicam. In order to be entered into the study, patients had to score 4 or higher on a possible scale of 10 on 1 of 2 self-administered, 10-cm visual analog scales evaluating fibromyalgia symptoms or pain (see below). All patients discontinued analgesics, antiinflammatory medications, antidepressants, sleeping medications, and any other central nervous system–active medications for 72 hours prior to their initial visit. During the study, the patients were allowed to take 2 acetaminophen tablets (650 mg) every 4 hours, if needed for severe pain, but otherwise could take only the study medication. Approximately 10% of the patients stated that they took acetaminophen during the trial. These patients were equally distributed among the treatment groups. The study was approved by the Boston University Institutional Review Board and all patients gave written, informed consent before entry.

Sixty-two patients met the entry criteria. After admission to the study, each patient was randomly assigned to 1 of 4 treatment groups using a method that assured balanced assignment (19): group 1 (A + N) received 500 mg of naproxen twice a day and 25 mg of amitriptyline every night; group 2 (N) received 500 mg of naproxen twice a day and placebo; group 3 (A) received 25 mg of amitriptyline every night and placebo; group 4 (PL) received double doses of placebo.

Patients, as well as the examining physician, were "blinded" as to specific treatment. Patient dropouts were defined as those patients who failed to return for a second visit. All other patients were included in the analysis, even though 2 patients in group 1 did not complete the study, since they were not available for examination at the last visit. There were 4 dropouts, 1 in each treatment group. Two dropouts simply did not return (groups 2 and 3). The group 1 dropout stopped taking medication because of excessive daytime somnolence and headache; the group 4 dropout discontinued the medicine because of epigastric distress.

So the outcome of therapy could be evaluated, the patients completed a self-administered survey. This survey contained a 10-cm visual analog scale that evaluated global fibromyalgia symptoms (0 = not troublesome at all; 10 = extremely troublesome), pain or stiffness (0 = none; 10 = very severe), and fatigue (0 = no fatigue; 10 = extreme fatigue). In addition, we asked 2 questions about sleep: (a) Do you have difficulty sleeping? (0 = no difficulty; 10 = extreme sleep difficulty) and (b) How do you feel when you first wake up? (0 = fine and refreshed; 10 = exhausted). Such outcome measures have been previously validated and have been used in prior clinical trials of patients with fibromyalgia (20). Furthermore, the results of these self-administered visual analog scales correlated highly with those of an interview-administered survey, in which the symptoms were graded ordinally (21). The physician evaluation included a 10-cm visual analog global evaluation and a tender point examination with computation of tender point scores.

The tender point examination was performed by 1 individual who exerted a uniform amount of manual finger pressure on each of 10 bilateral anatomic sites: the midpoint of the trapezius muscle, the middle of the sternocleidomastoid muscle, the second costochondral junction, the lateral epicondyle, the medial epicondyle, the upper-outer quadrant of the buttock, the fat pad of the knee overlying the medial collateral ligament, L4–L5 and L5–S1 interspinous ligaments, the supraspinatus muscle origin above the scapular spine, and the mid-rhomboid muscle (5). The right and left anatomic sites were considered as one, since both were generally equally tender. The sites were graded as: not tender or mildly tender = 0; moderately tender = 1; severely tender = 2. A tender point score was computed by the addition of these graded points.

Patients were evaluated at the initial pretreatment examination and then at 2, 4, and 6 weeks. The patients were asked to return the medication bottles at each visit, and 49 of the 58 patients who completed the trial returned empty bottles at each visit. Remaining pills were counted at each visit, or the patient was asked whether he or she had finished the allocated medications. All patients stated that they missed fewer than 4 of the 28 pills during each 2-week session.

Table 2. Clinical characteristics of 62 patients in the fibromyalgia treatment study

Mean age (range)	43.8 (21–69)
Mean years of chronic pain (range)	3.5 (0.25–20)
No. of females	59 (95%)
Race	
White	54 (87.1%)
Hispanic	7 (11.3%)
Black	1 (1.6%)
Fatigue	59 (95%)
Morning stiffness	59 (95%)
Numbness	45 (73%)
Swelling (subjective)	45 (73%)
Sleep disturbance	45 (73%)
Irritable bowel syndrome	37 (60%)
Headaches	37 (60%)

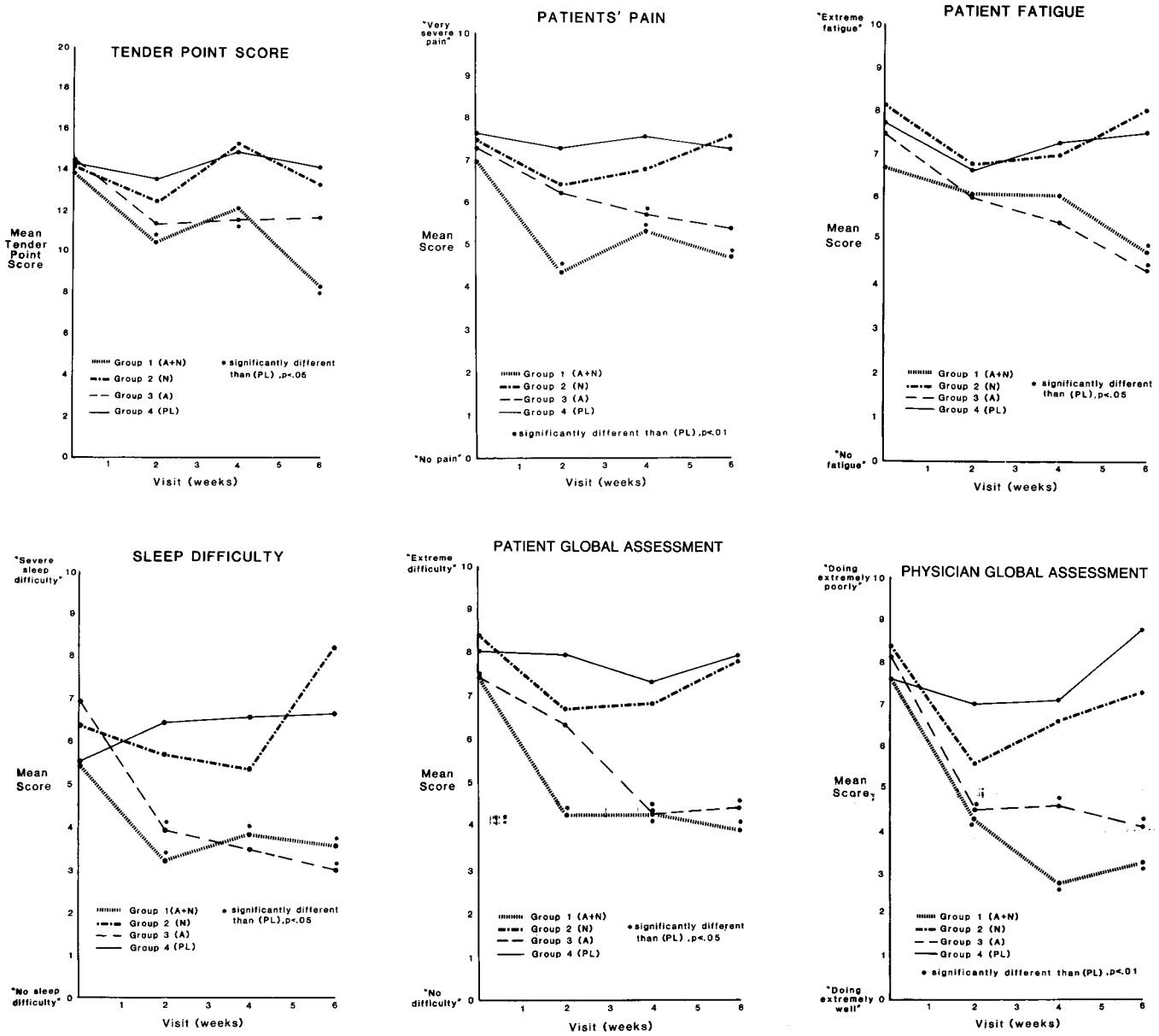

Figure 1. Responses of fibromyalgia patients over time to various therapeutic regimens, by group. A = amitriptyline; N = naproxen; PL = placebo.

Our original estimates of drug effectiveness indicated an effect difference of 1 between treatment and control groups on a 1–10 visual analog scale. We also estimated a standard deviation of the change score of 1 for controls. These estimates yielded an N of 32. A power analysis done before the trial indicated that a study size of 32 ($\alpha = 0.05$, $\beta = 0.20$) would be needed to demonstrate a drug's efficacy (50% of patients receiving each drug), but this number would not be sufficient to demonstrate the effectiveness of one regimen versus another. Calculations also indicated that a study size of 78 ($\alpha = 0.05$, $\beta = 0.20$) would permit us to evaluate interregimen efficacy.

Because of the complex design of the trial, which included 2 drugs, 4 treatment groups, and repeated determinations of response, we used a type of repeated measures analysis of variance called profile analysis (22). Profile analysis determined whether the response curves for drug treatments were parallel over time, with time 0 controlled for as a covariate. This consisted of a multivariate two-way analysis of variance, the 2 class variables being amitriptyline and naproxen. To compare the individual therapeutic regimens at each point in the trial, levels of response for each regimen were compared at visits 2, 3, and 4, using a one-way analysis of variance. If the analysis of variance showed a

significant effect, individual regimens were compared using *t*-tests adjusted by Duncan's multiple range test for multiple comparisons (22). A 2-tailed value of 0.05 was considered significant.

RESULTS

The clinical characteristics of the 62 patients were similar to those in other recent reports of patients with fibromyalgia (Table 2). None of the patients had an elevated erythrocyte sedimentation rate or evidence of a systemic illness or connective tissue disorder. Each patient had more than 6 tender points on examination and had no evidence of arthritis or myositis.

There were no significant differences with respect to race, duration of fibromyalgia symptoms, prevalence of sleep disturbances, or morning tiredness among the 4 randomly assigned treatment groups. There was also no difference in the number of patients in each group who had been receiving amitriptyline or another central nervous system–active medication before the trial. The average tender point score for the 4 groups on entry was 14.2 (13.8 in group 1, 14.1 in group 2, 14.5 in group 3, and 14.2 in group 4). Neither the tender point score nor any other outcome measure differed significantly between groups at study onset.

Eight patients complained of adverse side effects, but did not discontinue the study medication. These complaints included dry mouth in 4 patients (all in groups 1 and 3), dyspepsia in 2 patients (1 each in groups 2 and 4), and diarrhea in 2 patients (1 each in groups 2 and 4).

The profile analysis tested the efficacy of each drug, not each regimen; thus, the analysis evaluated whether patients receiving amitriptyline (group 1 and group 3) did significantly better than those groups not receiving amitriptyline (group 2 and group 4) throughout the trial. Amitriptyline was found to be a highly significant cause of patient improvement for all outcome variables, including patient and physician global assessments, pain, sleep difficulty, fatigue, morning tiredness, and tender point score (for each outcome variable, $P < 0.001$, with F values ranging from 4.8 for patient pain to 12.17 for physician global assessment). Similar testing of the efficacy of naproxen (50% of patients in the trial) showed no significant effect on any outcome parameter. As part of the analysis, naproxen–amitriptyline synergy was evaluated to determine whether the 2 drugs were significantly more effective than either alone. No significant synergy was found.

Table 3. Change in outcome measures (mean values) for patients treated with amitriptyline and naproxen (A + N) or with amitriptyline alone

	Visit 1 (Pre-trial)	Visit 4 (End of trial)
Tender point score		
A + N	13.8	8.2*
A	14.5	11.6†
Pain		
A + N	6.9	4.7†
A	7.3	5.4†
Fatigue		
A + N	6.7	4.7†
A	7.5	4.3†
Sleep		
A + N	5.5	3.6
A	6.9	3.0*
Patient global assessment		
A + N	7.5	3.9*
A	7.5	4.5*

* Significantly different from initial scores by paired *t*-test, $P < 0.01$.
† Significantly different from initial scores by paired *t*-test, $P < 0.05$.

Patients who received amitriptyline-containing regimens had greater improvement (Figure 1). For example, the mean tender point score for group 1 patients decreased from 13.7 to 8.5 during the 6 weeks, and for group 3 patients it decreased from 14.5 to 11.6. The group 1 tender point score was significantly different from that of group 4 at visits 2 and 4, and the score for group 3 was significantly different from that of group 4 at visits 2 and 3. Similar results were noted for each outcome variable.

We also evaluated whether amitriptyline-containing regimens caused significant improvement over time (Table 3). In all outcomes, patients taking amitriptyline (groups 1 and 3) improved significantly from the initial visit to the end of the trial. In contrast, there was no significant improvement in any of the outcome variables in patients taking naproxen alone or those taking placebo. We also investigated whether treatment response depended on preexisting sleep problems. We found no significant association of initial sleep difficulty or tiredness on awakening with the patient's response to amitriptyline.

DISCUSSION

During the past 10 years, fibromyalgia has received renewed interest as a specific and common

clinical musculoskeletal syndrome (4–14,23–25). The etiology of this disorder is unknown, but possible associations with chronic pain conditions (4–6), sleep disturbances (15–17), and psychiatric diagnoses (8–12) have been reported. It has been postulated that treatment with antiinflammatory agents might be beneficial in this condition. Although no controlled study has reported the effects of salicylates or other nonsteroidal antiinflammatory drugs (NSAIDs) in fibromyalgia, Clark et al, in a placebo-controlled, double-blind trial, found that prednisone was not effective in this condition (26).

In recent reviews (5,6,8), sleep disorders have been described in 60–90% of patients with fibromyalgia. Seventy-five percent of our patients reported a sleep disturbance. Moldofsky et al described an alpha wave intrusion of delta sleep in patients with fibromyalgia (17). They experimentally produced stage 4 sleep deprivation in normal subjects, and reported the appearance of musculoskeletal and mood symptoms identical to those of fibromyalgia (16). They postulated that fibromyalgia symptoms are related to a disorder of nonrestorative sleep and speculated that a disorder of serotonin metabolism may be present. Moldofsky and Lue (15) then randomized 15 patients to receive 5 gm of L-tryptophan or 100 mg of chlorpromazine in a 3-week, double-blind study, with sleep electroencephalograms (EEGs) performed before and after medication (15). The L-tryptophan had no effect on delta sleep or the patient's symptoms, but chlorpromazine caused an increase in delta sleep and an improvement in patient pain rating and tender point scores, as measured by dolorimeter.

A recent report by Campbell et al described therapeutic efficacy of cyclobenzaprine in patients with fibromyalgia (20). One hundred twenty patients with fibromyalgia randomly received 10–40 mg of cyclobenzaprine or placebo in a 12-week, double-blind study. There was significant improvement in local pain, sleep, and number of tender points in the patients treated with cyclobenzaprine, compared with those treated with placebo. Cyclobenzaprine, a tricyclic compound, is structurally similar to amitriptyline and may have similar central nervous system effects.

Although there are reports that amitriptyline and other tricyclic medications may be effective in the treatment of fibromyalgia (5,6,18), only 1 other controlled study has previously evaluated this class of compounds in patients with fibromyalgia (27). We chose a low dose of amitriptyline, in an attempt to separate any possible antidepressant activity from its sleep effect, since 25 mg of amitriptyline daily generally does not achieve therapeutic antidepressant activity. Furthermore, the blood amitriptyline level in 6 patients selected randomly (3 each from groups 1 and 3) was 0 or subtherapeutic. Naproxen was used in a dose that has been commonly employed in the treatment of inflammatory conditions such as rheumatoid arthritis.

This 6-week, double-blind trial demonstrated that amitriptyline and naproxen, or amitriptyline alone, is significantly better than placebo in each patient and physician outcome variable evaluated. The nature of the individual patient response was uniform across all outcome variables. In contrast, although there was some initial improvement in pain in the naproxen only (group 2) patients at 2 weeks, naproxen was not associated with significant differences in any parameters compared with placebo (group 4) at any time in the trial. Carette et al recently reported that 50 mg of amitriptyline at bedtime improved the fatigue, pain, and global assessment of patients with fibromyalgia, but did not improve the tender point score (27). However, a study of 20 patients with fibromyalgia reported that only 2 responded favorably to 50–75 mg/day of imipramine (28).

Although our study demonstrates the efficacy of amitriptyline in fibromyalgia, it leaves a number of questions unanswered. First, while naproxen was not effective as a single agent, it is not clear whether it (or other NSAIDs) may enhance the effectiveness of amitriptyline. Our study was not large enough to find statistical differences between the combined therapy group (A + N) and the group receiving amitriptyline alone. Although these differences seem minor, a large study might yield more definitive results. Second, our study was not large enough to reliably characterize amitriptyline responders from nonresponders. Third, although amitriptyline is effective for 6 weeks of therapy, this does not necessarily mean it continues to be effective for a longer period, and future studies should address this issue. We have found that fibromyalgia symptoms persist to some degree in the majority of patients, regardless of treatment (21). For example, 82% of patients needed daily medication to control fibromyalgia symptoms 2 years or more after diagnosis, and many of those receiving amitriptyline continued to be symptomatic (21).

Furthermore, the mode of action of amitriptyline in fibromyalgia is not clear. Its efficacy may be related to its effect on the sleep disturbances associated with fibromyalgia. However, our results

suggest that the reason for amitriptyline's efficacy does not lie solely in its effect on sleep. It is certainly possible, however, that patients may have had unrecognized qualitative sleep abnormalities, and that amitriptyline ameliorated these. Sleep EEGs done before and after therapy, and then correlated with the patient's clinical response, will be necessary in order to demonstrate that amitriptyline improves sleep disturbance in patients with fibromyalgia. Amitriptyline and other tricyclic antidepressants have also been effective in the therapy of other chronic painful conditions such as diabetic neuropathy (29) and postherpetic neuralgia (30). It is postulated that the central analgesic effect of these medications may be related to blocking the removal of serotonin from synaptic clefts, or related to the effect of the tricyclics on endogenous opioids, such as endorphins or enkephalins (31,32).

Chronic pain, depression, and sleep disturbances often occur simultaneously (31). Chronic pain may cause a reactive depression; furthermore, depression and chronic pain may share some common psychobiologic characteristics. Our previous studies of patients with fibromyalgia revealed information consistent with this latter hypothesis (33). Fibromyalgia may represent a chronic, painful musculoskeletal response to a variety of conditions. Once subsets of this syndrome are recognized, treatment may be better tailored to the individual patient. However, until that time, therapy must be empiric. Our trial demonstrated that amitriptyline alone, or amitriptyline and naproxen given over a 6-week period, is an effective treatment for patients with fibromyalgia, and should be considered in patients with symptoms of this common condition.

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A&R to Begin Using SI Units

Metric units should be used throughout all articles submitted to *Arthritis and Rheumatism.* In keeping with a policy adopted by the American Medical Association in December 1984, each metric unit should be followed by its Système International (SI) unit equivalent given in parentheses. This will facilitate a gradual conversion to the sole use of SI units. An explanation of SI units, including a detailed conversion table, is given in the May 2, 1986 issue of the *Journal of the American Medical Association* (Lundberg GD, Iverson C, Radulescu G: Now read this: the SI units are here [editorial]. JAMA 255:2329–2339, 1986). Contributors to *A&R* are strongly encouraged to consult that article.