EVALUATION OF AMITRIPTYLINE IN PRIMARY FIBROSITIS

A Double-Blind, Placebo-Controlled Study

SIMON CARETTE, GLENN A. McCAIN, DAVID A. BELL, and ADEL G. FAM

Seventy patients with primary fibrositis satisfying Smythe's criteria were studied in a 9-week double-blind trial comparing 50 mg amitriptyline with placebo. Fifty-nine patients completed the trial: 27 were treated with amitriptyline, and 32 took a placebo. The patients who received amitriptyline improved significantly in their morning stiffness and pain analog scores at 5 and 9 weeks, compared with baseline scores, whereas no changes were noted in these parameters in the placebo group. Fibrositic point tenderness did not improve significantly in either of the treatment groups. When compared with the placebo group, the amitriptyline group improved significantly with respect to sleep pattern and patient and physician global assessments. Our data indicate that amitriptyline has some therapeutic benefit in patients with primary fibrositis.

Fibrositis is a disorder characterized by diffuse, widespread musculoskeletal aching and stiffness, multiple tender points, and nonrestorative sleep (1–3). The syndrome is defined as primary when no underlying disease can be demonstrated, and secondary when it is found in association with other conditions.

From Le Centre Hospitalier, Laval University, Quebec City, Quebec; University Hospital, University of Western Ontario, London, Ontario; and Sunnybrook Medical Centre, University of Toronto, Toronto, Ontario, Canada.

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Simon Carette, MD, FRCP(C): Associate of the Arthritis Society, Laval University; Glenn A. McCain, MD, FRCP(C): Assistant Professor of Medicine, University of Western Ontario; David A. Bell, MD, FRCP(C): Professor of Medicine, University of Western Ontario; Adel G. Fam, MD, FRCP(C): Associate Professor of Medicine, University of Toronto.

Address reprint requests to Dr. Simon Carette, 2705 boulevard Laurier, Quebec City, PQ, Canada, G1V 4G2

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The pathophysiology of the disorder is poorly understood. Moldofsky et al have described distinct sleep abnormalities which have been demonstrated on electroencephalography (EEG) and are characterized by the intrusion of alpha waves during stages 3 and 4 of the non–rapid eye movement (REM) sleep (4,5). When artificially reproduced in healthy volunteers, these EEG abnormalities were associated with the appearance of symptoms of fibrositis (6). The same authors have reported an inverse relationship between plasma-free tryptophan, a serotonin precursor, and pain severity in fibrositis (7) that is consistent with the hypothesis that low brain serotonin may be related to the low pain threshold found in patients with fibrositis.

Amitriptyline, a tricyclic antidepressant agent, has been claimed to be helpful in the management of patients with fibrositis (2,8,9). The drug has serotonergic and anticholinergic activities (10). At low doses, it has predominantly hypnotic properties, causing REM suppression and prolongation of stages 3 and 4 non-REM sleep (11–13).

This double-blind, placebo-controlled study was designed to define the value of amitriptyline in the treatment of primary fibrositis. Our results indicate that amitriptyline produces a significant improvement in local pain, stiffness, and sleep pattern, but has little effect on fibrositic point tenderness.

PATIENTS AND METHODS

Patient population. Patients studied had primary fibrositis and were treated at outpatient rheumatology clinics in 3 Canadian university centers. Seventy patients were accepted into the trial after a preliminary evaluation consisting of a detailed history, physical examination, and laboratory assessment. The patients were randomized to receive either amitriptyline or placebo for 9 weeks.

The criteria used for the diagnosis of fibrositis were those proposed by Smythe (8), and included each of the following: 1) widespread aching of more than 3 months duration, 2) local tenderness at 12 of 14 specified sites, 3) disturbed sleep with morning fatigue and stiffness, 4) absence of traumatic, neurologic, muscular, infectious, osseous, endocrine, or other rheumatic conditions, and 5) normal Westergren erythrocyte sedimation rate, creatine phosphokinase level, latex fixation result, antinuclear antibody factor, and thyroid stimulating hormone (TSH) level.

Nonsteroidal antiinflammatory drugs, hypnotic drugs, and antidepressant agents were discontinued for a minimum of 3 weeks before entry into the trial. Only acetaminophen was permitted during the study, and each dose was recorded. Patients treated with amitriptyline within the preceding year and those with previous hypersensitivity reaction to the drug were excluded. Patients with a history of glaucoma, urinary retention, ischemic heart disease, arrhythmia, or congestive heart failure were also excluded.

Treatment plan. Patients who were randomly assigned to the amitriptyline group received 10 mg daily at bedtime for the first week, 25 mg for the second through the fourth weeks, and 50 mg for the last 5 weeks of the trial. This schedule was chosen based on our previous observations that many patients experienced significant side effects when started directly on 50 mg of amitriptyline. The amitriptyline was in capsules that were identical to the placebo capsules. In the event of adverse reactions, the drug was discontinued or the dosage was reduced to the previous level (i. e., 50 mg to 25 mg, 25 mg to 10 mg, placebo to placebo).

Efficacy evaluations. Patients were evaluated at baseline and at the end of weeks 5 and 9. The same physician examined each patient throughout the trial. Four physicians participated in the study.

Patients' assessments included: (a) duration of morning stiffness in minutes; (b) assessment of overall pain, using an analog scale of 1–10, with 10 = tolerable—patients were asked to indicate the extent of pain experienced during the previous week; (c) evaluation of sleep quality as compared with baseline values, scored as 1 (feeling more rested upon awakening in the morning), 2 (feeling less rested upon awakening in the morning), or 3 (no change); (d) overall assessment of disease as compared with baseline values, on a scale of 1 (worse), 2 (unchanged), 3 (minimally improved), 4 (moderately improved), or 5 (markedly improved).

Physicians' assessments included measurement of fibrositic point tenderness with the aid of a 9-kg dolorimeter (Chatillon, New York, NY). Before beginning the trial, the investigators met on several occasions to standardize among themselves the technique of use of the dolorimeter. The target sites were first located with brief preliminary palpation, and the endpoint measured with the dolorimeter was the pain threshold. We arbitrarily elected to limit our measurements to the following 8 (4 paired) points: the midpoint of the upper fold of the trapezius, second costochondral junction, 2 cm distal to the lateral epicondyle, and over the medial fat pad of the knee. The individual scores were summed to give the total myalgic score (TMS). Physicians' assessments also included the examiner's overall assessment of disease as compared with baseline, on a scale of: 1 (worse), 2 (unchanged), 3 (minimal improvement), 4 (moderate improvement), or 5 (marked improvement). This evaluation was not based on strict criteria, but on the clinical judgment of the observer.

Statistical analysis. A sample size of 32 patients from each of the 2 treatment groups was calculated to be adequate to test at the 5% level with 80% power, an estimated improvement of 55% in the amitriptyline group versus 25% in the placebo group. A dropout rate of less than 10% was expected. A meaningful improvement was arbitrarily defined as a moderate or marked improvement by the patient's overall assessment and/or an increase in the TMS by 8 kg or more (mean of 1 kg for each tender point).

All data were entered into an IBM 4381 computer and statistical analysis was performed using the SAS Statistical Package. Means were tested with Student's 2-tailed *t*-test, and proportions by chi-square test with Yates' correction.

RESULTS

Fifty-nine patients completed the trial. Twenty-seven received amitriptyline (A), and 32 received placebo (P). The demographic and clinical characteristics of these patients at entry are shown in Table 1. The randomization resulted in 2 comparable groups with respect to age, sex, duration of morning stiffness, pain analog scores, and total myalgic scores. The duration of symptoms before study entry was slightly longer in patients receiving placebo ($P = 0.04$).

Eleven patients (7 A, 4 P) withdrew from the trial: 4 withdrew, for reasons believed to be drug-related (drowsiness [1 A, 1 P], agitation [1 A], gastrointestinal symptoms [1 P]); 4 for lack of cooperation (3 A, 1 P); 2 for intercurrent illnesses (varicella [P], pneumonia [A]); and 1 for insufficient therapeutic effect (A).

Patients who received amitriptyline improved significantly in their morning stiffness and pain analog scores at 5 and 9 weeks as compared with baseline scores; whereas, no changes were noted in these parameters in the placebo group (Table 2). The difference between the 2 treatment groups, however, was not significant for either of the parameters. Twelve patients (44%) in the amitriptyline group had ≥50% improvement in their morning stiffness or pain analog scores, and 10 patients (37%) had improvement in both scores. This compared with 7 patients (22%) and 5 patients (16%), respectively, who received the placebo ($\chi^2 = 2.44$, $P = 0.12$; $\chi^2 = 2.48$, $P = 0.12$).

Total myalgic scores did not improve significantly over baseline values in either of the treatment groups (Table 2). The changes observed in TMS after 5 weeks in patients who received amitriptyline were statistically significant but clinically minimal (mean

Table 1. Demographic and clinical measures of fibrositis patients at study entry*

	Amitriptyline group (n = 27)	Placebo group (n = 32)
Age	41.8 ± 10.4	40.1 ± 10.5
Sex (F/M)	25/2	29/3
Duration of fibrositis (months)	71 ± 58	97 ± 87†
Duration of morning stiffness (minutes)	75 ± 72	78 ± 71
Pain analog score	6.3 ± 2.3	5.8 ± 2.4
Total myalgic score	22.5 ± 6.7	24.8 ± 7.9

* All values except sex are mean ± SD.
† $P < 0.05$ by Student's t-test.

Table 2. Morning stiffness, pain analog scores, and total myalgic scores in patients receiving amitriptyline (A) or placebo (P)*

	Prestudy	5 weeks	9 weeks
Morning stiffness (minutes)			
A	75 ± 72	41 ± 58†	48 ± 61†
P	78 ± 71	71 ± 80	66 ± 76
Pain analog score			
A	6.3 ± 2.3	3.8 ± 2.3†	4.3 ± 3.0†
P	5.8 ± 2.4	5.3 ± 2.7	5.0 ± 3.0
Total myalgic score			
A	22.2 ± 6.7	27.1 ± 9.0†	25.2 ± 8.1
P	24.8 ± 7.9	26.7 ± 9.0	26.2 ± 8.9

* Values are mean ± SD.
† $P < 0.05$, compared with prestudy value.

increase of 0.5 kg for individual myalgic scores). Overall, TMS improved in 26 of the 35 patients who reported an overall improvement, while scores remained unchanged or decreased in 15 of the 24 patients who assessed their disease as unchanged or worse. Only 11 patients (6 A, 5 P) had ≥8 kg improvement in their TMS.

Seventy percent of patients who received amitriptyline believed that the quality of their sleep had improved, compared with 34% of patients taking the placebo at 5 weeks and 40% at 9 weeks. These differences were significant ($\chi^2 = 7.1$, $P = 0.008$; $\chi^2 = 5.32$, $P = 0.02$, respectively).

In the amitriptyline group, 77% of patients experienced overall improvement at 5 weeks and 70% at 9 weeks (Figures 1 and 2). In the placebo group, 43% experienced improvement at 5 weeks and 50% at 9 weeks. These differences were significant at 5 weeks ($\chi^2 = 7.26$, $P = 0.008$), but not at 9 weeks ($\chi^2 = 2.55$, $P = 0.11$).

The magnitude of improvement was qualitatively higher in patients who received amitriptyline than in those who took the placebo. Thus, 15 patients (55%) treated with amitriptyline assessed their disease as moderately to markedly improved at 5 weeks, as compared with 7 patients (22%) who received the placebo ($\chi^2 = 5.73$, $P = 0.02$). At 9 weeks, 17 patients (63%) in the amitriptyline group and 10 patients (32%) in the placebo group described their overall improvement as moderate or marked ($\chi^2 = 4.72$, $P = 0.03$).

Physicians agreed with the patients' overall assessments in 68% of the total cases. When there was disagreement, the physician gave a more pessimistic assessment 70% of the time.

Minor side effects were reported by 19 patients (70%) receiving amitriptyline who completed the study and 4 (12%) taking the placebo. These side effects were, for the most part, drowsiness and xerostomia. In only 3 patients, all taking 50 mg of amitriptyline, was the study drug decreased to the previous dosage level.

At a mean followup of 9 months, 9 of the 19 patients (47%) who improved with amitriptyline therapy were still taking the drug, 4 had discontinued because of improvement in symptoms, and 3 stopped the medication because of worsening of their symptoms. Three patients were lost to followup.

DISCUSSION

The treatment of fibrositis is generally unsatisfactory. Conservative measures, such as reassurance, rest, local heat, massage, stretching exercises, and analgesic and nonsteroidal antiinflammatory drugs, are too often inadequate to effectively relieve symptoms. So far, only 2 medications have been studied in controlled trials: cyclobenzaprine and prednisone (14,15). The former was shown to produce significant

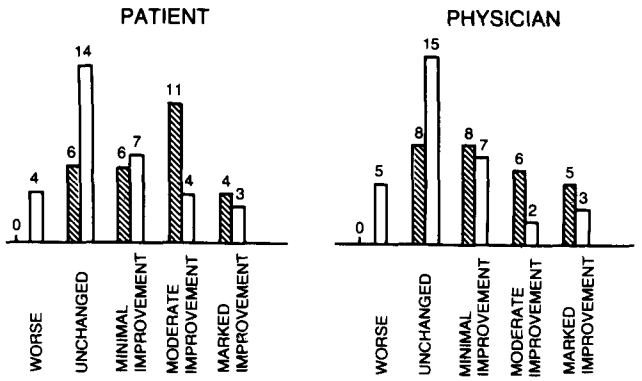

Figure 1. Patient and physician global assessments at 5 weeks. Hatched bars represent patients receiving amitriptyline; open bars represent patients taking placebo.

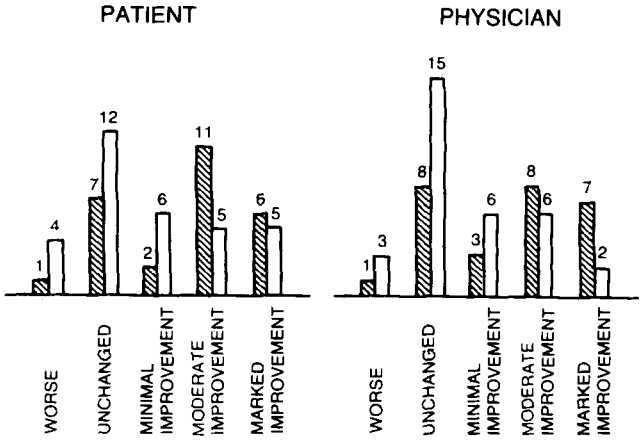

Figure 2. Patient and physician global assessments at 9 weeks. Hatched bars represent patients receiving amitriptyline; open bars represent patients taking placebo.

improvement in localized pain, sleep disturbances, and trigger points, as compared with placebo, in a 12-week double-blind trial involving 118 patients (14). In the second study (15), which involved 20 patients in a 2-week crossover study of 20 mg/day of prednisone versus placebo, prednisone proved to be ineffective. There was even a trend toward deterioration in most measured variables while the patients were receiving prednisone.

The present trial confirms previous uncontrolled observations that amitriptyline is useful in the treatment of patients with primary fibrositis (2,8,9). This study indicates that amitriptyline is superior to placebo with respect to sleep improvement and patient and physician global assessments. Furthermore, the improvement of morning stiffness and pain analog scores was distinctly higher in patients receiving amitriptyline, although not statistically different from the placebo group. Only TMS did not change significantly over baseline values.

There were several difficulties involved in this study. The first problem was that of maintaining the double-blind nature of the trial, since such a high proportion (70%) of the amitriptyline patients developed anticholinergic side effects, which in some cases unblinded both patients and observers. We have no way of knowing how this may have affected the ultimate assessments, except to note that the 8 patients taking amitriptyline who did not experience side effects had an improvement similar to those who did (2 markedly improved, 2 moderately improved, 2 minimally improved, and 2 unchanged). The use of an active placebo such as neostigmine was discussed before starting this trial, but the idea was discarded due to the possibility of unblinding the study in the opposite direction, and also because the effects of pure anticholinergics in primary fibrositis are unknown.

The second difficulty of the study, inherent to the nature of fibrositis itself, was the necessity of limiting our observations, for the most part, to subjective parameters. Contrary to trials in other rheumatic diseases in which objective variables can be measured, such as number of tender and swollen joints, grip strength, hemoglobin, and sedimentation rate, there are few, if any, objective parameters to evaluate disease in patients with fibrositis. Lacking these, we chose the patients' overall assessments of their conditions as the most significant measure of outcome. A recent survey has shown that this measure is perceived as the most important by a majority of clinicians (16).

Previous authors have used analog scores to evaluate pain, sleep, fatigue, and morning stiffness (14,15). Since the value of analog scores has been demonstrated predominantly for the evaluation of pain (17), we chose standard assessments for the evaluation of morning stiffness (duration in minutes) and sleep (global changes compared with baseline values).

The rationale for using fibrositic point tenderness as the sole objective outcome measure was based on the assumption that an improvement of symptoms would be associated with an elevation of pain threshold as measured by dolorimetry. Although an actual increase in TMS occurred in 74% of the patients who subjectively improved (in both the amitriptyline and the placebo groups), as opposed to 29% of those who didn't, the magnitude of this increase was much less than originally expected (mean of less than 0.5 kg for each tender point). This suggests that the measurement of point tenderness by dolorimetry is not a sufficiently sensitive marker for evaluation of outcome in short-term trials of patients with fibrositis.

Sixteen patients (50%) believed their symptoms decreased overall while they were taking placebo. In 10 patients (31%), this improvement was meaningful by our definition. This may reflect relative insensitivity of this outcome measure in assessment of a true placebo effect. Considering that many patients with fibrositis often think that their disease "is not taken seriously," it is possible that the increased attention given to these patients by according them the special status of study subjects could have accounted for this favorable response in the placebo group. Recognition

of this potential high placebo effect will have to be accounted for in the design of future trials, to avoid Type II errors.

In conclusion, our data indicate that amitriptyline is effective in relieving symptoms of fibrositis but has little effect on fibrositic point tenderness.

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