ARTHRITIS & RHEUMATISM
Vol. 39, No. 11, November 1996, pp 1852–1859

A RANDOMIZED, DOUBLE-BLIND CROSSOVER TRIAL OF FLUOXETINE AND AMITRIPTYLINE IN THE TREATMENT OF FIBROMYALGIA

DON GOLDENBERG, MICHAEL MAYSKIY, CHRISTOPHER MOSSEY, ROBIN RUTHAZER, and CHRISTOPHER SCHMID

Objective. **To study the effect of fluoxetine (FL) and amitriptyline (AM), alone and in combination, in patients with fibromyalgia (FM).**

Methods. **Nineteen patients with FM completed a randomized, double-blind crossover study, which consisted of 4 6-week trials of FL (20 mg), AM (25 mg), a combination of FL and AM, or placebo. Patients were evaluated on the first and last day of each trial period. Outcome measures included a tender point score, the Fibromyalgia Impact Questionnaire (FIQ), the Beck Depression Inventory (BDI) scale, and visual analog scales (VAS) for global well-being (1 completed by the physican and 1 by the patient), pain, sleep trouble, fatigue, and feeling refreshed upon awakening.**

Results. **Both FL and AM were associated with significantly improved scores on the FIQ and on the VAS for pain, global well-being, and sleep disturbances. When combined, the 2 treatments worked better than either medication alone. Similar, but nonsignificant, improvement occurred in the BDI scale, the physician global VAS, and the VAS for fatigue and feeling refreshed upon awakening. Trends were less clear for the tender point score.**

Conclusion. **Both FL and AM are effective treatments for FM, and they work better in combination than either medication alone.**

Clinical trials of medications for the treatment of fibromyalgia (FM) have demonstrated modest or little efficacy. Tricyclic and tetracyclic "antidepressant" drugs have been the most commonly studied agents. Amitriptyline (AM) and cyclobenzaprine (CY), tricyclic medications that inhibit both serotonin and norepinephrine uptake, have been evaluated in a number of randomized, controlled trials (1–6). In each of these studies, approximately one-third of patients had a clinically meaningful response to these tricyclic medications. Other tricyclic drugs have demonstrated similar modest efficacy (7,8).

Most of these studies have been of short duration. In a 6-month randomized, clinical trial of 208 patients with FM, 21% of AM-treated patients and 12% of CY-treated patients versus 0% of placebo-treated patients showed significant improvement at 1 month compared with baseline (9). However, at 6 months there was no significant difference in response between those taking active drugs and those taking placebo. It has been suggested that certain symptoms of FM may respond better to drugs that primarily affect serotonin, whereas drugs that affect norepinephrine uptake may improve other symptoms (7).

Fluoxetine (FL), a selective serotonin reuptake inhibitor, has been evaluated for the treatment of FM in 2 previous studies. An open, uncontrolled study of 20–40 mg/day of FL demonstrated improvement in sleep, but not in pain or tender point score (10). A double-blind, controlled trial of 20 mg/day of FL demonstrated no improvement in pain, fatigue, Health Assessment Questionnaire, global severity, or tender point scores (11). Our study was designed to answer 3 questions: 1) Is FL an effective treatment for FM? 2) What is the comparable efficacy of FL, a selective serotonin reuptake inhibitor, to that of AM in the treatment of FM? and 3) Would the combined regimen of FL and AM be more effective than either alone?

PATIENTS AND METHODS

Patient selection criteria. Patients were recruited from a registry of FM patients who met the American College of

Presented at the Fifty-Ninth National Meeting of the American College of Rheumatology, San Francisco, CA, November 1995.

Supported by Lot Page Fund, Newton-Wellesley Hospital, Newton, Massachusetts.

Don Goldenberg, MD, Michael Mayskiy, MD, Christopher Mossey, MA: Newton-Wellesley Hospital, Newton, Massachusetts; Robin Ruthazer, MPH, Christopher Schmid, PhD: New England Medical Center, Boston, Massachusetts.

Address reprint requests to Don L. Goldenberg, MD, 2000 Washington Street, #304, Newton, MA 02162.

Submitted for publication February 26, 1996; accepted in revised form May 10, 1996.

Rheumatology (ACR) classification criteria for FM (12). These patients had been diagnosed individually and followed up in a tertiary referral center by a rheumatologist (DG) who has a known interest in FM. The research protocol, approved by the Institutional Review Board for Human Research, was sent by mail or given to eligible patients at the time of routine office visits.

Criteria for study eligibility consisted of 1) no current or past history of systemic illness, including cardiac, kidney, hematologic, or liver disease; 2) age within the range of 18–60 years; and 3) willingness to discontinue all central nervous system active medications, nonsteroidal antiinflammatory drugs, and analgesics (other than acetaminophen) for at least 1 week prior to the study. Interested patients were then evaluated by the rheumatologist (DG) to ensure that they currently met all study criteria and to verify that each patient currently satisfied the ACR criteria for FM. At the intake visit, each patient had to have a score of ≥30 (maximum 100) on the visual analog scale (VAS) for pain. Furthermore, in order to exclude patients with major depression, each patient had to have a score of ≤18 on the Hamilton Rating Scale for Depression, which was administered by a physician (MM).

Study design. The study was a randomized, double-blind crossover study, composed of 4 6-week trials, each separated by a 2-week washout phase. Using randomization tables, the pharmacy assigned patients to 1 of the following 4 regimens: 1) placebo in the morning and 25 mg of AM at bedtime; 2) 20 mg of FL in the morning and placebo at bedtime; 3) 20 mg of FL in the morning and 25 mg of AM at bedtime; or 4) placebo both in the morning and at bedtime. All tablets were identical in appearance. The order of treatment was generated from a table of random numbers. Randomization was performed in the hospital pharmacy.

Patient evaluation. Participants were evaluated 8 times during the study: once at the beginning and once at the end of each of the 6-week trial periods. All evaluations were done by a physician (MM) who had no prior contact with the patients. At each visit, the physican performed a manual tender point examination, scoring each pair of 9 tender points as 0 = none, 1 = moderate, and 2 = severe, as previously reported (2). The composite tender point score was the sum of these scores. Dolorimetry was not performed. The physican also completed a 100-mm VAS that measured the patient's global well-being. This physician global VAS was anchored with the measures, 0 = not troublesome at all to 100 = extremely troublesome.

At each visit, the patient completed 5 100-mm VAS for pain, sleep disturbance, fatigue, feeling refreshed upon awakening, and global well-being. These VAS were anchored with the following measures: global well-being, 0 = not troublesome at all to 100 = extremely troublesome; pain, 0 = no pain to 100 = very severe pain; sleep, 0 = no sleep trouble to 100 = a lot of sleep trouble; fatigue, 0 = not fatigued at all to 100 = extremely fatigued; and feeling refreshed upon awakening, 0 = fine and refreshed to 100 = extremely tired. Patients also completed the Fibromyalgia Impact Questionnaire (FIQ) (13) and the Beck Depression Inventory (BDI) scale (14) at each evaluation. Adverse reactions to medications were noted by the physician at each visit, and routine laboratory tests were monitored according to physician discretion.

Statistical analysis. *Pre-study power analysis.* We postulated that FL was as effective as AM in the treatment of FM. We also hypothesized that the combined therapy would be more effective than either medication alone. Based on the crossover study design and previous studies of treatment response in FM, we calculated that a total of 20 patients would provide a conservative sample size for detecting at least a 25-point change in the global VAS, with an SD of 20 and a 90% power to detect change. We recruited 31 patients for entry into the study.

Data analysis. We used the score at the end of each 6-week treatment period as the outcome in a repeated-measures analysis of variance, which included treatment and period effects. Because of the 8-week interval between outcome measures, including the 2-week washout periods, carry-over effects were not expected; thus, we made no statistical adjustment for them (15). All data on patients who completed at least 1 treatment period were analyzed for outcome, but patients who failed to complete a period had no outcome that could be measured. Inclusion of these incomplete data was appropriate as long as the missing values were missing at random (i.e., no information about the missing values was provided by the fact that they were missing) (16). Because patients were enrolled at different times throughout the year, period-by-treatment interactions were uninterpretable and were therefore not modeled. Models were constructed both with and without the initial measurement in each period, which was the baseline covariate. We also calculated change scores as the difference between the 6-week measurement and the 0-week measurement in each period. Calculations were performed using SAS, version 6.10 (SAS Institute, Cary, NC) (17). Values less than 0.05, by either chi-square analysis or 2-tailed *t*-test, were considered statistically significant.

RESULTS

Baseline data. The baseline characteristics of the 31 patients who were seen at the initial study visit are listed in Table 1. Of these 31 patients, 28 (90%) were women. All patients (mean ± SD age 43.2 ± 9.1 years) were white, and 22 (71%) were married. The mean ± SD duration of the FM symptoms at the initial visit was 72.6 ± 48.1 months, with a minimum duration of 24 months and a maximum of 240 months. Nineteen patients (61%) were working, 11 (36%) were disabled, and 1 (3%) was retired (Table 1).

At the initial visit, mean ± SD scores for all 31 patients were recorded for each of the FM activity measures. These initial scores were 57.3 ± 17.6 for the FIQ, 68.4 ± 20.4 for VAS pain, 66.6 ± 24.5 for VAS global well-being, 68.0 ± 26.6 for VAS sleep, 12.4 ± 8.5 for BDI score, 63.3 ± 22.0 for physician global VAS, 73.0 ± 21.5 for VAS fatigue, 76.4 ± 20.4 for VAS feeling refreshed upon awakening, and 20.6 ± 5.8 for tender point score (Table 1).

Patient withdrawals. Twelve patients (38.7% of those enrolled) did not complete the study (Table 1). The mean number of days in the study for these 12

Table 1. Baseline characteristics of the study patients

Variable	Baseline total	Completed	Dropped out	P*
Demographic				
Total no. (%) of patients	31 (100.0)	19 (61.3)	12 (38.7)	–
White, no. (%) of patients	31 (100.0)	19 (100.0)	12 (100.0)	1.00
Sex, no. (%) of patients				0.84
Female	28 (90.3)	17 (89.5)	11 (91.7)	–
Male	3 (9.7)	2 (10.5)	1 (8.3)	0.04
Work status, no. (%) of patients				
Working	19 (61.3)	9 (47.4)	10 (83.3)	–
Disabled	11 (35.5)	9 (47.4)	2 (16.7)	–
Retired	1 (3.2)	1 (5.3)	0 (0.0)	–
Marital status, no. (%) of patients				0.69
Married	22 (71.0)	13 (68.4)	9 (75.0)	–
Single	5 (16.1)	3 (15.8)	2 (16.7)	–
Divorced	3 (9.7)	2 (10.5)	1 (8.3)	–
Widowed	1 (3.2)	1 (5.3)	0 (0.0)	–
Mean ± SD duration of symptoms, months	72.6 ± 48.1	82.5 ± 56.3	57.0 ± 26.1	0.15
Mean ± SD age, years	43.2 ± 9.1	42.9 ± 9.6	43.7 ± 8.4	0.81
Fibromyalgia activity†				
FIQ	57.3 ± 17.6	54.9 ± 15.4	61.2 ± 20.7	0.35
VAS pain	68.4 ± 20.4	70.6 ± 18.4	64.6 ± 23.9	0.45
VAS global	66.6 ± 24.5	66.6 ± 22.8	66.5 ± 28.3	0.99
VAS sleep	68.0 ± 26.6	65.8 ± 28.3	71.7 ± 24.2	0.57
BDI	12.4 ± 8.5	11.7 ± 6.3	13.5 ± 11.7	0.66
Physician VAS	63.3 ± 22.0	63.9 ± 20.0	62.3 ± 26.0	0.85
VAS fatigue	73.0 ± 21.5	68.8 ± 23.4	80.2 ± 16.3	0.17
VAS refreshed	76.4 ± 20.4	73.2 ± 23.1	82.0 ± 14.2	0.27
Tender point score	20.6 ± 5.8	19.9 ± 5.8	21.8 ± 5.9	0.41

* Patients who completed versus those who dropped out of the study, either by chi-square test or, for duration of symptoms, age, and fibromyalgia activity, by 2-sample *t*-test.
† Values for fibromyalgia activity are the mean ± SD for each measure. FIQ = Fibromyalgia Impact Questionnaire; VAS = visual analog scale; BDI = Beck Depression Inventory.

patients was 39 (range 2–86). Seven of these patients withdrew during the first 6-week trial. Five patients completed the first trial, but dropped out during the second trial period. Four patients dropped out while receiving FL, 1 while receiving AM, 5 while receiving both drugs, and 1 while receiving placebo. One patient dropped out during a washout period following the trial of both drugs.

Five patients (1 receiving FL, 3 receiving FL and AM, and 1 receiving placebo) cited an adverse reaction to the medication as the reason for dropping out of the trial. Four patients (3 receiving FL and 1 during the washout period) cited increased FM symptoms, and 3 patients (2 receiving FL and AM, and 1 receiving AM alone) withdrew for reasons other than FM symptoms or adverse side effects to the medication. There were no statistically significant differences in baseline characteristics and baseline responses between the 19 patients who completed the study and the 12 who dropped out (Table 1), except that those who dropped out were more likely to be working. There were no significant differences in the type of adverse reaction in patients during any of the 4 trial periods.

Treatment effects. Treatment group mean values for each outcome measure, obtained at the 6-week end points, are presented in Table 2. There was statistically significant improvement, compared with the placebo-treated group, for both the AM- and FL-treated groups, as measured by the FIQ and by the VAS for pain, global well-being, and sleep (Figure 1 and Table 2). When used in combination, AM and FL produced significantly better results than did either drug alone, based on these 4 outcome measures (Figure 1 and Table 2). When the baseline value for each trial period was included in these analyses as a covariate, the results changed very little. Generally, the improvement with combination treatment was twice that with either treatment given individually. Similar, but not statistically significant, trends for both single-drug and combination-drug therapy were noted using the BDI scale, physician global VAS, VAS fatigue,

Table 2. Mean outcome measures at the 6-week end points, by treatment group*

Outcome measure	No. of patients, mean (SD) outcome measure score				*P*†		
	P	AM	FL	AM + FL	AM	FL	Interaction
FIQ	19	21	22	19			
	58.5 (17.1)	52.3 (22.9)	47.6 (19.8)	38.0 (21.2)	0.03	0.006	0.94
VAS pain	19	21	22	18			
	81.5 (16.5)	64.4 (28.3)	57.5 (25.7)	42.9 (28.5)	0.02	<0.001	0.55
VAS global	19	21	22	18			
	76.8 (24.8)	61.6 (29.5)	60.9 (24.9)	48.2 (29.7)	0.02	0.02	0.40
VAS sleep	19	21	22	18			
	74.6 (23.9)	57.0 (34.8)	66.0 (26.6)	39.9 (29.2)	<0.001	0.04	0.79
BDI	19	20	22	18			
	9.3 (6.5)	8.7 (6.0)	7.8 (4.7)	7.4 (4.4)	0.52	0.35	0.49
Physician VAS	18	20	22	18			
	74.7 (19.9)	64.2 (25.2)	68.0 (17.8)	55.5 (22.1)	0.04	0.08	0.76
VAS fatigue	19	21	22	18			
	73.7 (25.1)	67.7 (29.9)	68.6 (24.1)	57.2 (31.6)	0.26	0.22	0.88
VAS refreshed	19	21	22	18			
	75.1 (25.9)	69.6 (29.1)	67.2 (23.3)	59.4 (31.5)	0.40	0.13	0.70
Tender point score	19	21	22	18			
	19.0 (7.5)	18.0 (7.2)	20.3 (7.5)	16.4 (7.1)	0.30	0.99	0.79

* P = placebo; AM = amitriptyline; FL = fluoxetine; see Table 1 for other definitions.
† *P* values from the general linear model, calculated by analysis of variance, were adjusted for period and patient main effects.

and VAS feeling refreshed upon awakening (Figure 2 and Table 2). Tender point score results were not as clear-cut, although the greatest improvement was noted following administration of combination therapy.

The overall correlation between the FIQ and the tender point score was 0.38 ($P = 0.0004$). This was based on all pairs of FIQ and tender point scores at the end of trial periods 1–4. To test our assumption that the BDI scale was an adequate self-reported measure of depression, we compared it with values from the Hamilton

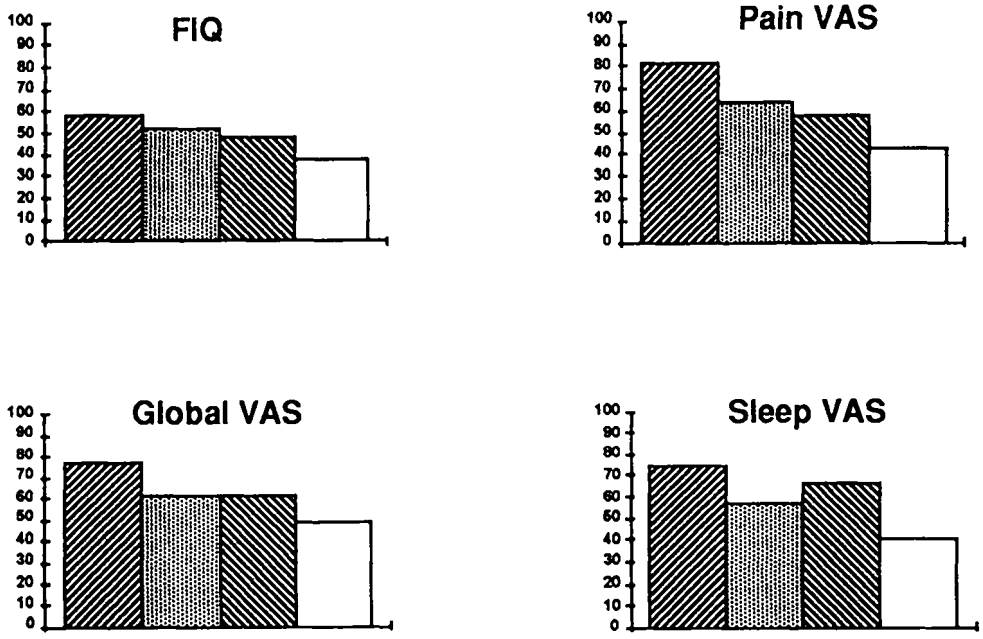

Figure 1. Mean outcomes (statistically significant changes) in the groups treated with either placebo (▨), amitriptyline (▩), fluoxetine (▧), or a combination of amitriptyline and fluoxetine (□), as measured by the Fibromyalgia Impact Questionnaire (FIQ) and by the visual analog scales (VAS) for pain, global well-being, and sleep.

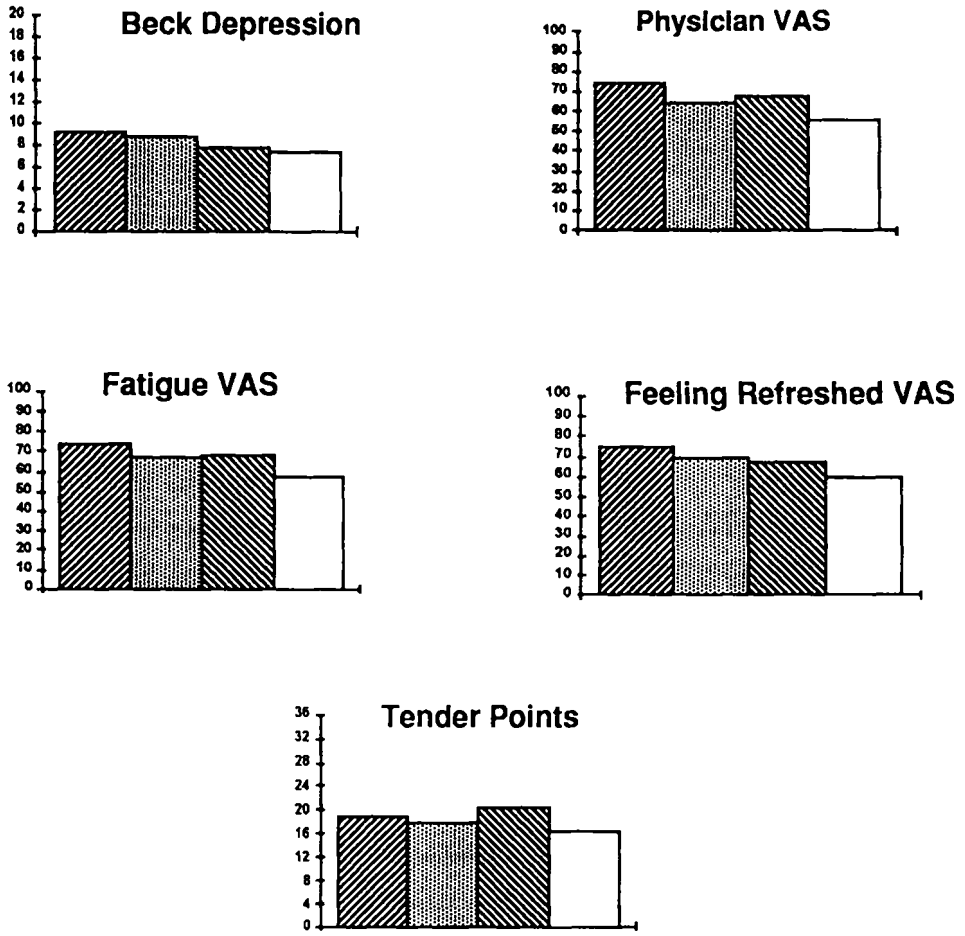

Figure 2. Mean outcomes (statistically nonsignificant changes) in the groups treated with either placebo (▨), amitriptyline (▩), fluoxetine (▧), or a combination of amitriptyline and fluoxetine (□), as measured by the Beck Depression Inventory scale, the visual analog scales (VAS) for physician assessment of global well-being, fatigue, and feeling refreshed upon awakening, and the tender point score.

Psychiatric Rating Scale, which were obtained at baseline. The correlation coefficient of these 2 measures was 0.92.

To focus on the treatment effects for individual patients rather than for groups, we calculated the percentage change in outcome measures from the beginning to the end of the trial period for each treatment. Similar to the group mean scores, individual patients improved most with the combination of AM and FL, and patients receiving placebo fared the worst. For example, combination treatment improved FIQ scores by >25% for 12 of 19 patients (63%). A >25% improvement in the FIQ was also observed for 7 of 22 patients receiving FL (32%), 5 of 21 receiving AM (24%), and 1 of 19 receiving placebo (5%). Results were similar for the other significant outcome measures (VAS pain, VAS global well-being, and VAS sleep).

We also calculated a composite change score for each patient, adapting the preliminary criteria for a clinically meaningful response in FM, which have been proposed by Simms et al (18). The composite change score is the average of the changes in 4 outcome measures within each treatment period: the VAS global well-being, VAS pain, tender point score, and physician global VAS. All scores, including the tender point score (range 1–36), were normalized to a 100-point scale. The composite change score measures change within each treatment phase. An improvement of at least 25 points on the composite change score occurred in 5 patients

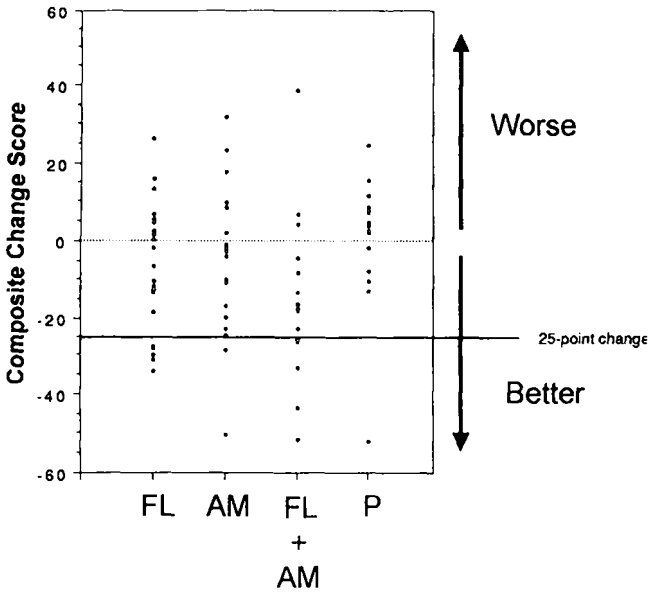

Figure 3. Composite change scores for 4 outcome measures. This score was the average of the change in the visual analog scales (VAS) for global well-being and for pain, the tender point score, and the physician global VAS. The tender point score was normalized to a 100-point scale. The change score reflected the change within each treatment period and was calculated as follows: (change in VAS global + change in VAS pain + [change in tender point score × 2.78] + change in physican global VAS) ÷ 4. Each open circle represents an individual patient. FL = fluoxetine; AM = amitriptyline, P = placebo.

who were receiving the combined regimen of FL and AM, 5 receiving FL alone, 2 receiving AM alone, and 1 receiving placebo (Figure 3).

Period effects. To check for an order effect on baseline measures, we performed 2 supplemental analyses. We compared the mean baseline scores following each treatment (AM, FL, AM and FL, or placebo) with the initial baseline value at period 1, using a repeated-measures analysis of variance. There were no significant differences among FIQ, VAS pain, VAS global well-being, VAS sleep, VAS fatigue, VAS feeling refreshed upon awakening, and tender point mean baseline values. Mean baseline BDI values after treatment with either FL or AM (7.8 and 8.7, respectively) were significantly lower than the initial baseline value (11.7). Mean baseline BDI scores after combination treatment (AM and FL) (9.4) or after placebo (10.1) were not significantly different than the initial baseline value. Mean physician global VAS score after treatment with FL (77.7) was significantly higher than the initial baseline mean value (65.2). However, the mean physician global VAS scores after treatment with AM, AM and FL, or placebo (75.6, 72.5, and 74.1, respectively) were not significantly different than the initial baseline value.

We also compared the 5 baseline mean values in order to check for a period effect. Again, a repeated-measures analysis of variance was used. There were no significant differences among the period means for the FIQ, VAS pain, VAS global well-being, VAS sleep, VAS fatigue, VAS feeling refreshed upon awakening, and tender point scores. There were differences in the mean baseline values for the BDI scale and the physician global VAS. Among the BDI baseline values, the means for periods 1–5 were 11.7, 9.2, 8.5, 9.3, and 10.0, respectively. This nonlinear distribution fails to indicate an increasing or decreasing trend. There were also significant differences between the physician global VAS baseline values, which showed an increase over time. The means for periods 1–5 were 63.9, 67.7, 73.1, 77.1, and 81.5, respectively. Of note, in the analysis of the crossover design, we included a factor for period effects. Due to the large number of comparisons done in these 2 supplemental analyses, it is hard to say whether these few significant differences truly reflected carryover or order effects or reflected random variation.

We used all available data in the analyses, including those from patients who did not complete the study. In the crossover analysis, each person served as his or her own control, so there was no need to adjust for factors such as age or sex. In the supplemental analysis, we adjusted for baseline measurements at each treatment period. Since the results were essentially the same as those from the unadjusted analyses, we have presented the results from the unadjusted, simpler analyses.

DISCUSSION

This is the first randomized clinical trial that compares the individual and combined efficacy of a tricyclic medication (AM) and a selective serotonin reuptake inhibitor (FL) in the treatment of patients with FM. Treatment with both AM and FL resulted in significant improvement in the patients' FIQ scores as well as in the VAS scores for global well-being, pain, and sleep. The combined regimen was more effective than either drug alone. Similar, but not significant, trends were noted for physician global VAS, VAS fatigue, VAS feeling refreshed upon awakening, tender point scores, and BDI scores. We found no significant relationship between the decrease in VAS pain and VAS global well-being scores and the modest decrease in the BDI score.

The tender point score did not change signifi-

cantly, despite improvement in the VAS pain, global well-being, and function scores. Prior clinical trials have also noted little change in tender point counts, and have found no correlation between change in tender point counts and decreased pain (1,4,9). In FM, as well as in rheumatoid arthritis, the tender point count has correlated best with general distress (19,20). Tender points may be related to pain, but are separately associated with fatigue and depression (20). Therefore, tender point scores and self-reported pain may represent different aspects of the pain response in FM (21).

The improved efficacy of the combination of FL and AM may relate to a more ideal balance of serotonin/norepinephrine/dopamine uptake inhibition than that provided by the individual medications. Clinically, since the 2 drugs have different actions as well as quite different side effects, the combination may be more tolerable to the patient, in addition to being more effective. For example, the daytime grogginess often noted with AM may be cancelled out by the morning dose of FL. Future trials should test other combinations of such medications and also test novel central nervous system active medications. The major limitation of our study was the 6-week duration of each medication regimen. Higher doses of these medications and longer duration of treatment should be evaluated.

Clinical observations and some basic investigations have suggested that neurotransmitters, such as serotonin, are important in FM. For example, low levels of biogenic amines (22) and high levels of substance P (23) have been found in the cerebrospinal fluid in FM. Abnormalities in imipramine uptake receptors have also been noted (24). Neurohormonal disturbances, including low levels of growth hormone and hypothalamic–pituitary–adrenal axis hypofunction, have recently been reported in FM (25–27).

We expected that FL, a selective serotonin antagonist, might improve certain FM symptoms, such as fatigue and depression. We were surprised that FL caused a significant reduction in FM pain. Despite the proven efficacy of FL and other selective serotonin uptake inhibitors in the treatment of mood disturbances, their efficacy as analgesics has not been established. For example, FL was not better than placebo in the treatment of pain associated with diabetic neuropathy, although AM and desipramine were effective as analgesics (28). We found that the improvement in FM pain resulting from treatment with 20 mg of FL was comparable to that with 25 mg of AM. The level of pain improvement was also similar to that with various tricyclic antidepressants in prior FM clinical trials (1,2).

In the only other double-blind, placebo-controlled study of FL in FM, Wolfe et al found no significant improvement in patient function or tender point counts (11). Eligibility and patient selection criteria were roughly the same in that study as in the present study. In the study by Wolfe et al, patients who received FL showed a significant improvement only in depression and sleep. However, 57% of patients receiving placebo, compared with 29% of those treated with FL, dropped out of that trial. Therefore, the study had inadequate power to evaluate the effectiveness of FL. Furthermore, the mean baseline VAS global score for our patients was higher than that in Wolfe et al's study (66.6 versus 49.8). Thus, our patients may have had a greater severity of FM at baseline.

It is unlikely that the improvements in global well-being and function were primarily related to improvement in mood, since the BDI score did not significantly decrease. Both AM and FL were used in doses that are considered inadequate to treat major depression. Improvement in pain occurred sooner than would be expected if this effect was related to improved mood. Furthermore, we excluded from our study those patients who scored ≥ 18 on the Hamilton Rating Scale, a commonly used cut-off score for major depression. The global improvement seen in our patients may simply have reflected improved sleep, since improved sleep was noted in the patients who were taking each of the active medications. However, prior trials of AM and CY did not find a correlation of FM global response with improvement of the alpha wave intrusion pattern commonly found in FM (5,29).

FL and AM improved the FM symptoms of pain, global well-being, sleep disturbances, and function. The 2 medications in combination were better than either 1 alone. Other drugs and combinations of medications that have different potential effects on the central nervous system and on pain perception should also be tested in the treatment of patients with FM.

ACKNOWLEDGMENT

We thank Kevin Messina for assistance in study coordination and data management.

REFERENCES

1. Carette S, McCain GA, Bell DA, Fam AG: Evaluation of amitriptyline in primary fibrositis: a double-blind, placebo-controlled study. Arthritis Rheum 29:655–659, 1986

2. Goldenberg DL, Felson DT, Dinerman H: A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 29:1371–1377, 1986
3. Jaeschke R, Adachi J, Guyatt G, Keller J, Wong B: Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N-of-1 randomized controlled trials. J Rheumatol 18:447–451, 1991
4. Bennett RM, Gatter RA, Campbell SM, Andrews RP, Clark SR, Scarola JA: A comparison of cyclobenzaprine and placebo in the management of fibrositis: a double-blind controlled study. Arthritis Rheum 31:1535–1542, 1988
5. Reynolds WJ, Moldofsky H, Saskin P, Lue FA: The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. J Rheumatol 18:452–454, 1991
6. Quimby LG, Gratwick GM, Whitney CD, Block SR: A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. J Rheumatol (suppl 16) 19:140–143, 1989
7. Caruso I, Sarzi Puttini PC, Boccassini L, Santandrea S, Locati M, Volpato R, Montrone F, Benvenuti C, Beretta A: Double-blind study of dothiepin versus placebo in the treatment of primary fibromyalgia syndrome. J Int Med Res 15:154–159, 1987
8. Wysenbeek AJ, Mor F, Lurie Y, Weinberger A: Imipramine for the treatment of fibrositis: a therapeutic trial. Ann Rheum Dis 44:752–753, 1985
9. Carette J, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG, Bellamy N, Guimont C: Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia: a randomized, double-blind clinical trial. Arthritis Rheum 37:32–40, 1994
10. Geller SA: Treatment of fibrositis with fluoxetine hydrochloride (Prozac). Am J Med 87:594–595, 1989
11. Wolfe F, Cathey MA, Hawley DJ: A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 23:255–259, 1994
12. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 33:160–172, 1990
13. Burckhardt CS, Clark SR, Bennett RM: The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 18:728–733, 1991
14. Kaplan KH, Goldenberg DL, Galvin-Nadeau M: The impact of a meditation-based stress reduction program on fibromyalgia. Gen Hosp Psychiatry 15:284–289, 1993
15. Senn S: Crossover Trials in Clinical Research. New York, Wiley, 1993
16. Little RJA, Rubin DB: Statistical Analysis with Missing Data. New York, Wiley, 1987
17. SAS Institute, Inc.: SAS/STAT Software. Cary, NC, SAS Institute, Inc., 1989
18. Simms RW, Felson DT, Goldenberg DL: Development of preliminary criteria for response to treatment in fibromyalgia syndrome. J Rheumatol 18:1558–1563, 1991
19. Croft P, Schollum J, Silman A: Population study of tender point counts and pain as evidence of fibromyalgia. BMJ 309:696–699, 1994
20. Urrows S, Affleck G, Tennen H, Higgins P: Unique clinical and psychological correlates of fibromyalgia tender points and joint tenderness in rheumatoid arthritis. Arthritis Rheum 37:1513–1520, 1994
21. Jocobs JWG, Rasker JJ, van der Heide A, Boersma JW, de Blecourt ACE, Griep EN, van Rijswijk MH, Bijlsma JWJ: Lack of correlation between the mean tender point score and self-reported pain in fibromyalgia. Arthritis Care Res 9:105–111, 1996
22. Russell IJ, Vaeroy H, Javors M, Nyberg F: Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 35:550–556, 1992
23. Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, Lopez Y, MacKillip F: Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum 37:1593–1601, 1994
24. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA: Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. J Rheumatol 19:104–109, 1992
25. Bennett RM, Clark SR, Campbell SM, Burckhardt CS: Low levels of somatomedin-C in patients with the fibromyalgia syndrome: a possible link between sleep and muscle pain. Arthritis Rheum 35:1113–1116, 1992
26. Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, Sternberg EM, Gold PW, Chrousos GP, Wilder RL: Hypothalamic–pituitary–adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum 37:1583–1592, 1994
27. Griep EN, Boersma JW, de Kloet ER: Pituitary release of growth hormone and prolactin in primary FS. J Rheumatol 21:2125–2130, 1994
28. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 326:1250–1256, 1992
29. Carette S, Oakson G, Guimont C, Steriade M: Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. Arthritis Rheum 38:1211–1217, 1995