Improvements in Pain Responsiveness in Patients with Fibrositis After Successful Treatment with Amitriptyline

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Abstract. **Thirty-six patients with fibrositis received low dose amitriptyline and placebo in a randomized double blind crossover study lasting 10 weeks. Amitriptyline was associated with significant changes on the outcome measures of pain, tender point sensitivity and patient assessment of well being. Clinically significant improvements for pain and tender point sensitivity and a statistically significant improvement in generalized pain responsiveness were found between patients who reported subjective improvement on amitriptyline and those who felt no change.** (*J Rheumatol 1989;* **(suppl 19) 16:98-103)**

Key Indexing Terms:
PAIN AMITRIPTYLINE TENDER POINTS FIBROSITIS FIBROMYALGIA

It has been shown that patients with fibrositis syndrome are significantly more sensitive to pressure pain stimuli compared to healthy subjects[1]. They are hypervigilant to pain; that is, they display lower than normal pain threshold levels[2]. Increased pain sensitivity has also been reported in other patient populations, e.g., myofascial pain dysfunction syndrome and migraine headache[3,4]. Further, it has been demonstrated in patients with myofascial pain dysfunction syndrome that successful treatment resulted in an elevation of pain threshold towards normal values[3,5]. In myofascial pain dysfunction syndrome, therefore, pain responsiveness may be taken as one indicator of effective treatment.

The adequate treatment of all patients with the diagnosis of fibrositis syndrome is yet to be found. However, Carette and coworkers[6] and others[7,8] have demonstrated that amitriptyline in low doses decreased pain levels, improved sleep quality and improved subjective feelings of well being. As well, statistically but not clinically significant improvements in tender point sensitivity in fibrositis syndrome resulted after treatment with amitriptyline.

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In view of these studies, we examined responsiveness to pain at local tender points in fibrositis syndrome and generalized sensitivity to pain at nontender points and attempted to replicate the clinical results of Carette *et al*[6]. We expected that pain responsiveness would improve after successful treatment with low doses of amitriptyline.

PATIENTS AND METHODS

Patient population. Thirty nine patients participated in the study. They were drawn from the outpatient population of the Rheumatic Diseases Unit of University Hospital, London, ON. The protocol was approved by the Health Sciences Ethics Committee and informed consent was obtained from the patients before they entered the study.

The criteria used for the diagnosis of fibrositis syndrome were those proposed by Smythe and Moldofsky[9] and included each of the following: (a) a widespread muscular aching lasting at least 3 months; (b) a nonrestorative sleep pattern; (c) morning stiffness and fatigue; (d) localized tenderness at 12 or more of 14 specific sites; and (e) normal erythrocyte sedimentation rates, TSH levels and roentgenograms, although age related degenerative changes were permitted.

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 a record was kept of the amount taken. Patients treated with amitriptyline within the previous year and those with a demonstrated hypersensitivity to it were excluded. Patients with a history of urinary retention, glaucoma, ischemic heart disease, cardiac arrythmia or congestive cardiac failure were also excluded from the trial.

Treatment plan and study design. A completely randomized double blind crossover design was employed. Patients were randomly assigned to one of 2 groups. Group 1 received amitriptyline for the first period of 4 weeks, followed by a 2-week washout period, and then a second period of 4 weeks during which time they received a placebo. Group 2 followed the same schedule as group 1 except that they received placebo in the first period and amitriptyline in the second period. Patients received 10 mg amitriptyline daily at bedtime for the first week, 25 mg daily for the second week and 50

mg daily for the final 2 weeks. The amitriptyline was in capsules which were identical to the placebo capsules. In the event of adverse reactions, the drug was discontinued.

Efficacy evaluations. Patients were evaluated at baseline, at the end of 4 weeks, at the end of the washout period (at 6 weeks) and at the end of the trial, at 10 weeks. All evaluations took place in the same environment between the hours of 8 am and 6 pm. An attempt was made to keep the time of evaluation within patients constant across testing sessions. Both subjects and tester were blinded as to treatment group for the duration of the trial. Blinding was broken only at the end of the trial or if the patient decided to withdraw from the trial. One tester took all measurements in the trial.

Pain responsiveness was assessed using a 9 kg dolorimeter which has a rubber tipped head with a surface area of 1.54 cm^2 (Chatillon, Kew Gardens, NY). Three measures of pain responsiveness were employed.

The Total Myalgic Score, which was taken as the sum of the tenderness, measured with the dolorimeter, at 8 predesignated fibrositis tender points. These bilateral points were at (a) the middle of the upper fold of the trapezius, (b) the second costochondral junction, (c) 2 cm distal to the lateral epicondyle, and (d) the medial fat pad of the knee.

Pain threshold. This was taken as the sum of the pain threshold levels taken at 4 predesignated nontender points. These bilateral points were at (a) the middle of the extensor aspect of the forearm with the arm pronated and supported, and (b) the midpoint of the anterior surface of the tibia, with the subject in the supine position and the leg extended and supported. Each of these 4 areas was palpated first by the tester to ensure that they were not spontaneously tender to light pressure before the measures were gathered. No patients reported spontaneous tenderness before testing.

For each of total myalgic scores and pain thresholds, pressure was increased with the dolorimeter at the rate of 1 kg/s and the subject was asked to say "now" at the time when the pressure was "just beginning to feel painful." The order of testing of the points was randomized between patients.

Pain tolerance. Pain tolerance was taken as the sum of the pain tolerance levels from each of the 4 points described for pain threshold. On a separate trial from pain threshold, pressure was increased at the rate of 1 kg/s with the dolorimeter until the subject indicated that he/she was not willing to withstand a further increase in pressure by saying "now." Again, the order of testing was randomized between patients.

The level of Pain Intensity was assessed using the McGill Pain Questionnaire[10]. This instrument, which has been used in many previous studies, consists of 78 words categorized along 20 subscales which each contain between 2 and 6 words. These words are ranked from 0 (no word chosen) to 6 (the highest ranking in a 6 word scale). In this manner, a score of 5 would indicate the 5th highest word on a 6 word scale. Subjects are required to a maximum of 1 word in each subscale.

The 20 subscales are also grouped along 4 dimensions: sensory, affective, evaluative and mixed. For this study, the 4 mixed subscales were omitted. Therefore, 16 subscales were presented in written form to the patient. It is the sum of the ranked values of these 16 subscales which is reported in this study as the Pain Rating Index.

An overall patient subject assessment of global treatment effectiveness was also used. This consisted of a 5 point ordinal scale described by the words (1) worse, (2) unchanged, (3) minimally improved, (4) moderately improved and (5) markedly improved. This scale, which has been used in a previous study[6], was administered on the second and subsequent visits.

Other measures, such as hypochondriasis, depression, anxiety, sickness impact and a daily pain diary were also taken during the study. However, these will not be reported here.

The main research question to be answered in our study was whether pain and pain responsiveness were influenced predictably by the treatment of fibrositis with low dose amitriptyline. It was expected that patients who responded well to treatment would show a significant improvement across the main study variables of pain, total myalgic score, pain threshold and pain tolerance.

Table 1. *Descriptive data of the study population*

Female:Male ratio		8:1
Subjects (no.)		36
Age (yrs)	$\bar{X}$	39.9
	SD	10.2
	Range	24–59
Duration of pain (yrs)	$\bar{X}$	5.1
	SD	4.6

Statistical analysis. A sample size of 35 was calculated to be adequate to test at the 0.05 level with 80% power, estimating a clinically significant improvement in total myalgic score of 50% while taking amitriptyline compared to an improvement of 25% while taking placebo. A dropout rate of 10% was expected.

All data were analyzed on a mainframe computer using the SPSS^x package. Because a predictable effect was expected from all 4 of the main study variables, initial analysis was by repeated measures multivariate analysis of variance (MANOVA) for 2 groups and 4 variables[11]. MANOVA, in this context, is used first to examine the overall effect of a particular treatment on a series of variables that might theoretically be related in a definite manner. It was planned *a priori* that if no significant effect was found for the group (i.e., placebo or amitriptyline first), then the data of the 2 groups would be collapsed into 2 time related periods, (a) amitriptyline and (b) placebo. Subsequent analyses were by analysis of variance and then by *post hoc* Tukey's HSD test[12]. Proportions were tested by the χ^2 test.

RESULTS

Thirty-six patients completed the trial. Nineteen received amitriptyline first and 17 received placebo first. There were 32 females and 4 males with a mean age of 39.9 years (Table 1). Two males were in each group. Three patients withdrew from the trial: 2 withdrew for reasons believed to be drug related drowsiness (1 in the amitriptyline first group, 1 placebo first group) and 1 withdrew for insufficient therapeutic effect (placebo first group). Using MANOVA, no significant effect was found for either group (Hotelling's t (4df) = 0.305, $p > 0.05$) or when grouped by time ($p > 0.05$). However, a significant effect was found for time (evaluation session) ($p < 0.01$) (Tables 2 and 3). Significant Pearson product moment correlations were found between all the measures of pain responsiveness taken at baseline (all $p < 0.01$) (Table 4). As well, the level of present pain was significantly correlated negatively with pain tolerance ($p < 0.05$). The only other significant correlation was between age and length of time in pain ($p < 0.05$).

Because no significant effect was found for either group, the data from the 2 periods were collapsed into 2 groups based on the treatment periods. This gives 2 new groups, 1 group of amitriptyline (based on the values when each of the subjects was taking amitriptyline) and one of placebo (based on the values when all the subjects were taking placebo).

Next, taking all the subjects together, univariate analysis of variance with repeated measures were performed on the

Table 2. *Multivariate analysis of variance*

	Value	Approx F	Hypoth df	Error df	Sig of F
Time Hotelling's t	0.5179	3.69	12.00	267.00	0.001
Group by time Hotelling's t	0.1258	0.89	12.00	267.00	0.550

Table 3. Univariate F tests for time with (3,102) df

Variable	Hypoth SS	Error SS	Hypoth MS	Error df	F	Sig of F
Total myalgic score	952.69	2836.50	317.56	31.51	10.07	0.001
Pain rating	354.06	2511.03	118.02	27.90	4.23	0.008
Pain threshold	152.69	2411.00	50.89	28.28	1.90	0.135
Pain tolerance	276.29	8239.23	92.09	91.54	1.00	0.394

Table 4. *Pearson correlations of the main study variables*

	Age	Length	Pain Rating	Total Myalgic Score	Pain Threshold	Pain Tolerance
Age	—					
Length	0.36*	—				
Pain rating	−0.19	−0.17	—			
Total myalgic score	0.02	0.02	−0.23	—		
Pain threshold	0.00	−0.08	−0.23	0.70†	—	
Pain tolerance	−0.03	0.19	−0.44*	0.61†	0.66†	—

*$p < 0.05$.
†$p < 0.01$.

main study variables (Table 3). Significant effects were found over time for the total myalgic score ($p < 0.001$) and the pain rating ($p < 0.01$). No significant effects were found for either of pain threshold or pain tolerance. Within the total myalgic score, *post hoc* Tukey's contrasts showed that the significant difference lay between the total myalgic score post amitriptyline and all other times (HSD = 3.74, $p < 0.05$) (Figure 1). The total myalgic score was significantly higher (i.e., they were less sensitive at the tender points) in the post amitriptyline testing sesion than at any other time. No other contrasts were significant. For the pain rating, it was found that pain levels were significantly lower after the amitriptyline period than at any other time (HSD = 3.54, $p < 0.05$).

This improvement in the pain rating and total myalgic score is reflected in the ratings of global treatment efficacy by the patients (Table 5). It can be seen that significantly more patients report improvement after amitriptyline than after placebo ($\chi^2 = 21.6$, $p < 0.001$). Eight patients (22%) reported some improvement after placebo.

The data were next reanalyzed by dividing the subjects into an "improved" group and an "unchanged" group, based on their ratings on global treatment efficacy after the amitriptyline period. Patients who reported themselves as being either moderately or markedly improved were classed as improved (n = 20) and those who reported themselves as being either worse, unchanged or mildly improved were classed as unchanged (n = 16). No significant differences were found between the 2 new subgroups in any of the demographic variables of age, sex ratio, or length of time of symptoms.

Table 5. *Patient ratings of global treatment efficacy after amitriptyline and placebo*

	After Amitriptyline (No.)	After Placebo (No.)
Rating		
Worse	3	9
Unchanged	6	20
Minimally improved	7	5
Moderately improved	12	2
Markedly improved	8	1

Table 6. *Multivariate analysis of variance for time in the unchanged group*

	Value	Approx F	Hypoth df	Error df	Sig of F
Hotelling's t	1.082	1.11	24.00	84.00	0.353

Table 7. *Multivariate analysis of variance for time in the improved group*

	Value	Approx F	Hypoth df	Error df	Sig of F
Hotelling's t	2.084	3.96	24.00	137.00	0.001

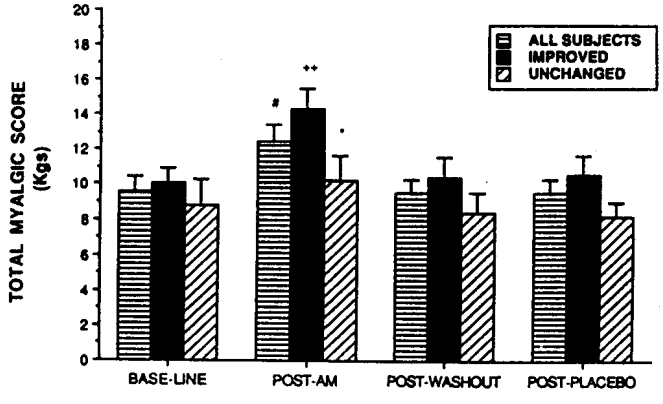

Fig. 1. #, $p < 0.05$ for all subjects post amitriptyline against all other times; *, $p < 0.05$ between the improved and unchanged groups after the amitriptyline period; ++, $p < 0.01$ for the improved group against all other times after the amitriptyline period. The error bars indicate 1 standard error of the mean.

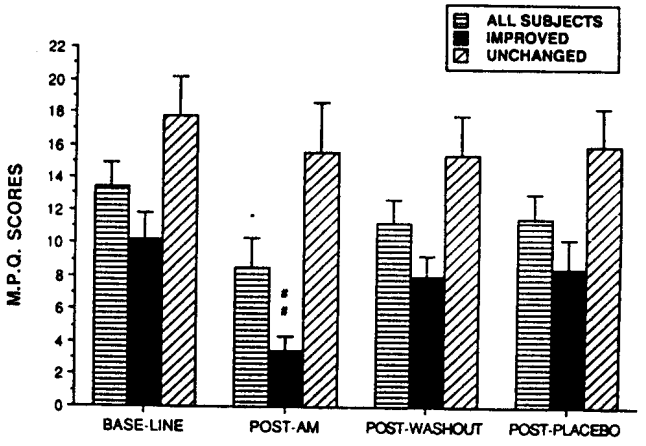

Fig. 2. *, $p < 0.05$ for all subjects post amitriptyline against all other times; ##, $p < 0.01$ between the improved and unchanged groups after the amitriptyline period; ++, $p < 0.01$ for the improved group against all other times after the amitriptyline period. The error bars indicate 1 standard error of the mean.

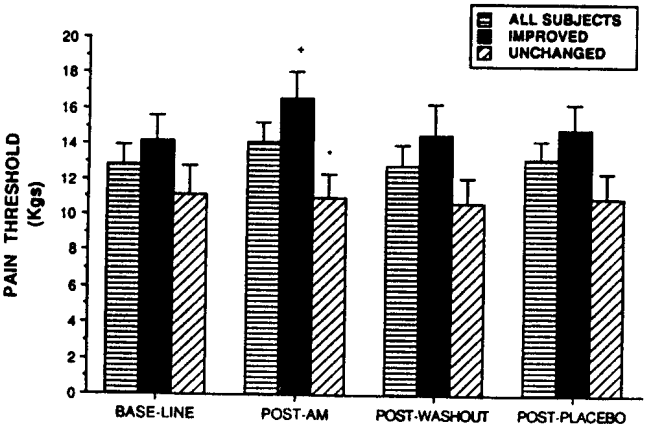

Fig. 3. +, $p < 0.05$ within the improved group after the amitriptyline period against baseline; *, $p < 0.05$ between the improved and unchanged groups after the amitriptyline period. The error bars indicate 1 standard error of the mean.

For the unchanged group, taking the 4 variables together, MANOVA showed no significant effect across time (Table 6, Figures 1, 2 and 3). None of the 4 variables changed across any time period. For the improved group, taking all the variables together, a highly significant effect was found for time ($p < 0.001$) (Table 7). For the individual variables, a highly significant effect was found for time within the total myalgic score and the pain rating ($p < 0.001$) (Table 8, Figures 1 and 2). Pain threshold also showed a mildly significant effect for time ($p < 0.05$) (Figure 3). No significant effects were found for pain tolerance across time.

Post hoc contrasts showed that total myalgic score was significantly higher after amitriptyline than at any other time (HSD = 4.97, $p < 0.01$). No other contrasts were significant. The pain rating was significantly lower after amitriptyline than at any other time (HSD = 4.36, $p < 0.01$). No other contrasts were significant. Pain threshold was significantly lower after amitriptyline than at the baseline period only (HSD = 4.34, $p < 0.05$). After amitriptyline, there was a significant difference between the groups ($t = 2.01$, $p < 0.05$). Total myalgic score was 36% higher after the amitriptyline period when compared to the score after the placebo period (14.32 kg vs 10.51 kg). The pain rating was 64% lower after the amitriptyline period when compared to the score after the placebo period (3.42 against 8.42).

Finally, in examining differences across the improved and unchanged groups, there was a significant difference at base-

Table 8. *Univariate analysis of variance for the main study variables in the improved group*

Variable	Hypoth SS	Error SS	Hypoth MS	Error df	F	Sig of F
TMS	1111.44	1815.71	370.48	33.62	11.10	0.001
PRI	476.56	1317.18	158.85	24.39	6.51	0.001
PTH	269.54	1388.43	89.84	25.71	3.49	0.022
PTOL	52.09	4767.38	17.36	88.28	0.19	0.898

line in the pain rating between the 2 groups ($t(34) = 2.59$, $p < 0.05$). This significant difference persisted across all other testing times and increased only after the amitriptyline period. At that time, the improved group was significantly lower on the pain rating at the 0.01 level ($t = 3.82$) than the unchanged group. Therefore, the level of perceived pain was significantly lower at the time of entry into the study and across all other times in those patients who rated themselves as either moderately or markedly improved after the amitriptyline treatment period.

DISCUSSION

The population studied was largely one of women in early middle age who had been experiencing pain for about 5 years, similar to previous studies of patients with fibrositis syndrome[6,7]. The main purpose of our study was to examine the effect of low dose amitriptyline on 4 pain related variables in patients with fibrositis. Taking all the variables together, a significant effect was present across the 2 treatment periods. However, most of this effect came from only 2 variables, the total myalgic score and the level of experienced pain. Pain decreased and the total myalgic score increased only after treatment with amitriptyline, after which the values of these 2 variables returned to baseline levels. These data are in agreement with Carette, *et al*[6] and other studies with amitriptyline[7,8].

Of more interest are the results that emerged after the creation of the 2 subgroups of patients, who were classified as being unchanged or improved on the basis of their response to categorical scale of global treatment efficacy. Fifty-five percent of the patients considered themselves to be either moderately or markedly improved after the amitriptyline treatment period, compared to 22% after the placebo period. No significant differences were found in any of the variables for the unchanged group at any testing session.

For the improved group, taking all the variables together, a highly significant effect was found over the 4 testing sessions. It was found that the total myalgic score was improved significantly only after the active treatment period, i.e., the tender points seen in fibrositis syndrome became less responsive to pressure. This improvement was both statistically and clinically significant. The over 30% change in total myalgic score falls within recent clinical guidelines for clinically significant changes in fibrositis[13].

The improvement in total myalgic score was mirrored by a statistically and clinically significant decrease in pain scores after the amitriptyline treatment period. For each total myalgic score and pain rating, the period after amitriptyline was significantly different from all other times, which implies that the 2 week washout period between the treatment periods was adequate. More important than this, however, is the fact that the total myalgic score changed quickly and in a predictable manner within the group of patients that responded well to treatment. These data from the total myalgic score are of great importance in fibrositis due to the lack of any other objective signs in this condition which can be used either diagnostically or in the assessment of treatment efficacy.

Pain threshold values also improved after the amitriptyline treatment period, although not with the same magnitude as either pain levels or total myalgic score. This change in pain threshold signifies that the patients in the improved group were less responsive generally to painful pressure. A similar response has been reported in other patient groups[3,5,14] in response to successful treatment. The term hypervigilance has previously been used to describe patients with fibrositis syndrome[1], implying that they are more attentive to a specific perceptual experience such as pain. The data from our study support that viewpoint. However, it also implies that part, or all, of this hypervigilance is founded on altered perceptual processing. Our data do not completely support that position, due to the presence of highly significant positive correlations between the variables of pain responsiveness, a finding that is common in other studies[17]. As total myalgic score improves, so does pain threshold.

It is possible, therefore, that the previously reported generalized increase in pain sensitivity[1] is due to underlying physiological changes—not yet fully identified—in fibrositis. Pain threshold levels are generally taken to be more reflective of peripheral sensory processes[15]. Pain tolerance levels, however, are presumed to be more influenced by higher level psychological processes[15]. In this study, no change was found in pain tolerance levels over time. These data imply that amitriptyline may have influenced peripheral sensory processes (threshold) but not higher level psychological processes (tolerance). Therefore, if hypervigilance exists in these patients, it may be more influenced by peripheral and neurochemical factors than psychological ones. Finally, patients who eventually responded well to amitriptyline re-

ported lower pain levels at the inception of the study than those who did not respond. Those patients who were less severely affected or those whose level of perceived pain was lower responded best to treatment. This has previously been reported with myofascial pain dysfunction syndrome patients[18].

Although the results of our study support the expectations of improvement in the pain related variables, some caution must be used in assessing their generalizability. The sample size was initially adequate for the proposed study design. But, the within group numbers were small after the creation of the subgroups. However, the consistency and size of the effects within the improved group would seem to indicate that the sample size may have been adequate to draw conclusions. Further, the length of the amitriptyline treatment period was short, but long enough to produce results. This satisfied the purpose of our study. However, since fibrositis is a chronic condition, studies with much longer treatment periods now seem to be appropriate. This is especially important in the light of the findings that levels of pain and the sensitivity of the tender points returned rapidly to baseline levels after withdrawal of amitriptyline.

Despite these limitations, the main findings of our study are important because they demonstrate, in common with other patient populations[19,20], that the use of the pressure dolorimeter is an efficient way of evaluating painful symptoms at tender points and nontender points and that these measures are responsive to change. This is significant in a condition in which there are, as yet, no firm objective measures of disease activity.

REFERENCES

1. Scudds RA, Rollman GB, Harth M, McCain GA: Pain perception and personality measures as discriminators in the classification of fibrositis. *J Rheumatol 1987*;14:563–9.
2. Chapman CR: Pain: The perception of noxious events. In: Sternbach RA, ed. *The Psychology of Pain*. New York: Raven Press, 1978:169–203.
3. Malow RM, Grim L, Olson RE: Differences in pain perception between myofascial pain dysfunction syndrome patients and normal subjects: A signal detection analysis. *J Psychosom Res 1980*;24:303–9.
4. Nattero G, Allais G, Biale L, De Lorenzo, C: Cutaneous pain thresholds in classic and common migraine. *Pan Minerva Med: 1987*;29:83–5.
5. Malow RM, Olson RE: Changes in pain perception after treatment for chronic pain. *Pain 1981*;11:65–72.
6. Carette S, McCain GA, Bell DA, Fam AG: Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. *Arthritis Rheum 1986*;29:655–9.
7. Goldenberg DL, Felson DT, Dinerman H: A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum 1986*;29:1371–6.
8. Connolly RG: Treatment of fibromyositis with fluphenazine and amitriptyline: a preliminary report. *Del Med J 1981*;53:189–91.
9. Smythe HA, Moldofsky H: Two contributions to understanding of the "fibrositis" syndrome. *Bull Rheum Dis 1977*;28:928–31.
10. Melzack R: The McGill pain questionnaire: Major properties and scoring methods. *Pain 1975*;1:277–99.
11. Marascuilo LA, Levin JR: *Multivariate Statistics in the Social Sciences*. Monterey, California: Brooks/Cole, 1983.
12. Winer BJ: *Statistical Principles in Experimental Design*. New York: McGraw-Hill, 1962.
13. Simms RW, Felson DT, Goldenberg DL: Criteria for response to treatment in fibromyalgia. *Arthritis Rheum 1988*;31:C117.
14. Philips HC, Hunter M: A laboratory technique for the assessment of pain behavior. *J Behav Med 1982*;5:283–94.
15. Wolff BB: Behavioral measurement of human pain. In: Sternbach RA, ed. *The Psychology of Pain*, 2nd ed, New York: Raven Press, 1986: 121–51.
16. Rollman GB: Measurement of experimental pain in chronic pain patients: Methodological and individual factors. In: Melzack R, ed. *Pain Measurement and Assessment*. New York: Raven Press, 1983:265–72.
17. O'Driscoll SL, Jayson MIV: The clinical significance of pain threshold measurements. *Rheumatol Rehabil 1982*;21:31–5.
18. Salter M, Brooke RI, Merskey H: Temporomandibular pain and dysfunction syndrome: The relationship of clinical and psychological data to outcome. *J Behav Med 1986*;9:97–109.
19. Fischer AA: Clinical use of the tissue compliance meter for documentation of soft tissue pathology. *Clin J Pain 1987*;3:23–30.
20. Jaeger B, Reeves JL: Changes in myofascial trigger point sensitivity following passive stretch. *J Orth Med 1987*;69–71.