The Journal of Rheumatology

The Journal of Rheumatology Volume 32, no. 10

Efficacy of milnacipran in patients with fibromyalgia.

R Michael Gendreau, Michael D Thorn, Judy F Gendreau, Jay D Kranzler, Saulo Ribeiro, Richard H Gracely, David A Williams, Philip J Mease, Samuel A McLean and Daniel J Clauw

J Rheumatol 2005;32;1975-1985
http://www.jrheum.org/content/32/10/1975

Efficacy of Milnacipran in Patients with Fibromyalgia

R. MICHAEL GENDREAU, MICHAEL D. THORN, JUDY F. GENDREAU, JAY D. KRANZLER, SAULO RIBEIRO, RICHARD H. GRACELY, DAVID A. WILLIAMS, PHILIP J. MEASE, SAMUEL A. McLEAN, and DANIEL J. CLAUW

ABSTRACT. ***Objective.*** Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread pain, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic antidepressants (TCA). Milnacipran, a nontricyclic compound that inhibits the reuptake of both serotonin and norepinephrine, may provide many of the beneficial effects of TCA with a superior side effect profile.

Methods. One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the target milnacipran dose of 200 mg.

Results. The primary endpoint was reduction of pain. Both the once- and twice-daily groups showed statistically significant improvements in pain, as well as improvements in global well being, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid depression, but placebo response rates were considerably higher in depressed patients, leading to significantly greater overall efficacy in the nondepressed group.

Conclusion. In this Phase II study, milnacipran led to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated. (J Rheumatol 2005;32:1975–85)

Key Indexing Terms:
FIBROMYALGIA PAIN MILNACIPRAN ANTIDEPRESSANT ANALGESIC

Fibromyalgia (FM), also known as fibromyalgia syndrome, is a common systemic disorder estimated to affect 2% to 4% of the population, second in prevalence in rheumatologic practice to osteoarthritis[1,2]. While considerable disagreement exists regarding its etiology and diagnosis, there is increasing evidence and acceptance that FM is indeed a medical problem reflecting a generalized heightened perception of sensory stimuli leading to a condition of chronic, widespread pain[3,4]. There has also been a parallel recognition that common somatic syndromes such as irritable bowel syndrome, tension and migraine headache, and temporomandibular syndrome share overlapping symptom expression and underlying mechanisms with FM[5-8].

In 1990, the American College of Rheumatology (ACR) established classification criteria that have standardized research of FM[1]. These criteria require that an individual have both chronic widespread pain involving the axial skeleton and all 4 quadrants of the body as well as the presence of 11 of 18 tender points on examination[1]. Although pain and tenderness are the defining features of this illness, individuals who fulfill these criteria commonly suffer a variety of other symptoms including fatigue, sleep disturbances, migraine or tension headaches, irritable bowel symptoms, and changes in urinary frequency. Although there is controversy about the terms used to describe this constellation of symptoms and whether these are "real diseases," they are extremely common and in many cases are refractory to presently available treatments[3].

A broad array of medications has been used to treat FM, including antidepressants, anticonvulsants, antispasticity agents, anxiolytics, sedatives, and opioids, with varying degrees of success[9]. Nonsteroidal antiinflammatory drugs (NSAID) and acetaminophen have also commonly been used, although there is little evidence of peripheral damage or inflammation in FM[10,11]. Unfortunately, while there are many potential medication options, few pragmatic clinical trials have been performed to inform clinician and patient decision-making. That there are no drugs currently approved

From Cypress Biosciences, San Diego, California; and the Chronic Pain and Fatigue Research Center, Division of Rheumatology, Department of Medicine, University of Michigan, Ann Arbor, Michigan, USA.

Supported by Cypress Biosciences, San Diego, California. Drs. M. Gendreau, J. Gendreau, and J. Kranzler are employees of Cypress Biosciences. Drs. Clauw, Gracely, and Williams are paid consultants for and shareholders in Cypress Biosciences. Drs. Mease and Thorn are consultants for Cypress Biosciences.

R.M. Gendreau, MD, PhD; J.F. Gendreau, MD; J.D. Kranzler, MD, PhD, Cypress Biosciences; M.D. Thorn, DrPH, Statistical Resources, Inc., Chapel Hill, NC; S. Ribeiro, MD, Department of Psychiatry, University of Michigan; R.H. Gracely, PhD, Chronic Pain and Fatigue Research Center, University of Michigan; D.A. Williams, PhD, Chronic Pain and Fatigue Research Center, Division of Rheumatology, Department of Medicine, University of Michigan; P.J. Mease, MD, Seattle Rheumatology Associates, Seattle, WA; S.A. McLean, MD, Chronic Pain and Fatigue Research Center, Department of Emergency Medicine, University of Michigan; D.J. Clauw, MD, Chronic Pain and Fatigue Research Center, Division of Rheumatology, Department of Medicine, University of Michigan.

Address reprint requests to Dr. R.M. Gendreau, Cypress Biosciences, 4350 Executive Drive, Suite 325, San Diego, CA 92121.
E-mail: mgendreau1@cypressbio.com

Accepted for publication May 30, 2005.

by the US Food and Drug Administration for use in FM emphasizes the urgent need for more clinical trials of promising medications.

Of all medication options in FM, tricyclic antidepressants (TCA) have the most evidence for treatment efficacy, and are the cornerstone of most treatment paradigms[12]. These medications block the reuptake of both serotonin and norepinephrine[13], and are believed to decrease pain by modulating pain processing in the spinal cord[14]. Because TCA have many potential side effects, selective serotonin reuptake inhibitors (e.g. fluoxetine) have been tried in FM, but have not been found to be effective pain medications[15,16]. This has led to the belief that the blockade of both serotonin and norepinephrine (dual reuptake inhibition) is needed for efficiacy in pain reduction, a belief supported by the positive results of phase II studies of duloxetine in FM[17].

Milnacipran is a well characterized small molecule that, in a manner similar to duloxetine, functions as a selective reuptake inhibitor of both serotonin and noradrenaline[18]. However, milnacipran is unique in its preference toward norepinephrine reuptake inhibition, and also binds to NMDA receptors[18]. Unlike the TCA, milnacipran does not interact with histaminergic or muscarinic receptors or sodium channels, and thus lacks many side effects of TCA[19]. The safety of milnacipran has been established in clinical trials and in its use as an approved antidepressant in 30 countries. However, no randomized clinical trials have evaluated the analgesic properties of milnacipran.

We evaluated the overall analgesic efficacy and safety of milnacipran in a sample of patients with FM. The primary endpoint was improvement in pain. Secondary objectives included assessment of the influence of dosing strategy (BID versus QD) and the effect of milnacipran on other symptoms of FM including fatigue, mood, physical function, and sleep disturbances.

This report includes data republished with permission from a report entitled, "A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia" (Hum Psychopharmacol 2004;1:S27-35. Copyright John Wiley and Sons)[20].

MATERIALS AND METHODS

Participants. Fourteen sites with extensive FM experience participated in the trial. The outpatient protocol for 12 sites was approved by a central institutional review board (Western Institutional Review Board). The remaining 2 centers were approved by local boards.

The screening assessment included a medical and psychological history, physical and laboratory examinations, and the Mini International Neuropsychiatric Interview (MINI)[21]. Patients were eligible for the study if they were aged between 18 and 70 years, met the ACR 1990 research criteria for FM, and reported a pain score ≥ 10 on a 20-point logarithmic pain scale (Gracely scale) at the time of the baseline assessment. In addition, patients had to be willing to use a contraceptive (if female) and to withdraw from all central nervous system-active therapies. Exclusion criteria included psychosis; active suicidality; alcohol or substance abuse; concurrent autoimmune, inflammatory, infectious, or malignant disorder; known sleep apnea or prostatic hypertrophy; and abnormal baseline liver or kidney function tests. After giving informed consent, patients taking antidepressants, antiepileptics, centrally-acting muscle relaxants, hypnotics, and opioids and their derivatives were required to discontinue their medications over a period of one to 4 weeks. Stable doses of NSAID, aspirin, and acetaminophen were allowed during the study.

Study design and procedures. The study was a 3-month, randomized, double-blind comparison of milnacipran to placebo. Patients were allowed to escalate up to 200 mg milnacipran daily, or to their maximum tolerated dose. In addition, patients were randomized to receive their study drug either in one daily dose (QD) or 2 divided doses (BID). As summarized in Figure 1, the study design involved 4 phases: screening and washout, baseline assessment, dose escalation, and stable-dose phase. This was a short term, acute discontinuation trial; subjects were not followed after the trial concluded, and the data presented cannot be extrapolated to longterm effects.

For most patients, the screening and washout phase (if necessary) lasted for 2 weeks prior to randomization into a study group. Patients who were taking fluoxetine upon enrollment completed a washout phase of 4 weeks before being randomized into a study group. Per study guidelines, data collection began at the start of the baseline phase, after study subjects completed the washout phase. During the 2-week baseline phase, patients recorded their level of pain on electronic diaries (e-diaries). During the dose escalation phase, patients began taking study medication after being randomized to one of three arms. Weekly dose increased if the patient did not experience dose limiting side effects. If side effects developed, dose was reduced to that which was tolerated previously. The stable-dose phase was an 8-week period during which patients took medications at the final dose achieved (either 200 mg or the maximum tolerated dose).

After 2 weeks of baseline assessments, patients entered the third phase. Randomized assignment allocated each patient to one of 3 study arms: placebo, single daily dosing of milnacipran (QD), or twice daily divided dosing of milnacipran (BID). Randomization was performed by an independent contract research organization that generated randomization assignments and packaged drug in a block size of 8, in a ratio of 3:3:2 for QD:BID:placebo. An automated telephone response system operated by the same firm performed the patient treatment assignments using the previously generated randomization table. QD patients received milnacipran as a single dose taken with the morning meal and a placebo with the evening meal. BID patients received milnacipran as a divided dose with the morning and evening meals. Placebo-treated patients received morning and evening placebo capsules. All capsules were visually identical, and patients and investigators remained blinded to patients' treatment allocation. At the beginning of the escalation phase, all patients were instructed to take capsules with morning and evening meals for the first week, after which they should telephone the study center to report dose-limiting side effects (see Figure 1). At each telephone call, the center advised them to maintain the current dose, discontinue from the trial, or escalate to the next higher dose. Patients not experiencing dose-limiting toxicity continued escalating for 3 weeks until they reached a target dose of 200 mg daily, either once or twice daily, or placebo as randomized. Patients who could not tolerate dose escalation maintained the maximum tolerated dose of 25 mg, 50 mg, or 100 mg for the remainder of their 12 weeks of treatment. Final efficacy assessments were made at the termination visit, and the study medication was discontinued following 12 weeks of drug treatment.

Blinding was rigorously maintained, as all patients took capsules morning and evening that were visually identical. There were no assessments or trial procedures that might have led to accidental unblinding.

Patient-reported outcome measures. Patients reported outcomes during the baseline and remaining study phases using multiple domains and methods. Three scales were used to assess pain: the Short-Form McGill Pain Questionnaire[22], the visual analog scale (VAS), and an Anchored Logarithmic Scale developed by Gracely and Kwilosz[23]. The Short-Form McGill Pain Questionnaire is a commonly used pain scale that can be used to assess different components of the experience of pain[22]. The VAS con-

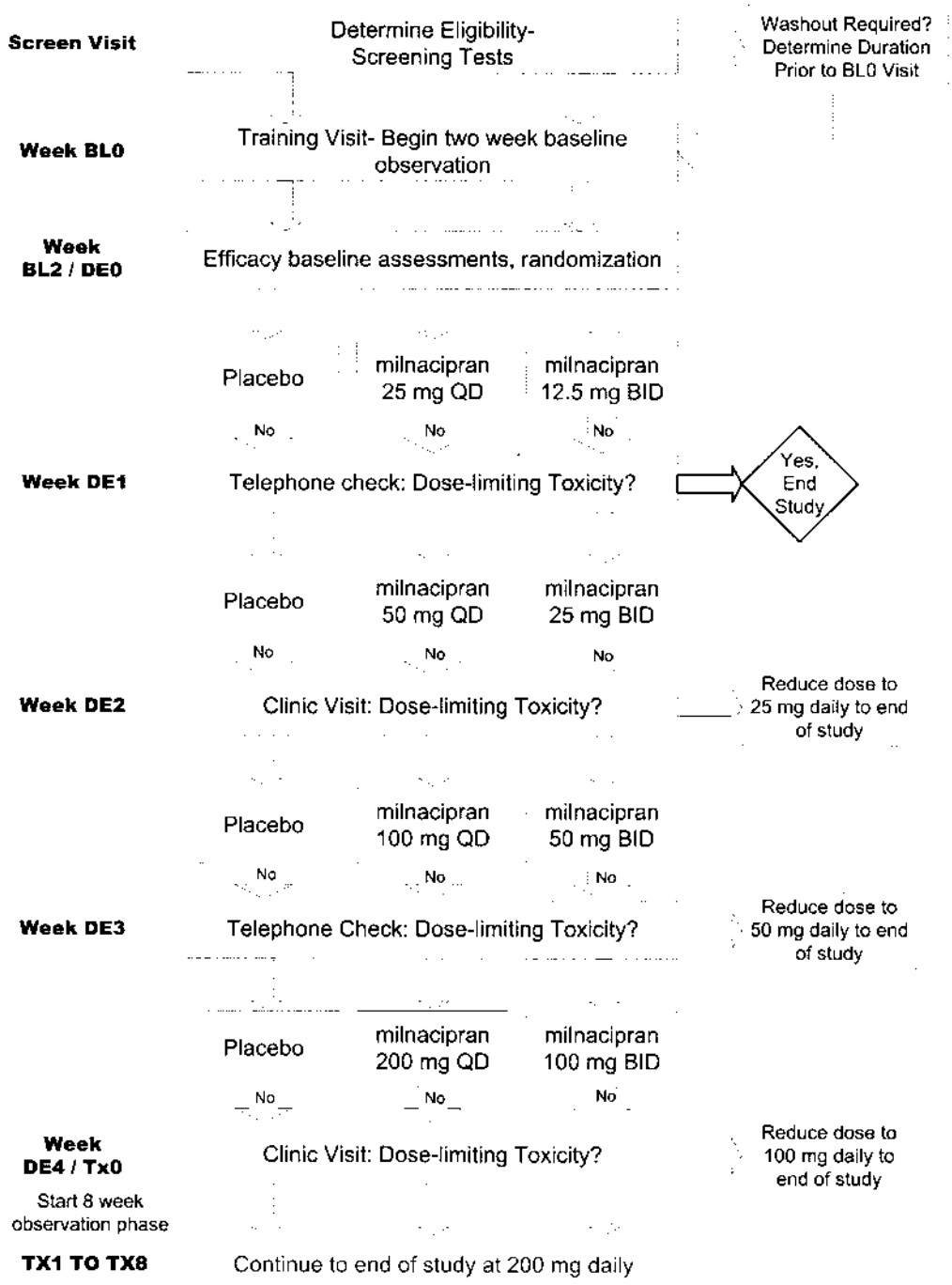

Figure 1. The schedule of milnacipran dosing and study activities. BID: twice daily dosing, QD: once daily dosing, BL: baseline phase, DE: dose escalation phase, TX: treatment phase, or stable-dose phase.

sisted of a simple 100 mm line with endpoints of "no pain" and "very severe pain" on which patients indicated symptom intensity. The Gracely scale was developed to account for the inherent logarithmic expression of many sensory responses. Like the VAS, the Gracely scale uses descriptive anchors spaced along the length of the scale. However, the Gracely scale allows one to measure changes in intensity over 2 logs, i.e., a 100-fold change in intensity. It is estimated that a decrease in 3.3 units in the Gracely scale corresponds to a 30% decrease in pain scores as measured by standard linear VAS, and 4 units in the Gracely scale corresponds to 50% decrease (unpublished observations).

Palm© based electronic diaries (e-diaries) were provided to all patients for the length of the study for the purpose of recording symptoms on a "real-time" basis. Patients were asked to rate their pain using the Gracely scale every morning (24-hour recall interval), every week (7-day recall interval), and in response to 4 to 6 prompts given randomly interspersed over the waking hours. These prompts were initiated by a sound cue from the diary, which could be terminated by entering a value for pain and/or by silencing the device. Real-time e-diaries were used because they eliminate

the bias involved in asking individuals to recall symptoms, and they improve compliance by prompting and time-date stamping each response[24]. Therefore, pain measures obtained from e-diaries were chosen to be the primary dependent variable for the measurement of pain improvement. In addition, patients also completed traditional paper assessments of pain and other measures at their monthly clinic visits.

At the end of the study, each patient was asked to complete the Patient Clinical Global Impression of Change, with queries about the status of his/her FM compared to the baseline assessment. Patients were asked to rate the change in their condition on a scale of 1 to 7, where 1 was "very much improved," 4 was "unchanged," and 7 was "very much worse." Additional assessments included the Fibromyalgia Impact Questionnaire (FIQ)[25], the Medical Outcomes Study Short Form-36 (SF-36)[26], the Jenkins sleep scale[27], and the Arizona Sexual Experiences Scale (ASEX)[28]. Sleep quality and quantity and quality of life were assessed both by e-diaries and by paper inventories. Adverse events and vital signs (temperature, standing and supine blood pressure, and pulse rates) were reported during monthly clinic visits.

Statistical analysis. The primary efficacy measure was the change of average daily pain scores recorded in the e-diary, comparing the final 2 weeks of the trial to the 2-week baseline period. A weekly average pain score was also calculated for each patient using the random-prompt pain score report, the daily recall pain score report, and the weekly recall diary pain score report. In addition to assessing the mean reduction in pain by treatment group, a binary responder analysis (using both a 30% and 50% reduction in pain as a definition of response) was also performed[29].

In an attempt to establish preexisting signs and symptoms, an FM signs and symptoms inventory was collected at the screening visit. Adverse events reported by study site were translated to preferred terms using a MedDRA dictionary[30]. Each individual adverse event was counted only once on the basis of the maximum intensity recorded, regardless of the number of times the patient reported the event.

Sample size calculations were performed assuming the 3:3:2 treatment allocation ratio, and assuming that roughly 50% of patients randomized to a milnacipran arm would escalate to the high-dose level. For planning purposes, the projected mean change in weekly average pain scores (calculated using either the daily or weekly pain score recorded on the e-diary) over baseline was assumed to be –20% for milnacipran and –4% for placebo. Last observation carried forward coupled with an intent-to-treat approach was used in all analyses other than the completer analyses. In the results, completer analyses are explicitly identified when performed. Continuous variables are analyzed with Student's t test while categorical endpoints are analyzed with Fisher's exact test. Nominal p values are displayed — each statistical hypothesis is assumed to be independent.

RESULTS

Study patients and demographics. A total of 184 patients were screened for inclusion in the study. Of these, 125 patients were enrolled in the study between March 20, 2002, and December 10, 2002, and then randomized to one of 3 treatment groups: milnacipran QD (46 patients), milnacipran BID (51 patients), or placebo (28 patients). Patient demographics are summarized in Table 1.

Table 1 indicates that subject demographics were similar between groups, with the exception of the prevalence of comorbid depression. Mean ages were similar among treatment groups, ranging from 46.2 to 48.0 years. The majority of patients in each treatment group were female (96% to 98%) and Caucasian (79% to 89%). The mean duration of FM ranged from 3.8 to 4.3 years among the 3 treatment groups. Most patients had experienced multiple treatment modalities prior to enrollment in the study, the most common being exercise (62%), hot-cold packs (60%), massage (50%), physical therapy or rehabilitation (34%), chiropractic treatment (30%), dietary changes (26%), and acupuncture and meditation (18% each). Eleven percent (11%) of patients had received psychotherapy, 9% stress management, and 5% psychiatric treatments.

Compliance and early terminations. Patient disposition is summarized in Figure 2. Seventy-two percent of enrolled patients completed the study, with no significant differences in dropout rates among the 3 groups (30.4%, 27.5%, and 25.0% in the milnacipran QD, milnacipran BID, and placebo groups, respectively). The most frequent reasons for discontinuation in the overall population were adverse events (14.4%) followed by therapeutic failure (8.8%; see below for detailed adverse event data). Among individuals who completed the trial, 95% of placebo, 81% of QD, and 92% of BID participants achieved dose escalation to the maximum dose of 200 mg. The mean daily dose of milnacipran was 174 mg in the QD participant group and 191 mg in the BID group.

Efficacy results: pain. As described above, information regarding patients' pain experience was collected using both electronic, real-time assessments and more traditional written recall measures. The primary outcome measure chosen *a priori* was the 2-week average daily pain score collected from the e-diary morning report. Secondary pain outcomes included changes in weekly pain score collected electronically, daily and weekly recall paper VAS and Gracely scales, and the McGill Present Pain Score (Table 2).

Binary responder analyses were also performed; these analyses classify patients into dichotomous groups of "pain responders" or "nonresponders" and were designed to detect clinically meaningful differences rather than merely statistically significant changes. However, such groupings depend on the use of potentially contentious criteria for determining responder threshold, and partial responses can be missed in the analysis if the threshold is set too high. In this trial, 2 different methods were used to define "pain responders": a 30% improvement in pain score and a 50% improvement in pain score over baseline. As described above, for Gracely scale measurements, a decrease of $\geq$ 3.3 units defined a 30% "responder," and a decrease of $\geq$ 4 units defined a 50% "responder."

As shown in Table 2, BID milnacipran was a more effective analgesic than QD milnacipran. Improvements in pain reached statistical significance for BID milnacipran on 9 of the 13 pain measures collected, whereas QD milnacipran results reached significance on none of the measures. Results also suggested that pain measures with longer recall (i.e., weekly electronic diary vs daily electronic diary) showed more significant improvements than measures collected in real-time or with shorter recall intervals.

Because we anticipated a differential response to therapy

Table 1. Demographics for patients receiving placebo or milnacipran dosed once daily (QD) or twice daily (BID).

Characteristic	Milnacipran BID, n = 51	Milnacipran QD, n = 46	Placebo, n = 28	Total, n = 125
Age, yrs				
Mean	47.4	46.2	48.0	47.0
SD	11.6	12.2	8.4	11.1
Minimum/maximum	20.0/68.0	19.0/69.0	24.0/63.0	19.0/69.0
Sex (%)				
Male	1 (2)	1 (2)	1 (4)	3 (2)
Female	50 (98)	45 (98)	27 (96)	122 (98)
Race (%)				
Caucasian	42 (82)	41 (89)	22 (79)	105 (84)
African American	3 (6)	1 (2)	1 (4)	5 (4)
Hispanic	5 (10)	4 (9)	3 (11)	12 (10)
Asian	0 (0)	0 (0)	1 (4)	1 (1)
Other	1 (2)	0 (0)	1 (4)	2 (2)
Duration of FM, yrs since diagnosis				
Mean	4.0	4.3	3.8	4.1
SD	3.8	4.8	3.7	4.2
Minimum/maximum	0.1/18.0	0.1/21.3	0.1/12.2	0.1/21.3
Comorbid depression (%)	8 (16)	3 (7)	9 (32)	20 (45)

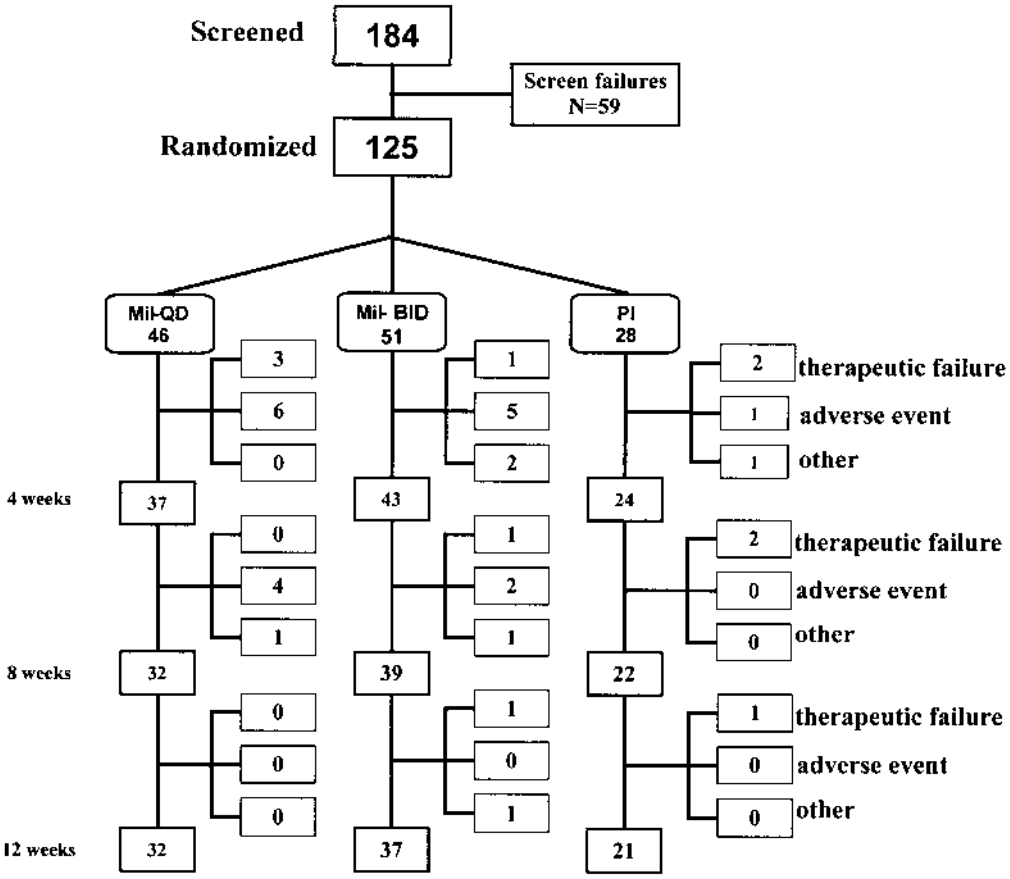

Figure 2. Number of patients screened and randomized into study groups; and number of patients reporting therapeutic failure, adverse events, or other issues at study Weeks 4, 8, and 12. Mil: milnacipran, Pl: placebo.

Table 2. Analyses of pain measures (intent to treat analyses using last observation carried forward method). A. Continuous pain measures, or mean change in pain measures from baseline less placebo change. B. Dichotomous pain measures, or the proportion of "responders" for each assessment.

A.	Milnacipran BID, n = 51 [p]	Milnacipran QD, n = 46 [p]	Placebo Score Change from Baseline, n = 28
Daily E-diary pain scores (0–20)	–3.0 ± 3.5 [0.191]	–2.2 ± 3.2 [0.635]	–1.86 ± 3.74
Weekly E-diary pain scores (0–20)	–3.1 ± 3.5 [0.025]	–2.5 ± 3.9 [0.139]	–1.14 ± 3.79
Paper Gracely pain scores (0–20)	–4.7 ± 4.8 [0.010]	–2.9 ± 4.8 [0.317]	–1.7 ± 4.1
Paper VAS pain scores (0–10)	–2.5 ± 2.8 [0.030]	–2.0 ± 3.2 [0.180]	–0.9 ± 2.9
McGill present-pain intensity (0–10)	–2.2 ± 2.7 [0.023]	–1.4 ± 3.2 [0.315]	–0.6 ± 2.7
B.	**BID, n = 51 (%) [p]**	**QD, n = 46 (%) [p]**	**Placebo, n = 28 (%)**
Daily E-diary proportion of responders			
30% pain reduction (≥ –3.3 units)	18 (35) [0.125]	10 (22) [0.772]	5 (18)
50% pain reduction (≥ –4.0 units)	18 (35) [0.066]	10 (22) [0.546]	4 (14)
Weekly E-diary proportion of responders			
30% pain reduction (≥ –3.3 units)	20 (39) [0.023]	13 (28) [0.255]	4 (14)
50% pain reduction (≥ –4.0 units)	19 (37) [0.040]	10 (22) [0.550]	4 (14)
Paper Gracely pain scores			
30% pain reduction (≥ –3.3 units)	23 (45) [0.007]	16 (35) [0.183]	5 (18)
50% pain reduction (≥ –4.0 units)	19 (37) [0.040]	13 (28) [0.250]	4 (14)
Paper VAS pain scores			
30% pain reduction (≥ –3.3 units)	20 (39) [0.136]	16 (35) [0.297]	6 (21)
50% pain reduction (≥ –4.0 units)	15 (29) [0.595]	12 (26) [0.783]	6 (21)

in depressed and nondepressed patients, further analyses were performed examining this issue. MINI results were used for identifying the presence of comorbid depression. As noted, randomization did not equally distribute depressed individuals among the 3 groups. The rate of comorbid depression for those randomized to BID milnacipran was 16%, for QD milnacipran 7%, and for placebo 32%. Thus, as a percentage of participants, more placebo patients had comorbid major depression disorder than either milnacipran group.

Statistically greater improvements in pain reduction were seen in nondepressed patients versus depressed patients treated with milnacipran. However, this difference did not occur because milnacipran was more effective among nondepressed patients, but rather because the placebo response rate was considerably higher among depressed patients. This is exemplified in Table 3, which presents the results of a binary responder analysis for BID milnacipran using e-diary assessment data. In response to placebo, 44% of depressed patients (vs 0% of nondepressed patients) reported a 50% reduction in pain on daily assessments, and 33% of depressed patients (vs 5% of nondepressed patients) reported a 50% reduction in pain on weekly assessments. Similar findings were noted for other pain measures, as well as for most other outcomes (data not shown).

Table 4 shows the same continuous pain measures as Table 2, but for nondepressed participants only. As would be expected from the different placebo response rates, there were significantly greater decreases in pain score between treated and placebo participants in this nondepressed subset as compared to the total group.

Efficacy results: other measures. Patients' global assessment of their clinical improvement during the trial was an important secondary outcome measure. Among individuals who

Table 3. 50% pain responders* taking milnacipran BID by baseline major depressive episode (MDE) status (intent to treat analyses using last observation carried forward method).

	All Patients, n (%) [p]	MDE Patients, n (%) [p]	Non-MDE Patients, n (%) [p]
Daily E-diary 50% pain reduction			
Milnacipran BID	18 (35) [0.066]	2 (25) [NS]	16 (37) [0.001]
Placebo	4 (14) —	4 (44) —	0 (0) —
Weekly E-diary 50% pain reduction			
Milnacipran BID	19 (37) [0.040]	3 (38) [NS]	16 (37) [0.012]
Placebo	4 (14) —	3 (33) —	1 (5) —

* ≥ 4.0 unit reduction on Gracely pain scale.

Table 4. Continuous pain measures (nondepressed FM patients only). Intent to treat analyses using last observation carried forward method. Mean change from baseline in pain measures less placebo change.

	Milnacipran BID, n = 43 [p]	Milnacipran QD, n = 43 [p]	Placebo Score Change from Baseline, n = 19
Daily E-diary pain scores (0–20)	–3.0 [0.013]	–2.2 [0.081]	–0.94
Weekly E-diary pain scores (0–20)	–3.1 [0.001]	–2.4 [0.018]	–0.23
Paper Gracely pain scores (0–20)	–4.7 [0.002]	–2.5 [0.110]	–0.7
Paper VAS pain scores (0–10)	–2.5 [0.006]	–1.8 [0.092]	–0.4
McGill present-pain intensity (0–10)	–2.0 [0.014]	–1.2 [0.192]	–0.1

completed the trial, those who received either BID or QD milnacipran were significantly more likely than those who received placebo to rate themselves as improved (73% BID, 77% QD, 38% placebo; p = 0.013 for BID milnacipran vs placebo, p = 0.008 for QD milnacipran patients versus placebo; Figure 3).

A number of other secondary outcome measures were assessed, using the FIQ, SF-36, Jenkins Sleep Scale, and ASEX. Because the above evidence indicated that BID milnacipran was a more effective analgesic than QD milnacipran, the analysis of these other secondary outcome measures focused on the BID milnacipran dose. On the FIQ, patients taking BID milnacipran reported significant improvement in "feel good" at the p = 0.05 level (p = 0.038), improvement in physical function at the trend level (p = 0.074), and a nonsignificant trend toward improvement in the FIQ total score (p = 0.188). Not surprisingly for a 12-week trial, there was no effect of BID milnacipran on job performance or absenteeism. The FIQ also contains a series of VAS scores, and the BID milnacipran group had statistically significant improvements in pain (p = 0.032), fatigue (p = 0.032), and morning stiffness (p = 0.047) compared to the placebo group, with trends toward improvement in depression and anxiety (Figure 4). There were also nonsignificant improvements in self-reported physical function for patients taking BID milnacipran as measured by the Physical Component summary score on the SF-36 (p = 0.124). Similarly, nonsignificant improvements were seen in sleep as measured by the Jenkins composite score (p = 0.229). Sexual function, as measured by the ASEX, improved equally in BID milnacipran and placebo-treated patients.

Safety and tolerability results. No unexpected safety concerns arose from this trial. There were no serious adverse events, and 88% of reported adverse events were rated as mild or moderate in severity. No patient discontinued due to clinically significant laboratory abnormalities. Consistent with previous trial results involving depressed patients, 7% of milnacipran-treated patients versus 4% of placebo-treated experienced mild elevations in alanine transferase and/or aspartate transferase, although no patient experienced elevations above 2 times the upper limits of normal, and no

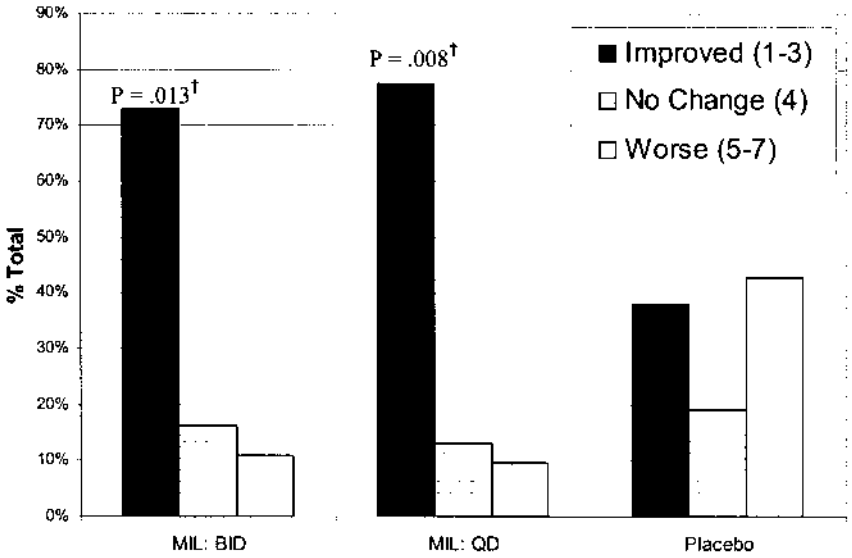

Figure 3. Self-report of change in overall status. Patients were asked to assess their global impression of change in FM severity over the course of the study. The percentage of patients completing the trial who thought they improved, got worse, or experienced no change is illustrated. †Milnacipran (MIL) vs placebo.

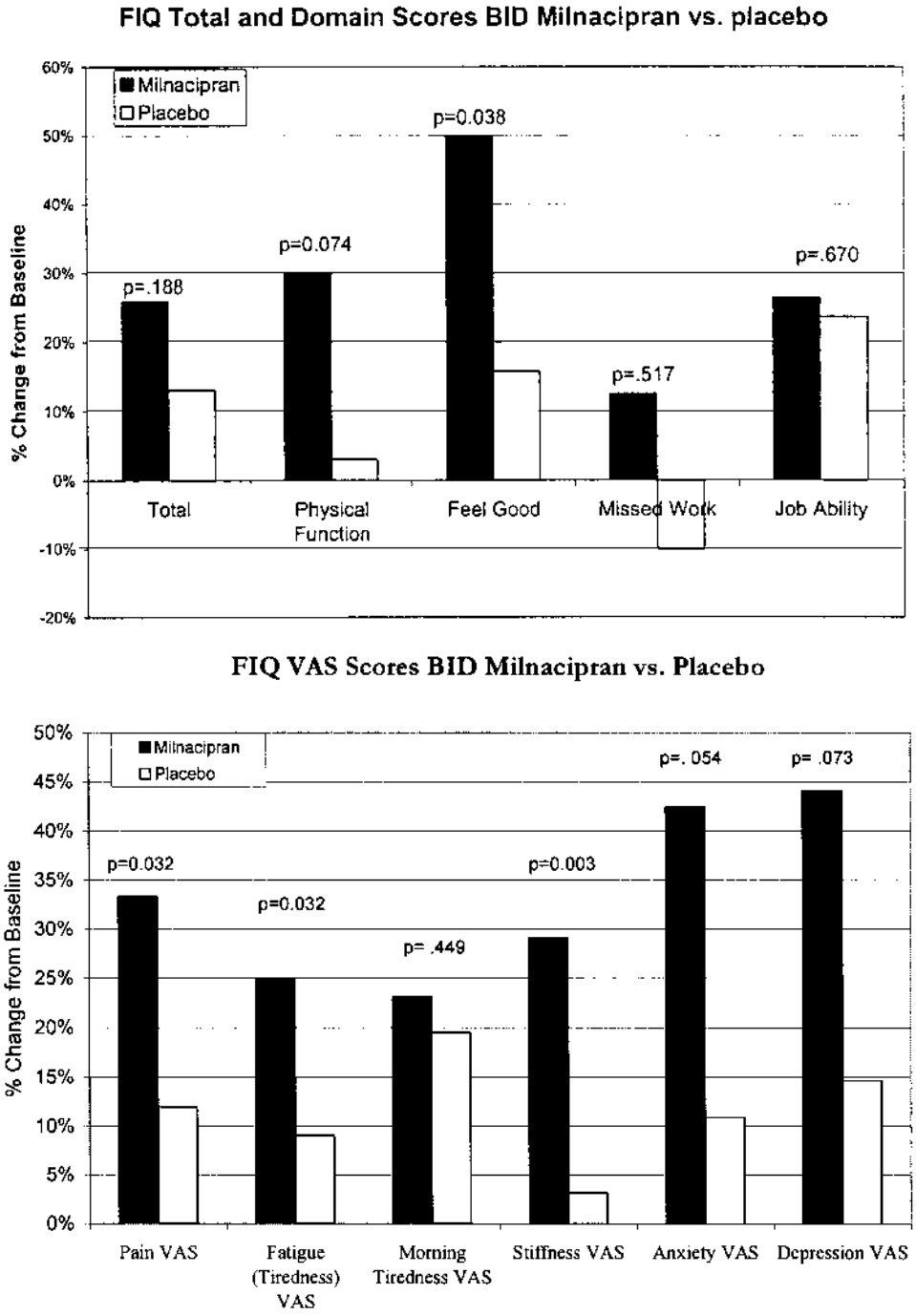

Figure 4. Scores from the Fibromyalgia Impact Questionnaire (FIQ) were used to determine between-group changes in non-pain outcomes among patients completing the trial, including the total FIQ score, specific domain scores, and visual analog scale (VAS) scores.

patient experienced any concomitant elevation in alkaline phosphatase or bilirubin.

Overall, 14.4% of patients discontinued the study prior to endpoint due to adverse events, including 13.7% of patients receiving BID milnacipran (7 patients), 21.7% of patients receiving QD milnacipran (10 patients), and 3.6% of patients receiving placebo (one patient). The majority (67%) of discontinuations secondary to adverse events occurred during the first 4 weeks of the trial, while patients were undergoing dose escalation. Headache and gastrointestinal (GI) complaints (nausea, abdominal pain, increased GI upset, and constipation) were the most frequent reasons stated for early termination. Other reasons for discontinuation included orthostatic dizziness, exacerbation of hypertension,

depression, lethargy, increased sweating, and hot flashes. One patient experienced a moderate exacerbation of preexisting hypertension that precluded dose escalation above 50 mg milnacipran BID, and led to early termination at Day 28. A second patient halted dose escalation at 50 mg milnacipran BID due to moderate postural dizziness, later discontinuing at Day 35 for persistence of this effect. Two milnacipran-treated patients discontinued due to depression, the first of whom had both a history of depression and a diagnosis at screening of current major depressive episode (MDE), as determined by the MINI. This patient discontinued after 13 days on study drug due to worsening depression, while receiving 50 mg milnacipran QD. The second patient had a history of depression, but was not MDE-positive at screening. She terminated from the trial after 35 days of treatment due to depressive episode, nausea and headache, after escalating to only 25 mg milnacipran QD.

Cardiovascular adverse events reported among the 97 milnacipran-treated patients included 6 reports of palpitations (5 mild, one moderate severity), 6 reports of postural dizziness (5 mild, one moderate), 2 reports of moderate exacerbation of hypertension, and one report of moderate increased heart rate upon standing. As described above, 2 of these patients discontinued early from the trial — one due to an exacerbation of hypertension and the other due to postural dizziness.

Previous trials indicated that milnacipran induces mild to moderate increases in mean pulse rates (+3 to +8 bpm), and our results were comparable. Mean blood pressure among milnacipran treatment groups showed a slight increase, ranging from 1.5 to 3.4 mm Hg for supine systolic pressures (–1.1 to 2.7 mm Hg in the placebo group) and 2.6 to 3.7 mm Hg for supine diastolic pressures (–3.5 to 1.2 mm Hg in the placebo group). These changes were not statistically different among treatment groups. Two milnacipran-treated patients (2.1%) reported exacerbation of hypertension. Both patients had preexisting hypertension and were receiving antihypertensive drug therapy.

A specific focus of this trial was the tolerability of high-dose (200 mg daily) milnacipran. Among patients who completed the 12-week study, 92% of BID and 81% of QD milnacipran-treated patients were successfully escalated to 200 mg daily. Only 9 milnacipran patients who completed the study (6 QD and 3 BID) were taking doses less than 200 mg daily. In addition to the greater rate of intolerance in the QD group, the higher incidence of adverse events, as well as the higher dropout rate due to adverse events, suggested that once-daily dosing was not as well tolerated as twice-daily dosing. Most notable was the increased incidence of nausea, abdominal pain, constipation, dizziness, postural dizziness, hot flushes/flushing, and palpitations among QD patients. Together, these observations suggest that for the larger doses, BID dosing is better tolerated, and peak drug level may be a significant factor in the generation of certain adverse effects.

DISCUSSION

Administration of milnacipran to patients with FM led to significant improvements in global well being, fatigue, (some measures of) pain, and a variety of related symptom domains. Twice-daily milnacipran had significantly better analgesic properties than once-daily milnacipran. Milnacipran was generally well tolerated, especially with BID dosing. The majority of adverse events were rated as mild or moderate, and no serious adverse events were reported.

Even though this drug has antidepressant properties, there was a greater statistical improvement noted in nondepressed FM patients than in those with FM and comorbid depression. This increased effect size did not occur because milnacipran was more efficacious in nondepressed patients (37% of nondepressed vs 38% of depressed patients experienced a 50% reduction in pain on weekly e-diary assessments), but instead, because of a much higher placebo response among depressed FM patients (33%) compared to nondepressed (5%). Thus, although milnacipran was originally developed as an antidepressant, it does not appear that the analgesic and other beneficial effects in FM occur strictly on the basis of improvements in mood. This is consistent with other classes of compounds, such as tricyclics, where analgesic effects are somewhat or largely independent of antidepressant effects[13,31-33].

In addition to demonstrating efficacy on most measures of pain, a significant proportion of the patients randomized to milnacipran showed improvement across a number of other symptom domains. Statistical differences between BID milnacipran and placebo were noted in physical functioning, fatigue level, and degree of reported physical impairment. Nonsignificant trends toward improvement were found on many other domains. Sleep was the one common symptom of FM that did not show evidence of significant improvement. This is not surprising, since milnacipran is an "activating" agent, presumably because of its noradrenergic effects. However, it is important to note that there were no detrimental effects on sleep.

The most striking evidence of a beneficial effect of milnacipran treatment in this trial was in the patient global outcome measure. Over 70% of completers in both milnacipran treatment groups reported an improvement in their overall status, while only 10% reported worsening. In the placebo arm, the most frequent category reported was "worsening," with over 40% of the placebo patients who completed the trial rating themselves as worse at endpoint. It is conceivable that milnacipran improved many of the symptoms of FM, and that this outcome measure essentially represents a summation of those improvements.

Because this was one of the first phase II trials conducted for FM, a greater number of outcomes were collected

than would ordinarily be collected in a typical randomized, controlled trial. In particular, pain was assessed using a variety of different methodologies. A rich body of literature suggests that asking individuals to recall their pain and other symptoms introduces many biases, and that even paper-and-pencil diaries, which theoretically sample symptoms on a real-time basis, are fraught with compliance problems[34]. E-diaries have the advantage of increased accuracy because these methods use electronic time-stamps that ensure patients actually record their symptoms at the requested time, rather than "backward-filling" (completing several days' worth of diaries at once) or "forward-filling" (completing diaries in advance of the time the symptom is asked to be recorded) their diaries[23,34-36].

We found that the pain results collected on e-diaries generally revealed less significant differences between milnacipran and placebo groups than the classic written instruments completed at the clinic visits. Further studies will be necessary to determine if this is a consistent finding when comparing these 2 methods of data collection, or if this effect is unique to this drug or to this trial. Because milnacipran led to a global improvement in many symptoms and in overall well being, it is possible that patients who were asked to recall their pain over a longer interval were positively influenced by their overall improved status. This would be consistent with previous reports that recall measures of pain report are highly influenced by how the individual feels at the time he/she completes the instrument (i.e., if he/she has worse pain or is depressed, he/she will record higher recall pain values, and vice-versa) rather than being a true "average" of how the individual feels over the recording interval[37].

The presence of 11/18 tender points on physical examination is part of the ACR diagnostic criteria for FM[1], and all study participants received a tender point count to verify that they met ACR criteria for FM prior to enrollment. However, a tender point count was not used as part of outcomes assessment, because tender points may not reflect changes in pain sensitivity/processing[38,39], and because tender points are strongly influenced by patient distress[38,39]. Because of this, any improvements in tender point count in our trial would likely be strongly influenced by milnacipran's known effects on psychological function, whereas the focus of the trial was milnacipran's analgesic properties.

The difference in the analgesic effect of BID and QD milnacipran was unexpected. It is possible that the mechanisms and the pharmacology by which milnacipran provides analgesia may be different from the processes by which milnacipran benefits other symptoms of FM, as both QD and BID milnacipran patients reported similar global improvement scores. It is possible that QD patients may have had inadequate drug levels of milnacipran at the end of the day (the half-life is 6–8 hours), and this may have contributed to the less effective pain relief.

From a safety perspective, milnacipran was generally well tolerated by the study population, especially in patients who received their daily milnacipran in split dosage (BID). By design, the trial allowed patients to stop the dose escalation process prior to reaching the maximum dose of 200 mg daily because there was an expectation of potentially serious high-dose drug intolerance. However, 92% of BID patients who completed the trial escalated to the maximum dosage, with little evidence of persistent dose intolerance or late-onset adverse effects. The majority of adverse events recorded were transient and mild to moderate in severity, and no serious adverse events were recorded.

Although it is difficult to compare the clinical benefit of one drug to another except if the 2 drugs are directly compared in a clinical trial, these data allow some preliminary sense of their efficacy for FM. For pain relief, for example, Arnold, *et al* performed a metaanalysis of randomized controlled trials of tricyclics in FM, and determined that the overall effect size was 0.52, in the moderate range[40]. This is very similar to the effect size seen for pain relief in our trial (0.48 for pain diary, 0.52 for paper-and-pencil VAS).

Milnacipran dosed BID at 200 mg per day was an effective analgesic for the symptom of pain in patients with FM, and had beneficial effects on a wide range of FM symptoms, including fatigue, physical function, and quality of life. In addition, patients taking milnacipran dosed either QD or BID reported significantly improved global clinical improvement. This medication did not appear to be acting solely as an antidepressant, because impressive separation between drug and placebo treated patients was noted in nondepressed patients. As with any initial trial, further studies with variable dosages and larger numbers of patients are needed to support and extend these findings.

REFERENCES

1. Wolfe F, Smythe H, Yunus M, Bennett R, Bombardier C, Goldenberg D. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
2. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. Curr Pain Headache Rep 2001;5:320-9.
3. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? Arthritis Rheum 2002;46:1136-8.
4. Staud R. Fibromyalgia pain: do we know the source? Curr Opin Rheumatol 2004;16:157-63.
5. Bragdon EE, Light KC, Costello NL, et al. Group differences in pain modulation: pain-free women compared to pain-free men and to women with TMD. Pain 2002;96:227-37.
6. Chang L, Berman S, Mayer EA, et al. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. Am J Gastroenterol 2003;98:1354-61.
7. Bendtsen L. Central sensitization in tension-type headache — possible pathophysiological mechanisms. Cephalalgia 2000;20:486-508.
8. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
9. Leventhal LJ. Management of fibromyalgia. Ann Intern Med

1999;131:850-8.
10. Yunus M. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation [editorial]. J Rheumatology 1992;19:846-50.
11. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Arthritis Rheum 2000;43:378-85.
12. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95.
13. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305-16.
14. Millan MJ. Descending control of pain. Prog Neurobiol 2002;66:355-474.
15. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255-9.
16. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia — a randomized, double-blind, placebo-controlled study. Eur J Pain 2000;4:27-35.
17. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191-7.
18. Moret C, Charveron M, Finberg JP, Couzinier JP, Briley M. Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug. Neuropharmacology 1985;24:1211-9.
19. Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. Int Clin Psychopharmacol 1997;12:99-108.
20. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33;quiz 34-57.
21. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19 Suppl 1:S27-35.
22. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191-7.
23. Gracely RH, Kwilosz DM. The Descriptor Differential Scale: applying psychophysical principles to clinical pain assessment. Pain 1988;35:279-88.
24. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. Control Clin Trials 2003;24:182-99.
25. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 1991;18:728-33.
26. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
27. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41:313-21.
28. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000;26:25-40.
29. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
30. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety 1999;20:109-17.
31. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med 2002;162:19-24.
32. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433-45.
33. Carter GT, Sullivan MD. Antidepressants in pain management. Curr Opin Investig Drugs 2002;3:454-8.
34. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002;324:1193-4.
35. Hufford MR, Shields AL, Shiffman S, Paty J, Balabanis M. Reactivity to ecological momentary assessment: an example using undergraduate problem drinkers. Psychol Addict Behav 2002;16:205-11.
36. Shiffman SS, Hufford M, Paty J. Subject experience diaries in clinical research. Part 1: the patient experience movement. Appl Clin Trials 2001;10:46-56.
37. Shalev AY, Sahar T, Freedman S, et al. A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. Arch Gen Psychiatry 1998;55:553-9.
38. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:593-609.
39. Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. Ann Rheum Dis 1997;56:268-71.
40. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41:104-13.