# Effect of Milnacipran on Pain in Patients with Rheumatoid Arthritis with Widespread Pain: A Randomized Blinded Crossover Trial

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***ABSTRACT. Objective.*** Clinical trials have shown that serotonin norepinephrine reuptake inhibitors, such as milnacipran, decrease pain in noninflammatory pain conditions such as fibromyalgia and osteoarthritis. We examined the effect of milnacipran on self-reported pain intensity and experimental pain sensitivity among patients with rheumatoid arthritis (RA) with widespread pain and stable RA disease activity.

***Methods.*** In this double-blind, crossover study, patients with RA with widespread pain, receiving a stable treatment regimen, were randomized (by a random number generator) to receive milnacipran 50 mg twice daily or placebo for 6 weeks, followed by a 3-week washout and crossed over to the other arm for the remaining 6 weeks. The primary outcome was change in average pain intensity, assessed by the Brief Pain Inventory short form. The sample size was calculated to detect a 30% improvement in pain with power = 0.80 and $\alpha = 0.05$.

***Results.*** Of the 43 randomized subjects, 41 received the study drug, and 32 completed the 15-week study per protocol. On a 0–10 scale, average pain intensity decreased by 0.39 (95% CI –1.27 to 0.49, p = 0.37) more points during 6 weeks of milnacipran treatment compared with placebo. In the subgroup of subjects with swollen joint count ≤ 1, average pain intensity decreased by 1.14 more points during 6 weeks of milnacipran compared with placebo (95% CI –2.26 to –0.01, p = 0.04). Common adverse events included nausea (26.8%) and loss of appetite (9.7%).

***Conclusion.*** Compared with placebo, milnacipran did not improve overall, self-reported pain intensity among subjects with widespread pain receiving stable RA medications. Trial registration: ClinicalTrials.gov NCT01207453. (First Release December 1 2015; J Rheumatol 2016;43:38–45; doi:10.3899/jrheum.150550)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS PAIN ANALGESIA

Patients with rheumatoid arthritis (RA) most frequently seek medical care because of pain[1]. Over the past 20 years, the development of strong biologic disease-modifying antirheumatic drugs (DMARD) has enabled aggressive, early treatment of RA, leading to higher rates of remission. However, despite improvements in disease activity, the majority of patients with early RA report incomplete relief of pain[2], and up to 34% of patients with RA report chronic widespread pain over a followup period of 5 years[3]. Pain in this subgroup of patients with RA is often related to noninflammatory factors, such as structural changes, psychological factors, and central pain mechanisms[4,5,6,7,8,9].

Several studies have documented the effect of central pain mechanisms in osteoarthritis[10,11,12], but data regarding the involvement of central pain mechanisms in RA is scarce. To our knowledge, no studies have examined the effects of serotonin norepinephrine reuptake inhibitors (SNRI) on pain in RA, although some have suggested that tricyclic antidepressants, which exert their effects through serotonin and norepinephrine, are effective[13,14,15]. In addition, several studies have examined the involvement of SNRI in chronic pain conditions associated with defects in central pain processing [e.g., fibromyalgia (FM)][16,17,18,19]. Milnacipran, the most recent US Food and Drug Administration-approved

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drug for FM, reduced pain severity in randomized clinical trials of FM[20,21,22].

The objective of our study was to evaluate whether milnacipran reduces pain severity among patients with RA with pain in a widespread distribution compared with placebo. We chose to focus on patients with RA with widespread pain because these individuals are more likely to have aberrancies in central nervous system pain regulating mechanisms, which may be amenable to treatment with milnacipran.

Our study takes advantage of a crossover design to reduce the effects of confounding variables because each subject serves as his/her own control[23]. By minimizing the imbalances in covariates between treatment groups, the crossover design enhances statistical power, enabling the use of smaller sample sizes than parallel-group trials[24]. The main disadvantages of crossover studies are carryover effects (the first treatment has lingering effects that alter the outcome during the second treatment period) and order effects (the sequence of treatment affects the outcome). To assess the likelihood and adjust for these effects, we used linear mixed models, including covariates for study period and sequence. We hypothesized that subjects will experience greater reductions in pain severity during milnacipran treatment than placebo.

## MATERIALS AND METHODS

*Study population*. Patients with RA with pain at ≥ 5 body sites were recruited from the Arthritis Center of a large US academic medical center. Inclusion criteria included (1) age 24 years or older (excluded subjects < 24 yrs old because of black box warning for increased suicide risk among children, adolescents, and young adults), (2) diagnosis of RA as determined by a board-certified rheumatologist, (3) stable RA medication regimen [defined as stable doses of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids (≤ 20 mg prednisone daily), and/or DMARD] for ≥ 8 weeks prior to study initiation, (4) ability to maintain stable doses of NSAID, corticosteroids, and DMARD for the duration of the study, (5) average pain ≥ 4 on the Brief Pain Inventory short form at the screening visit[25], (6) ≥ 5 on the Regional Pain Scale at the screening visit (changed after study initiation from a requirement of ≥ 7 because of slow recruitment)[26], and (7) ability to give informed consent. Exclusion criteria included (1) primary diagnosis of FM, (2) cold-sensitive conditions (e.g., Raynaud syndrome, cryoglobulinemia, paroxysmal cold hemoglobinuria), (3) psychotic disorders (e.g., schizophrenia, schizoaffective disorder, delusional disorder, shared psychotic disorder), (4) treatment with thioridazine, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors; tricyclic, tetracyclic, or atypical antidepressants, (5) treatment with opioid analgesics, (6) hypersensitivity to milnacipran, (7) history of suicide or significant risk of suicide as assessed by the Beck Depression Inventory, (8) pregnant or breastfeeding, (9) actively pending worker's compensation claim, automobile no-fault claim, or litigation, (10) myocardial infarction within the past 12 months, active cardiac disease, acute congestive heart failure, or clinically significant cardiac rhythm or conduction abnormalities, (11) severe liver impairment, (12) severe or endstage renal disease, (13) recent history of seizures, (14) uncontrolled narrow-angle glaucoma, or (15) treatment with an experimental agent within the last 3 months. All subjects provided written informed consent. The Partners Institutional Review Board approved the study.

*Trial design*. In this 15-week, crossover study, 43 subjects were randomized 1:1 to Group A vs Group B by a random number generator, with 4 subjects per block. The institution's Investigational Drug Services generated the random allocation sequence and assigned subjects to treatment groups. Group A received 6 weeks of milnacipran, followed by a 3-week washout and 6 weeks of placebo. Group B received 6 weeks of placebo, followed by a 3-week washout and 6 weeks of milnacipran. The 6-week treatment period was chosen based on previous studies of milnacipran in FM showing significant differences between the milnacipran- and placebo-treated groups as early as 1 week after starting treatment, with the curve in improvement leveling off at 6 weeks after initiating treatment[21,22]. The dose was titrated to 50 mg twice daily. Subjects and study assessors were blinded to group allocation. The placebo tablets were identical in appearance to the milnacipran tablets. The dose was titrated according to the following schedule: (1) days 1–3: milnacipran/placebo 12.5 mg twice daily, (2) days 4–6: milnacipran/placebo 25 mg twice daily, and (3) days 7–42: milnacipran/placebo 50 mg twice daily. If subjects could not tolerate the full dose, the dose was decreased to the highest tolerated dose. The protocol is accessible on ClinicalTrials.gov (NCT01207453).

*Assessment of clinical variables*. Following screening, subjects were evaluated at baseline, 6 weeks, 9 weeks, and 15 weeks. The Disease Activity Score in 28 joints (DAS28) using C-reactive protein was used to assess inflammatory disease activity[27]. Pain was quantified using the Brief Pain Inventory short form[25] and the Symptom Intensity Scale, a 20-item scale that includes the Regional Pain Scale[26] and a visual analog scale for fatigue[28]. Mental health, sleep, and pain catastrophizing were assessed using the Hospital Anxiety and Depression Scale[29], the Medical Outcomes Study Sleep Scale[30], and the Pain Catastrophizing Scale[31].

*Quantitative sensory testing*. A Wagner FPK 20 algometer (Wagner Instruments) was used to assess pressure pain thresholds[9,32] in kg/cm$^2$. This instrument has an accuracy of ± 2 gradations for capacities through 2500 g and ± 1 gradation over 2500 g. The order of testing was standardized as follows: (1) right thumbnail, (2) left thumbnail, (3) right wrist, (4) left wrist, (5) right trapezius muscle, (6) left trapezius muscle, (7) right knee, and (8) left knee. We increased the pressure at a rate of about 1 kg/s from 0 kg to a maximum of 11 kg. The pressure pain threshold was defined as the pressure at which the subjects first felt pain. We performed 2 assessments at each site. As in previous studies[32], the first test was a trial run to acclimate subjects to testing procedures. The second trial was the test run, from which all reported data were obtained. We averaged pressure pain thresholds at bilateral sites to provide 1 value for each pair of body sites, a method that has been validated in previous studies[33].

Conditioned pain modulation (CPM) was tested using the cold pressor test, with immersion of the right hand in a 6°C water bath as the conditioning stimulus and pressure at the trapezius muscle as the test stimulus[34,35]. The conditioning stimulus is a painful stimulus that activates the descending analgesic pain pathways. The test stimulus is applied to assess changes in pain thresholds after activating the descending analgesic pain pathways. If the descending analgesic pathways are intact, application of the condition stimulus leads to an increase in pain thresholds. In our study, the specific paradigm involved first assessing the pressure pain threshold at the trapezius. Subjects were then instructed to immerse their right hand in the water bath for 30 s. At 20 s (while the hand was still immersed in water), pressure pain threshold at the trapezius was assessed again. We defined the magnitude of participants' CPM as the difference in pressure pain threshold between baseline and 20 s after cold water immersion. If participants were unable to keep their hand in the cold water bath for at least 20 s (because of overwhelming pain), the second measure of pressure pain threshold was assessed immediately after removing the hand from the cold water bath.

*Statistical analyses*. Both per protocol and intention-to-treat (ITT) analyses were performed (using a modified last observation carried forward method to handle missing data). For the ITT analyses, data from the first period were not carried over to the second period because this was a crossover study, and it was not advisable to apply data obtained during 1 treatment period to the other treatment period. When data were available for visit 3, but missing for visit 4, these data were carried over from visit 3 to visit 4; this remained consistent with the ITT concept of analyzing individuals as they were randomized.

The primary outcome was the change in the Brief Pain Inventory average pain intensity (measured on a 0–10 numeric rating scale) from baseline to Week 6 and from Week 9 to Week 15. Secondary outcomes included changes in the Symptom Intensity Scale score, pressure pain thresholds, and CPM from baseline to Week 6 and from Week 9 to Week 15. Effect sizes were calculated using least square means (for changes in pain within treatment groups), the difference of least square means (for differences in changes in pain between treatment groups), and 95% CI.

Paired Student t tests were used for unadjusted comparisons between treatments. To account for potential carryover effects, we fit a linear mixed model, including indicator variables for treatment group, study period, and sequence. A significant carryover effect was defined as $p < 0.05$ for the association between sequence and the dependent variable. Exploratory analyses were conducted in subgroups defined by baseline values of pain and inflammatory disease activity. These analyses were performed using paired Student t tests. No corrections for multiple testing were performed because of the exploratory design of these subgroup analyses. In posthoc analyses, we assessed the characteristics of responders (those with a ≥ 30% decrease in the Brief Pain Inventory short form average pain score) versus nonresponders. All statistical analyses were performed using the SAS 9.3 software package (SAS Institute).

*Power calculation*. Based on our pilot data, the average Brief Pain Inventory pain score among patients with RA with widespread, non-joint pain was 4.77 (SD 2.80). To detect a clinically important improvement in pain intensity of 30%[36] with an α level of 0.05, 32 participants were required to achieve 80% power. The trial was ended in November 2013 when 32 participants completed the study.

## RESULTS

Between January 2011 and July 2013, 228 individuals with RA completed the prescreening survey. Forty-nine met prescreening criteria and provided written informed consent (Figure 1). Forty-three were randomized, and 41 received study drug/placebo. Of these 41 participants, 19 (46.3%) correctly identified when they had received the study drug versus the placebo. Nine (22.0%) did not correctly identify when they received the study drug versus the placebo. Four (9.8%) did not answer this question, and 9 (22.0%) were not asked this question because they dropped out of the study before the question was asked. Thirty-two (milnacipran first: 17, placebo first: 15) completed the study and were analyzed by the original assigned groups (Table 1). Of these 32 participants, 31 (96.9%) had pain on both the left and right sides of the body. Thirty-one (96.9%) had pain both above and below the waist, and 28 (87.5%) had pain along the axial skeleton.

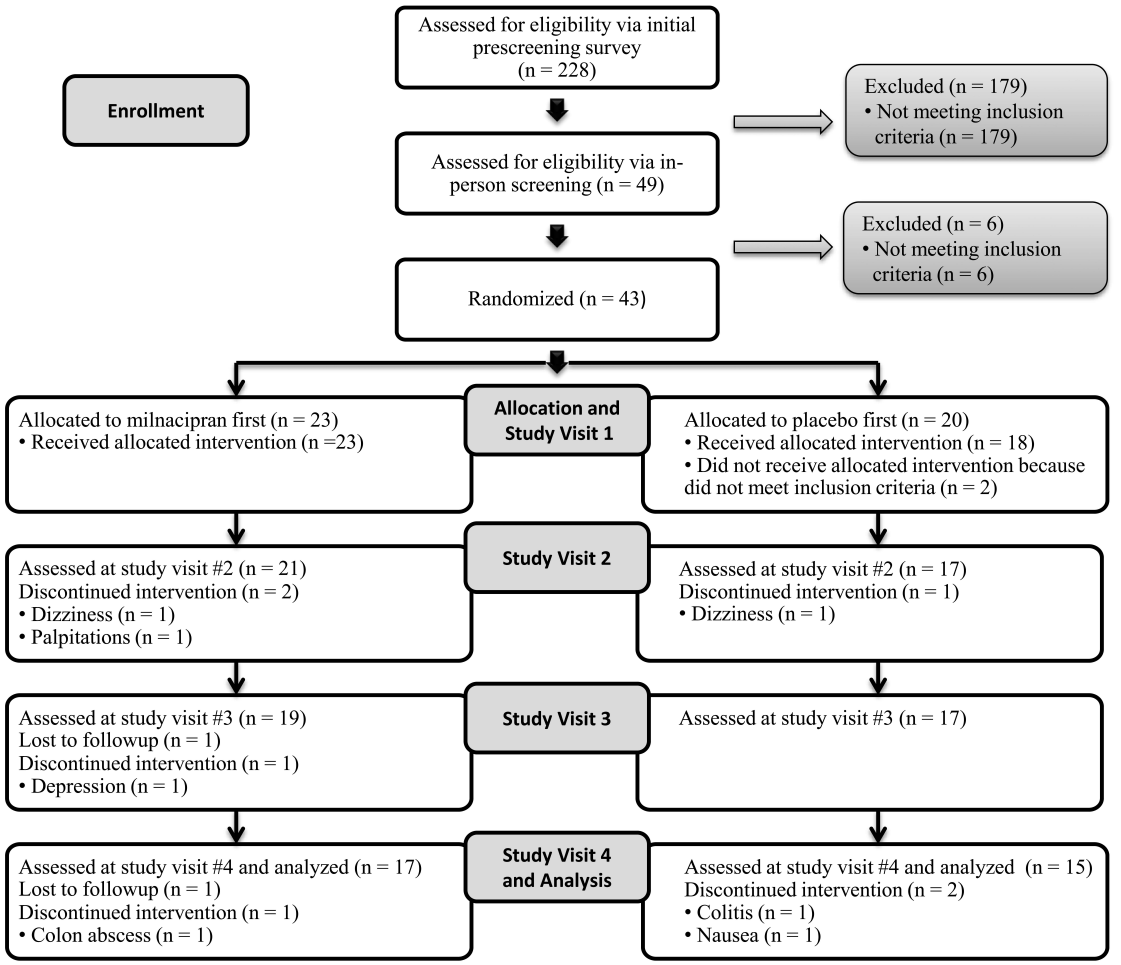


*Figure 1*. Flow diagram of the process from screening through study completion.

*Table 1*. Baseline characteristics of study subjects (n = 32). Values are mean (SD) or median (interquartile range) unless otherwise specified.

| Clinical Characteristics | Milnacipran First, n = 17 | Placebo First, n = 15 |
|---|---|---|
| Age, yrs | 54.2 (11.3) | 53.8 (14.1) |
| RA disease duration, yrs | 13.2 (11.8) | 9.37 (11.0) |
| Female, n (%) | 13 (76.5) | 12 (80.0) |
| White, n (%) | 11 (64.7) | 11 (73.3) |
| RF/CCP-positive, n (%) | 13 (76.5) | 7 (46.7) |
| DMARD use, n (%) | | |
| Nonbiologic | 11 (64.7) | 10 (66.7) |
| Biologic | 8 (47.1) | 6 (40.0) |
| Oral glucocorticoid use, n (%) | 5 (29.4) | 6 (40.0) |
| Glucocorticoid dose, mg of prednisone equivalents* | 4.4 (3.3) | 6.7 (7.0) |
| Meets ACR 2010 criteria, n (%) | 14 (82.4) | 12 (80.0) |
| SJC, 0–28** | 0 (0.0–1.0) | 1 (0.0–4.0) |
| Swollen wrists and/or knees, n (%) | 4 (23.5) | 3 (20.0) |
| TJC, 0–28** | 3 (2.0–7.0) | 8 (4.0–14.0) |
| Tender wrists and/or knees, n (%) | 11 (64.7) | 10 (66.7) |
| CRP | 1.8 (0.5–3.6) | 1.2 (0.5–3.3) |
| DAS28-CRP, 1–10 | 3.0 (2.6–3.6) | 3.6 (3.3–4.2) |
| Tender point count, 0–18 | 7 (3.0–8.0) | 7 (3.0–12.0) |
| HADS anxiety score, 0–21 | 5.7 (4.7) | 6.3 (4.6) |
| HADS depression score, 0–21 | 4.0 (4.6) | 4.5 (3.3) |
| Medical Outcomes Study Sleep Problems Index II score, 0–100 | 45.4 (20.3) | 47.0 (20.2) |
| Pain Catastrophizing Scale score, 0–52 | 33.1 (14.9) | 29.7 (12.8) |
| Regional Pain Scale, 0–19 | 9.1 (4.2) | 11.6 (3.4) |
| Symptom Intensity Scale, 0–9.75 | 5.2 (4.0) | 6.0 (1.3) |
| Brief Pain Inventory short form pain intensity, 0–10 | 6.2 (1.7) | 5.7 (1.6) |

* Among participants taking prednisone. ** SJC and TJC were done according to the guidelines for the DAS28. RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; DAS28: Disease Activity Score at 28 joints; HADS: Hospital Anxiety and Depression Scale.

Subjects randomized to receive milnacipran first (Group A) had similar clinical characteristics compared with subjects randomized to receive placebo first (Group B). The only statistically significant differences were the median tender joint count (Group A: 3 vs Group B: 8, p = 0.04) and median DAS28 (Group A: 3.0 vs Group B: 3.6, p = 0.03).

Seven subjects (Group A: 4, Group B: 3) withdrew because of adverse events (lightheadedness, nausea, anxiety, palpitations, colitis, colectomy), and 2 (both in Group A) were lost to followup (Table 2). Study completers were more likely to be seropositive for rheumatoid factor and/or cyclic citrullinated peptide antibodies (p = 0.02). Though not statistically significant, study completers were almost 10 years younger than excluded individuals. Five subjects could not tolerate the full dose of 50 mg twice daily of study drug and were reduced to 25 mg twice daily. All dose reductions occurred while subjects were taking milnacipran. Analyses did not show a statistically significant crossover effect.

*Table 2*. Baseline characteristics of study subjects who withdrew from the study or were lost to followup (n = 9). Values are mean (SD) or median (interquartile range) unless otherwise specified.

| Clinical Characteristics | Values, n = 9 |
|---|---|
| Age, yrs | 63.2 (14.5) |
| RA disease duration, yrs | 13 (14.3) |
| Female, n (%) | 9 (100.0) |
| White, n (%) | 7 (77.8) |
| RF/CCP-positive, n (%) | 2 (22.2) |
| DMARD use, n (%) | |
| Nonbiologic | 3 (33.3) |
| Biologic | 5 (55.6) |
| Oral glucocorticoid use, n (%) | 1 (11.1) |
| Meets ACR 2010 criteria, n (%) | 5 (55.6) |
| SJC | 1 (0.0–1.0) |
| TJC | 8 (3.0–17.0) |
| CRP | 1.9 (1.0–3.9) |
| DAS28-CRP | 3.3 (3.1–4.6) |
| Tender point count | 11 (2.0–16.0) |
| HADS anxiety score | 5.4 (5) |
| HADS depression score | 3.2 (2) |
| Medical Outcomes Study Sleep Problems Index II score | 42.5 (17.7) |
| Pain Catastrophizing Scale score | 25.8 (9.2) |

RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; DAS28: Disease Activity Score at 28 joints; HADS: Hospital Anxiety and Depression Scale.

When subjects were treated with milnacipran, the mean Brief Pain Inventory pain intensity score decreased by 0.67 points (95% CI –1.29 to –0.04) or 12.9% compared with a decrease of 0.28 points (95% CI –0.90 to 0.35) or 4.9% during placebo treatment. The difference between the decreases in pain intensity during milnacipran versus placebo treatment was –0.39 points (95% CI –1.27 to 0.49; Table 3). This difference was not statistically significant (p = 0.37). Similarly, the mean Symptom Intensity Scale score decreased by 0.71 points (95% CI –1.33 to –0.07) when subjects were treated with milnacipran and by 0.80 points (95% CI –1.43 to –0.17) during placebo treatment. The difference between the decreases in Symptom Intensity Scale score during milnacipran versus placebo treatment was 0.10 (95% CI –0.80 to 0.99, p = 0.83). At the thumbnails, pain threshold increased by 0.75 (95% CI 0.19–1.31) when subjects were treated with milnacipran and increased by 0.08 (95% CI –0.49 to 0.64) when subjects were treated with placebo. The difference between the changes in thumbnail pain threshold during milnacipran versus placebo treatment was 0.67 (95% CI 0.02–1.32, p = 0.04). In ITT analyses comparing changes in the above outcomes, the results were the same. In secondary analyses using only data from the first period of treatment, the results were the same except that the difference in change in thumbnail pain threshold was no longer statistically significant.

*Table 3*. Effect sizes and 95% CI for measures of pain in analyses by protocol.

| Variables | Unadjusted Analyses, n = 32 | | | Adjusted Analyses, n = 32 | | |
|---|---|---|---|---|---|---|
| | Change during Placebo | Change during Milnacipran | Difference between Placebo and Milnacipran | Change during Placebo | Change during Milnacipran | Difference between Placebo and Milnacipran |
| BPI-sf Pain* | –0.25 (–0.95 to 0.45) | **–0.72 (–1.33 to –0.11)** | –0.47 (–1.45 to 0.51) | –0.28 (–0.90 to 0.35) | **–0.67 (–1.29 to –0.04)** | –0.39 (–1.27 to 0.49) |
| SIS** | **–0.80 (–1.48 to –0.11)** | **–0.73 (–1.31 to –0.16)** | 0.06 (–0.90 to 1.03) | **–0.80 (–1.43 to –0.17)** | **–0.71 (–1.33 to –0.07)** | 0.10 (–0.80 to 0.99) |
| Thumbnail PPT† | 0.08 (–0.52 to 0.67) | **0.76 (0.25–1.27)** | **0.69 (0.04–1.34)** | 0.08 (–0.49 to 0.64) | **0.75 (0.19–1.31)** | **0.67 (0.02–1.32)** |
| Trapezius PPT† | **0.69 (0.13–1.26)** | 0.35 (–0.18 to 0.88) | –0.34 (–1.04 to 0.36) | **0.71 (0.16 to 1.26)** | 0.33 (–0.22 to 0.88) | –0.38 (–1.06 to 0.31) |
| Wrist PPT† | **0.81 (0.23–1.39)** | **0.77 (0.19–1.36)** | 0.04 (–0.68 to 0.76) | **0.75 (0.17–1.33)** | **0.79 (0.21–1.37)** | 0.04 (–0.69 to 0.78) |
| Knee PPT† | 0.21 (–0.47 to 0.90) | 0.37 (–0.16 to 0.90) | 0.16 (–0.64 to 0.95) | 0.20 (–0.42 to 0.83) | 0.37 (–0.26 to 0.99) | 0.16 (–0.64 to 0.97) |
| CPM† | 0.17 (–0.26 to 0.59) | 0.09 (–0.54 to 0.71) | –0.08 (–0.88 to 0.72) | 0.17 (–0.37 to 0.71) | 0.09 (–0.45 to 0.64) | –0.07 (–0.84 to 0.69) |

Significant data are in bold face. * Based on a 0–10 scale with 10 being worse pain. ** Based on 0–9.75 scale with 9.75 being greater intensity of symptoms consistent with fibromyalgia. † Units are kg/cm$^2$. BPI-sf: Brief Pain Inventory short form; SIS: Symptom Intensity Scale; PPT: pressure pain threshold; CPM: conditioned pain modulation.

Changes in thumbnail pain threshold were inversely correlated with changes in Brief Pain Inventory pain intensity score (Spearman r = –0.38, p = 0.008) during milnacipran treatment, but were not correlated with changes in pain intensity during placebo (Spearman r = 0.004, p = 0.97). Neither changes in pain thresholds at other sites nor changes in CPM differed between milnacipran and placebo treatment.

Among the subgroup of patients with RA with ≤ 1 swollen joint at baseline, the mean Brief Pain Inventory pain intensity score decreased by 1.05 points (95% CI –1.78 to –0.32) compared with an increase of 0.09 points (95% CI –0.76 to 0.94) during placebo treatment. The difference between the decreases in pain intensity during milnacipran versus placebo treatment was –1.14 points (95% CI –2.26 to –0.01; Table 4). Increases in pressure pain threshold during milnacipran treatment compared with placebo were again noted in the subgroup of patients with RA with ≤ 1 swollen joint at baseline and the subgroup with baseline average pain intensity ≥ 4 at baseline. No significant differences were noted in other subgroup analyses.

In analyses comparing responders to nonresponders, no differences were statistically significant (Table 5).

Of the 41 participants who received at least 1 dose of milnacipran and/or placebo, 24 (58.4%) reported ≥ 1 adverse effect. When participants were treated with milnacipran, the most common adverse effects were nausea (26.8%), loss of appetite (9.7%), insomnia (7.3%), and vomiting (7.3%). When participants were treated with placebo, the most common adverse effects were nausea (7.3%), insomnia (4.9%), headaches (4.9%), and paresthesias (4.9%). One serious adverse event was reported. A participant developed abdominal pain 1 day after starting the placebo phase of the trial (after completing 6 weeks with milnacipran and 3 weeks

*Table 4*. Effect sizes and 95% CI for measures of pain in subgroups of interest in analyses by protocol.

| Variables | Change during Placebo | Change during Milnacipran | Difference between Placebo and Milnacipran |
|---|---|---|---|
| BPI-sf average pain intensity* ≥ 4 at baseline, n = 29 | | | |
| BPI-sf pain intensity* | –0.31 (–1.07 to 0.45) | **–0.76 (–1.41 to –0.10)** | –0.45 (–1.51 to 0.61) |
| SIS** | **–0.87 (–1.62 to –0.12)** | **–0.69 (–1.31 to –0.07)** | 0.18 (–0.87 to 1.23) |
| Thumbnail PPT† | 0.06 (–0.60 to 0.72) | **0.78 (0.23–1.34)** | **0.72 (0.03–1.42)** |
| Trapezius PPT† | 0.42 (–0.13 to 0.97) | **0.72 (0.10–1.35)** | –0.30 (–1.06 to 0.45) |
| Regional Pain Scale ≥ 7 at baseline, n = 25 | | | |
| BPI-sf pain intensity* | –0.08 (–0.96 to 0.80) | –0.48 (–1.22 to 0.26) | –0.40 (–1.64 to 0.84) |
| SIS** | –0.64 (–1.48 to 0.20) | **–0.91 (–1.60 to –0.22)** | –0.27 (–1.41 to 0.87) |
| Thumbnail PPT† | 0.20 (–0.55 to 0.95) | **0.73 (0.13–1.33)** | 0.53 (–0.20 to 1.26) |
| Trapezius PPT† | **0.67 (0.10–1.24)** | 0.36 (–0.28 to 1.00) | –0.31 (–1.05 to 0.44) |
| Swollen joint count ≤ 1 at baseline, n = 22 | | | |
| BPI-sf Pain Intensity* | 0.09 (–0.76 to 0.94) | **–1.05 (–1.78 to –0.32)** | **–1.14 (–2.26 to –0.01)** |
| SIS** | –0.45 (–1.23 to 0.32) | **–1.02 (–1.71 to –0.34)** | –0.57 (–1.68 to 0.55) |
| Thumbnail PPT† | 0.06 (–0.60 to 0.73) | **0.95 (0.28–1.62)** | **0.89 (0.16–1.61)** |
| Trapezius PPT† | **0.65 (0.01–1.29)** | **0.82 (0.17–1.47)** | 0.17 (–0.61 to 0.94) |

Significant data are in bold face. * Based on a 0–10 scale with 10 being worse pain. ** Based on 0–9.75 scale with 9.75 being greater intensity of symptoms consistent with fibromyalgia. † Units are kg/cm$^2$. BPI-sf: Brief Pain Inventory short form; SIS: Symptom Intensity Scale; PPT: pressure pain threshold; CPM: conditioned pain modulation.

*Table 5*. Baseline characteristics of responders to milnacipran versus nonresponders to milnacipran (response ≥ 30% improvement in Brief Pain Inventory short form average pain intensity). Values are mean (SD) or median (interquartile range) unless otherwise specified.

| Clinical Characteristics | Nonresponders, n = 23 | Responders, n = 9 |
|---|---|---|
| Age, yrs | 53.4 (13.4) | 55.4 (10.2) |
| RA disease duration, yrs | 9.4 (10.8) | 16.5 (12) |
| Female, n (%) | 20.0 (87.0) | 5 (55.6) |
| White, n (%) | 15 (65.2) | 7 (77.8) |
| RF/CCP-positive, n (%) | 14 (60.9) | 6 (66.7) |
| DMARD use, n (%) | | |
| Nonbiologic | 15 (65.2) | 6 (66.7) |
| Biologic | 10 (43.5) | 4 (44.4) |
| Oral glucocorticoid use, n (%) | 6 (26.1) | 5 (55.6) |
| Meets ACR 2010 criteria, n (%) | 19 (82.6) | 7 (77.8) |
| SJC | 1 (0.0–3.0) | 0 (0.0–1.0) |
| TJC | 6 (3.0–9.0) | 3 (2.0–8.0) |
| CRP | 1.5 (0.4–3.4) | 1.7 (1.1–3.6) |
| DAS28-CRP | 3.6 (2.9–3.8) | 3.1 (2.4–3.6) |
| Tender point count | 7 (3.0–12.0) | 6 (3.0–9.0) |
| HADS anxiety score | 6.1 (5.1) | 5.6 (3.3) |
| HADS depression score | 4.7 (4.3) | 3.1 (2.8) |
| Medical Outcomes Study | | |
| Sleep Problems Index II score | 46.9 (20.5) | 44.1 (19.4) |
| Pain Catastrophizing Scale score | 29.9 (13.6) | 35.6 (14.4) |

RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; DAS28: Disease Activity Score at 28 joints; HADS: Hospital Anxiety and Depression Scale.

of washout). A computed tomography scan showed a colonic abscess, and she underwent partial colectomy.

## DISCUSSION

In the overall study population, in both per protocol and ITT analyses, we found no improvement in the Brief Pain Inventory average pain intensity or other pain measures when participants were treated with milnacipran 50 mg twice daily versus placebo. However, in subgroup analyses including only patients with RA with ≤ 1 swollen joint, the difference between changes in pain during milnacipran treatment and changes in pain during placebo treatment was statistically significant, suggesting that milnacipran may be efficacious for patients with RA with extremely well-controlled inflammation. The latter was an exploratory analysis, however, performed in a small subgroup, and in this subgroup the baseline pain intensity prior to milnacipran treatment was higher than the baseline pain intensity before placebo treatment. Thus, regression toward the mean may mix with the true treatment effect.

The finding of no difference in changes in average pain intensity or other pain measures during milnacipran versus placebo treatment suggests that central pain mechanisms may not be the predominant cause of pain in patients with RA with widespread pain. Among patients with RA, many potential causes of pain exist, including pain because of inflammatory joint disease and pain because of structural damage[37,38]. When multiple factors contribute to an individual's overall pain experience, it is likely that treating just 1 pathway (e.g., the serotonin-norepinephrine pathways involved in central pain processing) may not yield clinically important improvements in overall pain. Our observation that milnacipran only reduced pain among patients with RA with ≤ 1 swollen joint supports this hypothesis, indicating that inflammation needs to be very well-controlled for central-acting pain medications to be effective. In a previous study, we reported that the descending inhibitory pain pathways are dysregulated among patients with RA, resulting in greater sensitivity to experimental stimuli[32]. This phenomenon, known as hyperalgesia, may also be associated with an increased sensitivity to endogenous painful stimuli, such as inflammation at joint sites. Future studies with a larger sample size of patients with RA in remission or with low disease activity are necessary to elucidate the role of milnacipran and other central-acting pain medications in this population.

The adverse effects data contribute new knowledge to the published literature because nearly all previous studies of milnacipran excluded individuals with systemic inflammatory diseases such as RA[39,40,41]. Compared with previous study populations[42,43,44], which mostly consisted of patients with FM, our study population was older, less likely to be female, and more likely to be taking corticosteroids and DMARD. Despite these differences, the side effect profile was similar to what has previously been reported[45,46,47].

Strengths of the study include the randomized, crossover design. Because subjects served as their own controls, the effects of confounding were minimized. Critical to the crossover design was the 3-week washout phase, which minimized potential residual effects of milnacipran among participants who started the study in the milnacipran treatment group. The half-life of milnacipran is about 8 h[48,49], and it is recommended that the washout period be at least 5 times the half-life of the active ingredient[50]. Thus, 3 weeks should be more than sufficient to allow for drug washout.

A limitation of our study is the generalizability of the results. The inclusion/exclusion criteria were specifically selected to identify a subgroup of patients with RA who would be most likely to respond to milnacipran and least likely to have serious adverse effects. Thus, the results may not be generalizable to the overall RA population. In addition, the average RA disease duration of individuals in our study was 11.4 years (SD 11.4), and only 5 (15.6%) had disease duration ≤ 2 years. It is possible that individuals with established disease have more structural damage and are less likely to respond to milnacipran than individuals with early disease. A separate study of individuals with early RA is needed to adequately address this question.

A second limitation is that participants were often able to

identify when they were receiving the study drug versus the placebo, even though both study investigators and participants were blinded per study design. Based on conversations with study participants, this was most commonly because of the perception of side effects from the active drug. Of the 41 subjects who received the study drug, 9 dropped out because of side effects or were lost to followup. Although not statistically significant, the average age of subjects who dropped out was nearly 10 years higher than the average age of included subjects. Thus, the effect of milnacipran on older patients with RA needs further study.

Our randomized, blinded crossover trial of milnacipran versus placebo revealed no overall differences in changes in pain intensity, FM symptoms, and experimentally assessed pain measures. In exploratory analyses, we found some evidence for an effect of milnacipran in patients with RA with ≤ 1 swollen joint, but issues of regression to the mean and small sample size require that this finding be examined in a larger sample.


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