A Double-Blind, Placebo-Controlled, Parallel-Group Pilot Study of Milnacipran for Chronic Radicular Pain (Sciatica) Associated With Lumbosacral Disc Disease

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ABSTRACT

Objective: The current study investigates whether milnacipran, an equipotent serotonin-norepinephrine reuptake inhibitor, is effective in reducing chronic radicular pain in patients (N = 11) with lumbosacral disc disease.

Method: This study is a 10-week randomized, parallel-group, double-blind, placebo-controlled trial of milnacipran (100–200 mg/d, dosed twice a day). Subjects (enrolled from October 2010 to September 2011 through the Duke University Pain and Palliative Care Clinic, Durham, North Carolina) included patients with radiologically confirmed disc disease with nerve root compression. The primary outcome measure was radicular pain measured by visual analog scale score (VAS-Rad); patients were asked to specifically rate radicular pain ("shooting or electrical or prickly pain in 1 or both legs"). Secondary outcome measures included nociceptive low back pain by visual analog scale (VAS-Noc), Oswestry Low Back Pain Disability Questionnaire, Neuropathic Pain Questionnaire, Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey, Beck Depression Inventory, and State-Trait Anxiety Inventory. Between-group changes in outcome measures between baseline and endpoint were analyzed using Mann-Whitney U nonparametric measure of central tendency.

Results: Milnacipran treatment yielded statistically significant reduction in radicular pain (VAS-Rad, $P = .01$) and nociceptive low back pain (VAS-Noc, $P = .04$) compared to placebo. No statistically significant between-group differences were observed in the other secondary outcome measures.

Conclusions: In this small pilot study, milnacipran treatment was associated with reduction in radicular and nociceptive low back pain in patients with lumbosacral disc disease. Larger studies of milnacipran in this population are warranted.

Trial Registration: ClinicalTrials.gov identifier: NCT01777581.

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Lumbar radiculopathy caused by injury or irritation to lumbar nerve roots as a result of disc disease is the most common type of neuropathic pain syndrome, with a point prevalence of 4.5% in individuals over the age of 30 years.[1] Many patients report their lower extremity radicular pain to be more severe and disabling than their low back pain. Surprisingly, there are very few repeated-dose analgesic trials in chronic lumbar radicular pain. As such, treatment recommendations tend to be based on extrapolations from data supporting various pharmacologic interventions for other neuropathic pain syndromes such as diabetic peripheral neuropathy and postherpetic neuralgia.[2] Among these interventions are antidepressants, which inhibit both serotonin and norepinephrine.[3,4] The limited data related to the efficacy of such antidepressants on lumbar radiculopathy include a small study[5] suggesting benefit with nortriptyline (n = 5) and a more recent underpowered crossover study (n = 28) comparing nortriptyline monotherapy to morphine monotherapy, combination treatment with both agents, and active placebo[6]; numerical advantage (14% greater pain reduction) of nortriptyline over placebo was noted, although it did not reach statistical significance. Nortriptyline combined with morphine yielded 7% greater pain reduction than placebo.[6] Of note, studies of anticonvulsants have not yielded favorable results in the treatment of lumbar radiculopathy. Topiramate was only marginally effective in treating chronic sciatica in a crossover study of 29 patients,[7] and pregabalin did not reduce chronic lumbar radicular pain in a large industry-sponsored study.[8] Currently, there is reportedly in process a large (N = 204) randomized controlled trial (RCT) of pregabalin in patients with chronic lumbar radicular pain, and results have yet to be published.[9] An early study in 1968 with some methodological limitations showed the nonsteroidal anti-inflammatory drug (NSAID) indomethacin to be superior to placebo in patients with radicular pain, although curiously not superior in patients with only low back pain.[10]

Literature related to the treatment of acute (as opposed to chronic) lumbar radicular pain is more common but certainly not abundant. A multicenter RCT of adalimumab (2 subcutaneous doses), a tumor necrosis factor α inhibitor, was conducted in patients with acute severe radicular pain due to lumbar disc herniation; adalimumab outperformed placebo on visual analog scale (VAS) of leg pain and yielded a higher "response" rate, although the authors note a small effect size.[11] A smaller triple-blind randomized placebo-controlled trial of the tumor necrosis factor α inhibitor etanercept in patients (N = 15) with acute-onset lumbar radicular pain did not show etanercept to be superior to placebo by trend or statistical significance.[12] An RCT of the NSAID piroxicam in 208 patients with acute-onset lumbar radicular pain revealed that piroxicam failed to separate from placebo.[13] Similarly the benzodiazepine drug diazepam failed to show benefit in a double-blind, placebo-controlled trial in patients with acute radicular pain due to lumbar disc prolapse.[14] An RCT of oral prednisone (9-day taper) in acute sciatica demonstrated slightly quicker improvement compared to placebo.[15]

Milnacipran is a serotonin-norepinephrine reuptake inhibitor (SNRI) uniquely shown to inhibit the reuptake of serotonin and norepinephrine

Clinical Points

- Milnacipran (and potentially other serotonin-norepinephrine reuptake inhibitors) may be a useful treatment for neuropathic pain from lumbosacral radiculopathy ("sciatica").
- Milnacipran (and potentially other serotonin-norepinephrine reuptake inhibitors) may improve low back pain related to lumbosacral disc disease.

(in vitro and in vivo) with approximately equal potency.[16,17] SNRIs including milnacipran are believed to inhibit pain by activating descending serotonergic and noradrenergic pathways from brainstem nuclei, and this process may be most effective when ascending pathways are sensitized.[18] Milnacipran has demonstrated efficacy in pain syndromes such as fibromyalgia[19,20] and orofacial pain[21] and has shown benefit in case reports for phantom limb pain, trigeminal neuralgia, and chronic pain of various causes.[22] Other SNRIs have yielded positive results in studies of multiple pain syndromes including but not limited to fibromyalgia,[23] "functional" chest pain and dyspepsia,[24,25] diabetic neuropathy,[26–29] low back pain,[30] headache,[31] and osteoarthritis.[32–34] Research with "antidepressants" including milnacipran on pain syndromes has typically shown that the analgesic effects of these drugs are independent on any changes in mood or anxiety symptoms.[28,35,36] As such, the current study posits that milnacipran may have analgesic effects in patients with lumbosacral radiculopathy, presumably due to the enhancement of descending inhibitory pain pathways.

METHOD

Study Design

The study was a 10-week randomized, parallel-group, double-blind, placebo-controlled trial of milnacipran (100–200 mg/d, dosed twice a day) for radicular pain associated with lumbosacral disk disease. The protocol was conducted at Duke University Medical Center, Durham, North Carolina, and approved by the local Internal Review Board (ClinicalTrials.gov identifier: NCT01777581).

Subjects

Subjects were identified from October 2010 to September 2011 through the Duke University Pain and Palliative Care Clinic during routine follow-up with the investigators and staff and through advertisements placed in a local newspaper. Key inclusion criteria included (1) subject experiences chronic (>6 months) radiologically confirmed radicular pain at least 5 days a week described as sharp or shooting below the level of the knee associated with lumbar or sacral disc disease without suspicion of recent injury; remote (>1 year ago) history of surgical intervention (eg, "failed back syndrome") is allowed provided current symptoms meet severity criterion and (2) subject-rated VAS specifically related to radicular pain is ≥40 mm at screen and baseline visits. Subjects signed written informed consent to participate in the study. Key exclusion criteria included (1) subjects treated with antidepressant or anticonvulsant medication within 4 weeks of screening visit (6 weeks for fluoxetine); (2) subjects who have received procedural intervention (including but not limited to lumbar epidural steroid injection, facet median nerve block or radiofrequency ablation, spinal cord stimulator) within 3 months of screen; (3) subjects with history of bipolar disorder or psychosis as confirmed by the Mini-International Neuropsychiatric Interview (MINI)[37]; and (4) current or recent (within the last 6 months) drug dependence or substance abuse disorder according to *DSM-IV-TR* criteria (excluding nicotine).[38]

Table 1. Baseline Comparisons Between Placebo (n = 4) and Milnacipran (n = 7) on Primary and Secondary Outcome Measures[a]

Variable	Milnacipran	Placebo	*P* Value
VAS-Rad	58.7 (9.4)	67.7 (26.5)	.55
VAS-Noc	57.2 (17.2)	64.7 (43.0)	.69
Neuropathic Pain Questionnaire	415.1 (202.2)	601.0 (336.7)	.27
State-Trait Anxiety Inventory	88.4 (7.1)	86.5 (5.9)	.66
Beck Depression Inventory	13.8 (7.3)	14.3 (9.3)	.94
Oswestry Low Back Pain Disability Index	40.1 (7.5)	44.7 (11.2)	.65
SF-36	96.8 (6.3)	101.3 (4.0)	.25

[a]Values are presented as mean (SD).
Abbreviations: SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey, VAS-Noc = visual analog scale for nociceptive pain, VAS-Rad = visual analog scale for radicular pain.

Interventions

After a brief screening period to determine subject eligibility, appropriate subjects received twice-daily dosing of oral milnacipran or matching placebo according to the following schedule: day 1, 12.5 mg once daily in the morning; day 2–3, 12.5 mg twice daily; day 4–7, 25 mg twice daily, and day 8–70, 50 mg twice daily (potentially increased to 100 mg twice daily at the investigators' discretion on day 15 or later). Outcome measures and safety assessments were obtained at weeks 1, 2, 4, 6, 8, and 10. After the period of efficacy data collection, milnacipran was tapered as follows: day 71–74, 25 mg twice daily; day 75–78, 12.5 mg twice daily; and day 79–82, 12.5 mg once daily in the morning.

Outcome Measures

The primary outcome measure for the study was change in radicular pain as determined by the VAS pain score (VAS-Rad). Patients were asked to specifically rate their radicular pain ("shooting or electrical or prickly pain in 1 or both legs") in contrast to nociceptive or localized low back pain. Secondary outcome measures included the Neuropathic Pain Questionnaire,[39] VAS related to nociceptive pain component (VAS-Noc), Oswestry Low Back Pain Disability Questionnaire,[40] and Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey.[41] To evaluate whether any observed changes in pain/function outcome measures were confounded by changes in anxiety or depression, the self-report Beck Depression Inventory[42] and self-report

Table 2. Mann-Whitney U Comparative *P* Values Between Placebo (n = 4) and Milnacipran (n = 7) Using Change Scores of Final Visit Subtracted From Baseline[a]

Variable	Placebo Group Endpoint Score, Mean (SD)	Milnacipran Group Endpoint Score, Mean (SD)	Placebo Group Change Score	Milnacipran Group Change Score	*P* Value (change scores)[b]	Cohen Effect Size
VAS-Rad	59.7 (43.6)	13.6 (8.5)	8.0	45.1	**.01**	0.71
VAS-Noc	64.7 (46.3)	32.2 (30.4)	0.0	25.1	**.04**	0.64
Neuropathic Pain Questionnaire	511.3 (414.1)	238.3 (279.9)	90.1	176.8	.13	0.36
State-Trait Anxiety Inventory	84.0 (10.9)	90.0 (7.9)	2.5	−1.6	.63	−0.23
Beck Depression Inventory	13.3 (10.3)	11.6 (8.2)	1.0	2.2	.39	0.19
Oswestry Low Back Pain Disability Index	22.5 (15.0)	18.1 (8.0)	0.3	2.0	.63	0.19
SF-36	99.7 (8.9)	97.0 (5.8)	1.6	−0.1	.70	−0.14

[a]See Table 1 for baseline scores.
[b]Bold indicates significance at $P < .05$.
Abbreviations: SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey, VAS-Noc = visual analog scale for nociceptive pain, VAS-Rad = visual analog scale for radicular pain.

State-Trait Anxiety Inventory[43] were included as additional secondary measures.

Statistical Analysis

Summative scores were evaluated at baseline and final visit time points. Baseline values were analyzed using a Mann-Whitney U, a nonparametric measure of central tendency. Change scores were coded for each subject by taking the baseline value and subtracting the final visit score. A Mann-Whitney U was also used to compare between-subject differences in milnacipran versus placebo using the 7 unique outcome measures. An α value was set for significance at .05. We opted not to implement a Bonferroni correction since the Mann-Whitney U is an overtly conservative measure of difference and since we felt the dependent variables were unrelated in construct. In addition, as has been previously asserted, we felt that it was appropriate to waive Bonferroni correction given the small number of hypotheses, which were stated a priori, and the exploratory nature of the study.[44,45] An intention-to treat analysis was used involving the last recorded value in the 10-week trial. Effect sizes were calculated for change scores using the formula suggested by Cohen.[46] Cohen's provision of intervals corresponding to trivial, small, medium, and large effect sizes include < 0.20 (trivial), ≥ 0.20 to < 0.50 (small), ≥ 0.50 to < 0.80 (medium), and ≥ 0.80 (large). These values also correspond to percentages of the control group that fall below the mean values of those in the experimental group.

RESULTS

Two patients assigned to placebo did not complete any postrandomization study visits such that a total of 11 subjects met the criteria for analyses (7 in the milnacipran group and 4 in the placebo group). Three of the 11 did not complete the study and required intention to treat with last observation carried forward, 2 in the milnacipran group and 1 in the placebo group. There were no significant differences in baseline values for any of the outcome measures between the placebo and milnacipran groups (Table 1). Beck Depression Inventory and State-Trait Anxiety Inventory data indicate mild levels of depression in both groups, but no subject met diagnostic criteria for major depressive disorder or an anxiety disorder on the MINI.

The Mann-Whitney U identified statistically significant differences in mean change scores for the primary efficacy measure, the VAS-Rad ($P = .01$), and for the secondary measure, the VAS-Noc ($P = .04$). No significant differences were observed on the other secondary outcome measures. Baseline and endpoint values for all outcome measures as well as *P* values and Cohen effect sizes appear in Table 2.

In the placebo group, 3 subjects completed and 1 withdrew from the study due to lack of efficacy. In the milnacipran group, 5 subjects completed and 2 withdrew due to adverse events (1 subject withdrew due to palpitations in the absence of electrocardiographic changes deemed potentially related to milnacipran, 1 subject withdrew due to complications from gum implant surgery deemed unrelated to milnacipran). Adverse events in the milnacipran group deemed potentially related to study drug included headache (2 of 7 subjects), nausea (1 of 7 subjects), constipation (2 of 7 subjects), dizziness (1 of 7 subjects), elevated blood pressure (1 of 7 subjects), palpitations (1 of 7 subjects), dyspepsia (1 of 7 subjects), urinary hesitancy (1 of 7 subjects), and drowsiness (1 of 7 subjects). Adverse events in the placebo group included headache (2 of 4 subjects) and palpitations (1 of 4 subjects).

DISCUSSION

To the best of our knowledge, the current pilot study is the first to investigate the efficacy and tolerability of milnacipran or any SNRI in the treatment of patients with lumbosacral radiculopathy. This is surprising in light of the well-documented efficacy of SNRIs in other neuropathic pain syndromes. The study has the chief limitation of small sample size. Nonetheless, milnacipran demonstrated statistically significant superiority over placebo on the primary outcome measure of radicular pain and the secondary outcome measure of nociceptive (or "focal") low back pain. In contrast, milnacipran did not demonstrate statistically significant superiority over placebo on the Neuropathic Pain Questionnaire (although trend toward significance was noted). It is possible that a VAS for radicular pain is more sensitive to change than the Neuropathic Pain

Questionnaire such that the sample size was insufficient to detect significant difference between the 2 groups (type II error), although this warrants further investigation. In general, studies of radicular pain have utilized a variety of outcome measures, and a consensus has yet to be reached regarding the most appropriate measures to use. A strength of the current study was the inclusion of mood and anxiety rating scales; consistent with previous research on SNRIs, it does not appear that improvements in pain are due to changes in depressive or anxiety symptoms.

Milnacipran and other SNRIs have shown benefit in a variety of pain syndromes as described, and milnacipran may be particularly well suited as an analgesic in light of its equipotent serotonin and norepinephrine reuptake inhibition. In preclinical animal models, milnacipran has shown superior effects of ameliorating hyperalgesia and allodynia compared to some other antidepressant drugs.[18] Persistent pain results from changes in sensitivity within both ascending and descending pain pathways in the brain and the spinal cord, and both serotonin and norepinephrine are implicated in modulating descending inhibitory pain pathways in the central nervous system.

Although this study has a clear limitation in generalizability due to a small sample size, the notion of exploring the efficacy and tolerability of milnacipran in lumbosacral radiculopathy should be relevant based on a dearth of clinical trial data with SNRIs. In summary, the current double-blind, placebo-controlled, pilot study of milnacipran in patients with lumbosacral radiculopathy demonstrates superiority over placebo in reducing lower extremity pain as well as low back pain itself. In light of this finding and the well-established efficacy of milnacipran and other SNRIs in pain syndromes, larger well-powered studies of milnacipran in radicular syndromes are warranted.

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Potential conflicts of interest: **Dr Patkar** has served as a consultant to Braeburn, Bristol-Myers Squibb, Cubist, Otsuka, and Titan; has received grant/research support from EnVivio, Forest, Lundbeck, Shire, Sunovion, and Titan; has received honoraria from Alkermes Otsuka, and Pfizer; and has served on the speakers' or advisory boards of Alkermes, Otsuka, and Sunovion. **Drs Marks** and **Pae** report no conflicts of interest related to the subject of this article.

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