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Effects of Paroxetine and Milnacipran on Pain Disorder

Kenji SANADA[1)], Masaru MIMURA[2)], Eiji UCHIDA[3)],
Nobumasa KATO[1)] and Akira IWANAMI[1)]

Abstract: The outcomes of treatment for pain disorder are generally disappointing: symptoms are poorly controlled, they are seldom managed by experts, and they are often long standing. The aim of the present study was to compare the therapeutic effectiveness of paroxetine and milnacipran for outpatients with pain disorder. The study was performed on 43 consecutive outpatients with pain disorder diagnosed according to DSM-IV-TR criteria. Patients were treated with either antidepressant for 8 weeks. Pain was self-assessed using the Short-Form McGill Pain Questionnaire (SF-MPQ), the total Pain Rating Index (t-PRI), Present Pain Intensity (PPI), and visual analogue scale (VAS). In addition, pain was evaluated objectively using Pain Vision (a machine devised by NIPRO for semiquantitative measurements). Possible depressive symptoms were rated on the Hamilton Depression Scale (HAM-D) and the Zung Self-rating Depression Scale (SDS). Although VAS scores decreased significantly over the course of the 8-week trial in both the paroxetine- and milnacipran-treated groups (from 6.6 ± 2.3 to 4.8 ± 3.0 [$P = 0.01$] and from 7.5 ± 2.4 to 5.4 ± 3.3 [$P = 0.03$], respectively), the t-PRI decreased only in the paroxetine group (from 13.9 ± 10.1 to 7.6 ± 7.5; $P = 0.01$). The Pain Vision indicated a tendency for decreased pain in both groups, with no significant differences between them. There were no significant changes in the SDS in either group, but the HAM-D decreased significantly in the milnacipran-treated group (from 7.8 ± 4.0 to 6.7 ± 3.9; $P = 0.04$). The results of the present study suggest that both paroxetine (a selective serotonin reuptake inhibitor) and milnacipran (a selective serotonin–noradrenaline reuptake inhibitor) may decrease pain in individuals with pain disorder.

Key words: pain disorder, antidepressants, paroxetine, milnacipran

Introduction

Many people suffer from various types of chronic pain. Despite the heavy social burden, the outcomes of treatment for pain are disappointing: symptoms are poorly controlled, they

[1)] *Department of Neuropsychiatry, Showa University School of Medicine,* 6-11-11 Kita-Karasuyama, Setagaya-ku, Tokyo 157-8577, Japan.
[2)] *Department of Neuropsychiatry, Keio University School of Medicine.*
[3)] *Showa University, Office for Promoting Medical Research.*

are seldom managed by experts, and they are often long standing. In addition, the risk of suicide is increased in patients with chronic pain[1]. Many different somatic and psychiatric diseases may cause chronic pain. The latter include depression and somatization, delusional, and anxiety disorders. The definition of pain adopted by the International Association for the Study of Pain (IASP) is essentially that pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[2]. From this viewpoint, pain is an emotional experience, and it is easy to understand why chronic pain coexists with psychiatric diseases and mood changes.

There are no therapeutic guidelines for the treatment of pain disorder. In general, analgesics have limited effectiveness and may lead to drug abuse and/or dependence. Therefore, tricyclic antidepressants (TCAs) are often used to treat pain disorders. The guidelines of the American Society of Anesthesiologists[3] recommend the use of TCAs and selective serotonin-noradrenaline re-uptake inhibitors (SNRIs) for the relief of chronic pain of varying etiology. It is unclear whether there are any benefits of using selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines for the treatment of diabetic neuropathy and chronic pain. Although previous studies have reported that dual-action antidepressants with serotonergic and noradrenergic effects, such as TCAs and SNRIs, are more effective than single-action antidepressants, such as SSRIs, for pain relief[4–8], recent studies have also demonstrated the effectiveness of SSRIs in relieving pain[9,10]. Aragona *et al* compared the SSRI citalopram with the noradrenaline re-uptake inhibitor reboxetine in outpatients with pain disorder[9] and found that citalopram has a moderate pain-relieving effect for patients with pain disorder that appears to be independent of changes in depressive scores. Similarly, Inoue reported that the SSRI paroxetine was a strong blocker of $P2X_4$ receptors[10], and $P2X_4$ receptor antagonists may have excellent therapeutic potential in the treatment of neuropathic pain. Thus, the question as to whether there are any differences in efficacy between SSRIs and SNRIs remains unresolved.

In the clinical setting, pain is usually evaluated subjectively, such as by the McGill Pain Questionnaire (MPQ)[11] or the Short-Form McGill Pain Questionnaire (SF-MPQ)[12]. However, because of psychological reasons, it is difficult to evaluate pain accurately using subjective measures. Accordingly, objective or quantified evaluation of pain is warranted. The Pain Vision is a machine produced by NIPRO (Pain Vision PS-2100) that has been developed specifically to provide a semiquantitative measure of pain.

The aim of the present study was to compare the therapeutic effectiveness of paroxetine and milnacipran for outpatients with pain disorder. Pain was evaluated both subjectively (SF-MPQ) and objectively (Pain Vision).

Materials and Methods

Study subjects

The study subjects were selected from patients (20 years or older) who regularly attended

the psychiatry clinic at Showa University East Hospital. Exclusion criteria included pregnancy, thyroid gland malfunction, glaucoma, and urinary retention.

All participants were examined by a psychiatrist and had to fulfill the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision; DSM-IV-TR)[13] criteria for pain disorder, namely pain disorder associated with psychological factors or pain disorder associated with psychological factors and general physical diseases.

Study design

Patients were allowed to continue analgesic and anti-inflammatory medications at the same dose during the pretreatment period, although they were not allowed to increase medication doses during the treatment period. Patients were allowed to take low doses of benzodiazepines for sleep disturbances, but were not allowed to take anti-anxiety agents for pain relief.

Patients were randomly assigned to receive either paroxetine or milnacipran for 8 weeks using random tables with the first (and original) generator[14]. The doses of paroxetine ranged from 10 to 40 mg/day, whereas those of milnacipran ranged from 50 to 150 mg/day. The initial doses of paroxetine and milnacipran were 10 and 50 mg, respectively, although these doses were suitably adjusted during the treatment period.

Assessments

Patients were evaluated at baseline and then again after 4 and 8 weeks treatment. Pain was self-assessed using the SF-MPQ, the total Pain Rating Index (t-PRI), Present Pain Intensity (PPI), and using a visual analogue scale (VAS). In addition, pain was evaluated objectively with the Pain Vision. By using electrode pads attached to the subject's arm and measuring the current perception threshold and the current corresponding to the pain, the Pain Vision enables the magnitude of the pain to be semiquantified. The index relating to the magnitude of pain is based on the Pain Index and Pain Frequency. Possible depressive symptoms were rated in each of the subjects using the Hamilton Depression Scale (HAM-D) and Zung Self-rating Depression Scale (SDS).

All adverse events were recorded: those noted by psychiatrists during the treatment period and those of which the subjects complained. Newly expressed symptoms and symptoms that worsened during the treatment period were recorded as adverse events. If adverse events occurred, we recorded the symptoms, the severity of the symptoms, and the number of manifestations and took appropriate action.

The present study was performed in accordance with ethical guidelines and principles for clinical trials based on the Declaration of Helsinki. The study, including the risks and benefits of participation, was fully explained to patients in a written document. Before enrolling in the study, patients were required to provide written informed consent.

Statistical analysis

All data were analyzed using SAS 9.1.3® and managed using PROMASYS®. Efficacy measures were analyzed in the intent-to-treat population, which was defined as patients who underwent the randomization process and took at least one dose of paroxetine or milnacipran and had at least one post-baseline efficacy evaluation. Safety parameters were analyzed for all patients enrolled in the study who took at least one dose of study medication. If patients dropped out prematurely from the study or discontinued treatment, the last evaluation score of the day was treated as an evaluation score at 8 weeks using the Last Observation Carried Forward (LOCF) method.

Differences in demographic variables and clinical characteristics between the two treatment groups were assessed using Fisher's exact test for categorical variables and the *t*-test for continuous variables. The *t*-test was used to evaluate differences between baseline and the last evaluation score for the primary outcome variables (t-PRI, VAS, PPI) and the secondary outcome variables (Pain Vision, HAM-D, SDS) within each group. Two-sided $P < 0.05$ was considered significant. Unless indicated otherwise, data are presented as the mean ± SD.

Results

In all, 43 patients, enrolled in the trial, were randomly divided into two groups. Twenty-one patients were assigned to receive paroxetine and 22 were assigned to receive milnacipran. Eighteen patients were unable to complete the treatment period. Four patients were lost to follow-up at 4 weeks (one in the paroxetine group and three in the milnacipran group). Twelve patients (five in the paroxetine group and seven in the milnacipran group) dropped out because of adverse effects; another two patients in the milnacipran group dropped out due to inefficacy of the medication. Accordingly, at the end of the treatment period, there were 15 patients remaining in the paroxetine group (10 men; mean age 55.2 ± 16.3 years) and 10 patients remaining in the milnacipran group (four men; mean age 49.9 ± 13.6 years). The demographic characteristics of all study subjects are given in Table 1.

There was a significant decrease in t-PRI in the paroxetine-treated group at the end of the 8-week treatment period compared with baseline (7.6 ± 7.5 vs. 13.9 ± 10.1, respectively; $P = 0.01$), but no significant change in t-PRI in the milnacipran-treated group (7.9 ± 4.6 vs. 13.0 ± 9.1, respectively; $P = 0.11$; Fig. 1; Table 2). Pain scores on the VAS decreased significantly in both groups (from 6.6 ± 2.3 to 4.8 ± 3.0 in the paroxetine-treated group [$P = 0.01$]; and from 7.5 ± 2.4 to 5.4 ± 3.3 in the milnacipran-treated group [$P = 0.03$]). There was a tendency for PPI to decrease in both groups, but the differences failed to reach statistical significance (from 2.7 ± 1.2 to 1.9 ± 1.3 in the paroxetine-treated group [$P = 0.10$]; and from 3.0 ± 1.3 to 2.1 ± 0.9 in the milnacipran-treated group [$P = 0.07$]). When pain was evaluated semiquantitatively using the Pain Vision, no significant differences were observed between the two groups, although there were tendencies for decreases in the Pain Index and Pain Frequency in both groups following treatment. There were no significant changes in

Table 1. Demographic characteristics

Characteristic	Paroxetine (N = 15)	Milnacipran (N = 10)	*p* value
Gender			0.24
Male, N (%)	10 (66.7)	4 (40.0)	
Female, N (%)	5 (33.3)	6 (60.0)	
Age (years)	55.2 ± 16.3	49.9 ± 13.6	0.41
Range	32–79	27–68	

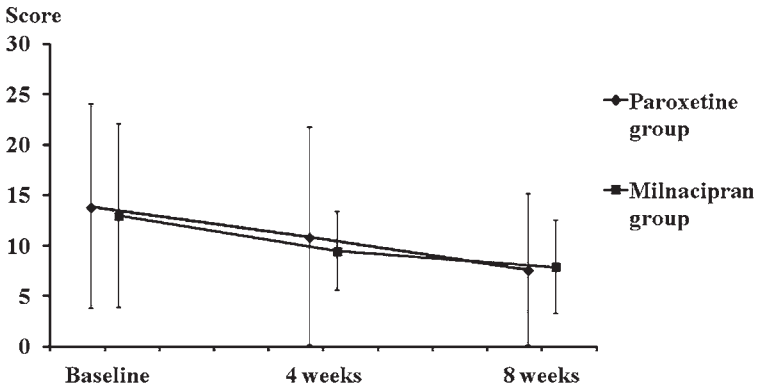

Fig. 1. Significant decreases were seen in the total Pain Rating Index (t-PRI) in the paroxetine-treated group over the course of the 8-week trial (from 13.9 ± 10.1 to 7.6 ± 7.5; $P = 0.01$), but there was no significant change in the milnacipran-treated group (from 13.0 ± 9.1 to 7.9 ± 4.6; $P = 0.11$). Data are the mean ± SD. $P < 0.05$ compared with baseline values.

SDS in either group (from 44.4 ± 13.9 to 43.9 ± 12.1 in the paroxetine-treated group [$P = 0.86$]; and from 45.2 ± 11.6 to 40.5 ± 9.7 in the milnacipran-treated group [$P = 0.11$]), but HAM-D decreased significantly after treatment in the milnacipran-treated group (from 7.8 ± 4.0 to 6.7 ± 3.9; $P = 0.04$; Table 2).

Seven patients (one in the paroxetine group and six in the milnacipran group) withdrew from treatment before the first outcome assessment. Eleven patients (five in the paroxetine group and six in the milnacipran group) withdrew from the study before the second outcome measurement.

Table 3 lists adverse events. Most adverse events were mild to moderate in severity, and no patient experienced any serious adverse event. The most common adverse events were nausea, somnolence, and constipation.

Discussion

To the best of our knowledge, the present study is the first to compare an SSRI with

Table 2. Inter-group comparison : change from baseline at the final visit

Scale	Paroxetine (N = 15)			*p* value	Milnacipran (N = 10)			*p* value	*p* value
	Baseline	Final visit	Change from baseline		Baseline	Final visit	Change from baseline		
SF-MPQ									
t-PRI	13.9 ± 10.1	7.6 ± 7.5	−6.3 ± 7.6	0.01	13.0 ± 9.1	7.9 ± 4.6	−5.1 ± 9.2	0.11	0.73
VAS	6.6 ± 2.3	4.8 ± 3.0	−1.8 ± 2.2	0.01	7.5 ± 2.4	5.4 ± 3.3	−2.1 ± 2.6	0.03	0.78
PPI	2.7 ± 1.2	1.9 ± 1.3	−0.7 ± 1.6	0.1	3.0 ± 1.3	2.1 ± 0.9	−0.9 ± 1.4	0.07	0.79
HAM-D	7.0 ± 3.1	5.4 ± 3.5	−1.6 ± 3.1	0.07	7.8 ± 4.0	6.7 ± 3.9	−1.1 ± 1.4	0.04	0.64
SDS	44.4 ± 13.9	43.9 ± 12.1	−0.5 ± 10.3	0.86	45.2 ± 11.6	40.5 ± 9.7	−4.7 ± 8.5	0.11	0.29
Pain Vision									
Pain Index	3.5 ± 3.0	2.3 ± 1.3	−1.2 ± 2.5	0.07	5.7 ± 3.5	4.3 ± 3.5	−1.4 ± 2.2	0.08	0.88
Pain Frequency	251.3 ± 298.8	126.9 ± 132.6	−124.4 ± 248.1	0.07	471.4 ± 353.3	332.5 ± 346.2	−138.9 ± 224.4	0.08	0.88

SF-MPQ, Short-Form McGill Pain Questionnaire ; t-PRI, total Pain Rating Index ; VAS, Visual Analogue Scale ; PPI, Present Pain Intensity ; HAM-D, Hamilton Depression Scale ; SDS, ZungSelf-rating Depression Scale. All data are expressed as mean and std. dev.

Table 3. Adverse events

Event	Paroxetine (N = 15) N (%)	Milnacipran (N = 10) N (%)
Somnolence	5 (33.3)	1 (0.1)
Nausea	1 (0.07)	5 (50)
Constipation	0	6 (60)
Giddy feeling	2 (13.3)	1 (10)
Residual urine	0	3 (30)
Palpitation	0	2 (20)
Fatigue	2 (13.3)	0
Headache	1 (0.07)	1 (10)
Insomnia	1 (0.07)	1 (10)

an SNRI for patients with pain disorder in the psychiatric setting. All participants in the present study were examined by a board psychiatrist and had to fulfill DSM-IV-TR criteria for pain disorder. In addition, pain was evaluated not only subjectively using the SF-MPQ and VAS, but also objectively using the Pain Vision. The results show that both paroxetine and milnacipran are beneficial in reducing pain. Although the VAS scores were significantly decreased over the course of the 8-week trial in both groups, t-PRI only decreased significantly in the paroxetine-treated group.

Previous studies demonstrated that antidepressants that affect noradrenaline, such as TCAs and SNRIs, are more effective pain relievers than single-action serotonergic anti-

depressants[4-8]. It has also been reported that SSRIs are less effective than TCAs and monoamine oxidase inhibitors (MAOIs) for the treatment of physical symptoms associated with depression[15]. There is more evidence supporting the alleviation of pain by dual-action antidepressants than single-action serotonergic antidepressants.

However, in the present study, paroxetine was as effective as milnacipran. This may be due, in part, to the fact that paroxetine is a strong blocker of $P2X_4$ receptors[10]. Activated microglia expresses $P2X_4$ receptors after nerve injury, and this upregulation of $P2X_4$ receptors results in the release of brain-derived neurotrophic factor, a key molecule in neuropathic pain. $P2X_4$ receptor antagonists may be candidate therapeutic drugs for the treatment of neuropathic pain. A recent study has suggested that citalopram, another SSRI, may have a moderate analgesic effect in pain disorders, which has clinical implications for those patients who are intolerant of TCAs[9]. Further studies are warranted to determine the pain-relieving effects of individual SSRIs.

Here, both paroxetine and milnacipran effectively ameliorated pain, but the mechanisms of action of each drug may be different. Although the SDS remained unchanged in both groups, the HAM-D decreased significantly after 8 weeks of treatment with milnacipran only, suggesting that milnacipran may have improved both pain and mood. Some studies have reported that antidepressants exert their analgesic and antidepressant effects independently[9, 16]. Because no firm conclusions can be reached on the basis of the results of the present study, future studies are needed to clarify whether the antidepressant and pain-relieving effects of the SSRIs and SNRIs are independent of each other.

There are several limitations to the present study. First, the sample size was small and the drop-out rate was high. Generally, high drop-out rates are common for pharmacological trials of somatoform disorders[17] because patients with somatization disorders, including pain disorders, are the most difficult to treat, with the conditions being largely treatment resistant. Further studies with a larger sample are needed to confirm the therapeutic effectiveness of paroxetine and milnacipran for pain disorder. Second, the dose of antidepressants used in the present study was not fixed over the course of the 8-week trial, and the flexible dosing of paroxetine and milnacipran may have affected the therapeutic effectiveness of the treatment regimen. Third, the present study focused only on paroxetine and milnacipran. There are many drugs in both the SSRI and SNRI categories, such as sertraline and s-citalopram (SSRIs) and duloxetine and venlafaxine (SNRIs), and it is not clear whether these drugs are as effective as paroxetine and milnacipran. This issue should be explored in future studies.

In conclusion, the present study is the first to compare the therapeutic effectiveness of paroxetine and milnacipran for pain disorder in a psychiatric setting. The main finding of the study is that both paroxetine and milnacipran are beneficial in reducing pain. Significant decreases were seen in t-PRI in the paroxetine group and in VAS scores in both groups during the trial. In contrast with previous studies, paroxetine, a single-action serotonergic drug, had the same pain-relieving effect as milnacipran, a dual-action serotonergic and

noradrenergic drug. Despite the limitations of the present study, the results indicate that both the SSRI and SNRI could reduce pain in individuals with pain disorder.

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References

1) Towards better control of chronic pain. *Lancet* **375**：1754（2010）
2) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommitee on Taxonomy. *Pain* **3**(Suppl.)：S1-S226（1986）
3) American Society of Anesthesiologists Task Force on Chronic Pain Management and American Society of Regional Anesthesia and Pain Medicine：Practice guidelines for chronic pain management：an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology* **112**：810-833（2010）
4) Fishbain DA：Evidence-based data on pain relief with antidepressants. *Ann Med* **32**：305-316（2000）
5) Fishbain DA, Cutler R, Rosomoff HL and Rosomoff RS：Evidence-based data from animal and human experimental studies on pain relief with antidepressants：a structured review. *Pain Med* **1**：310-316（2000）
6) O'Malley PG, Jackson JL, Santoro J, Tomkins G, Balden E and Kroenke K：Antidepressant therapy for unexplained symptoms and symptom syndromes. *J Fam Pract* **48**：980-990（1999）
7) Staiger TO, Gaster B, Sullivan MD and Deyo RA：Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* **28**：2540-2545（2003）
8) Van Tulder M and Koes B：Low back pain and sciatica（chronic）. *Clin Evid* **9**：1260-1276（2003）
9) Aragona M, Bancheri L, Perinelli D, Tarsitani L, Pizzimenti A, Conte A and Inghilleri M：Randomized double-blind comparison of serotonergic（citalopram）versus noradrenergic（reboxetine）reuptake inhibitors in outpatients with somatoform, DSM-IV-TR pain disorder. *Eur J Pain* **9**：33-38（2005）
10) Inoue K：Relational study of pain：activated microglia and P2X4 in neuropathic pain signaling. *Pain Res* **22**：163-169（2007）
11) Melzack R：The McGill Pain Questionnaire：major properties and scoring methods. *Pain* **1**：277-299（1975）
12) Melzack R：The short-form McGill Pain Questionnaire. *Pain* **30**：191-197（1987）
13) American Psychiatric Association：Diagnostic and Statistical Manual of Mental Disorders：DSM-IV-TR, 4th ed., text revision, American Psychiatric Association Press, Washington, DC（2000）
14) Gerard ED：Randomization.com, http://www.randomization.com/,（accessed 08/30/2012）
15) Jain R：Single-action versus dual-action antidepressants. *Prim Care Companion J Clin Psychiatry* **6**(Supple 1)：7-11（2004）
16) Onghena P and Van Houdenhove B：Antidepressant-induced analgesia in chronic non-malignant pain：a meta-analysis of 39 placebo-controlled studies. *Pain* **49**：205-219（1992）
17) Altamura AC：Psychopharmacological treatments of somatoform disorders. *Eur Neuropsychopharmacol* **5**：176-177（1995）

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