Milnacipran: Beyond a Role of Antidepressant

Chi-Un Pae, MD, PhD,† David M. Marks, MD,† Manan Shah, MD,† Changsu Han, MD, PhD,†‡ Byung-Joo Ham, MD, PhD,§ Ashwin A. Patkar, MD,† and Prakash S. Masand, MD†*

Abstract: Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI) with negligible effects on any presynaptic or postsynaptic receptors. Milnacipran has unique pharmacokinetic and pharmacodynamic characteristics that distinguish it from the other marketed serotonin and norepinephrine reuptake inhibitors, venlafaxine, desvenlafaxine, and duloxetine such as equipotent serotonin and norepinephrine reuptake inhibition and a linear dose-concentration trend at therapeutic doses. The half-life of milnacipran is approximately 8 hours. In addition, milnacipran does not inhibit the cytochrome P 450 system, indicating minimal propensity for drug-drug interactions. The antidepressant efficacy of milnacipran has been clearly established in a number of randomized, double-blind, placebo-controlled clinical trials, and it has been widely used for treating major depressive disorder. Moreover, evidence suggests that milnacipran is effective and tolerable in the treatment of fibromyalgia and may have usefulness for fatigue and anxiety symptoms. The current paper reviews researches conducted to date that is relevant to the efficacy, tolerability, and mechanism of action of milnacipran in the treatment of depression, fibromyalgia, and other psychiatric syndromes. Future directions of research are also identified.

Key Words: milnacipran, antidepressant, fibromyalgia, pain, fatigue, anxiety

(*Clin Neuropharm* 2009;32: 355–363)

Selective serotonin reuptake inhibitors (SSRIs) have become first-line treatments for major depressive disorder (MDD), anxiety disorders, and multiple other psychiatric disorders. The main advantages of SSRIs over the older tricyclic antidepressants (TCAs) are safety and tolerability, which ultimately affect compliance and clinical outcomes. Yet, the most recently proposed pathophysiology of MDD involves impairment in the neurotransmission of norepinephrine (NE) and serotonin (5-HT). The clinical ramifications of this notion are unclear, although it is plausible that enhancement of neurotransmission of both monoamines may offer advantages in efficacy. Such an idea led to the development of antidepressant drugs that inhibit the reuptake of 5-HT and NE known as 5-HT and NE reuptake inhibitors (SNRIs), and currently there are 4 commercially available SNRIs including venlafaxine (and venlafaxine extended release), desvenlafaxine, duloxetine, and milnacipran. Two recent large meta-analyses of studies comparing SNRIs to SSRIs in the treatment of MDD revealed 4.3% to 5.9% higher rate of remission in favor of SNRIs,[1,2] supporting the concept that enhancement of both neurotransmitter systems may confer efficacy advantage.

Among the aforementioned SNRIs, milnacipran has a unique property in that it blocks 5-HT and NE reuptake equally, whereas greater selectivity at 5-HT reuptake sites is characteristic of venlafaxine (30-fold) and duloxetine (10-fold). In addition, milnacipran does not have inhibitory effects on cytochrome P (CYP) 450 enzymes, and it shows less binding affinity to neurotransmitter receptors liable to cause adverse events and simple pharmacokinetics. Of note, in preclinical animal models, milnacipran has shown superior effects of ameliorating hyperalgesia and allodynia compared to some other antidepressant drugs.[1–5]

The present paper was aimed to review currently available data that are relevant to the efficacy, tolerability, and mechanism of action of milnacipran in the treatment of fibromyalgia and other psychiatric syndromes such as fatigue and anxiety. Future directions of research are identified as well.

A comprehensive search of Medline was performed using the terms milnacipran, MDD, anxiety, fibromyalgia, pain, and fatigue with no restriction on year. The manufacturer clinical trial registry, abstracts, and posters from recent academic society meetings such as the American Psychiatric Association and American Academy of Pain Medicine were also reviewed.

PHARMACOKINETICS

Milnacipran is well absorbed after oral dosing, reaching 85% bioavailability,[6] and the rapidity and extent of absorption of

*Department of Psychiatry, Holy Family Hospital, The Catholic University of Korea College of Medicine, Bucheon, Kyounggi-Do, Republic of Korea; †Department of Psychiatry and Behavioral Medicines, Duke University Medical Center, Durham, NC; ‡Department of Psychiatry, The Korea University; and §Department of Psychiatry, Hangang Sacred Heart Hospital, Hallym University Medical Center, Seoul, South Korea.

Address correspondence and reprint requests to Chi-Un Pae, MD, PhD, Department of Psychiatry, Holy Family Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Pucheon, Kyounggi-Do 420-717, Republic of Korea; E-mail: pae@catholic.ac.kr

Dr Pae has received a research grant from GlaxoSmithKline Korea, GlaxoSmithKline, AstraZeneca Korea, Janssen Pharmaceuticals Korea, Eli Lilly and Company Korea, Korean Research Foundation, Otsuka Korea Pharmaceuticals, Wyeth Korea, Catholic Medical Center, and Korean Institute of Science and Technology Evaluation and Planning; has received honoraria and is on the speaker's bureaus of GlaxoSmithKline Korea, Lundbeck Korea, AstraZeneca Korea, Janssen Pharmaceuticals Korea, Eli Lilly and Company Korea, McNeil Consumer and Specialty Inc, and Otsuka Korea Pharmaceuticals, Inc.

Drs Shah and Ham report no conflicts of interest.

Dr Marks is a consultant for Bristol-Myers Squibb, is on the speakers' bureau of Eli Lilly and Company, and has received research support from DOV, Endo, Janssen, GlaxoSmithKline, Pfizer, Bristol-Myers Squibb, Johnson & Johnson, Eli Lilly and Company, Saegis Pharmaceuticals, Sepracor, and Somaxon.

Dr Han has received Korea University Alumni Grant.

Dr Patkar is a consultant for Bristol-Myers Squibb, GlaxoSmithKline, and Reckitt Benckiser; is on the speaker's bureau of Bristol-Myers Squibb, GlaxoSmithKline, and Reckitt Benckiser; has received research support from National Institutes of Health, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, McNeil Consumer and Specialty Inc, Organon, Jazz Pharmaceuticals, and Pfizer, Inc.

Dr. Masand is a consultant for Bristol-Myers Squibb, Cephalon Inc, Eli Lilly and Company, Forest laboratories Inc, GlaxoSmithKline, i3CME, Janssen Pharmaceutica, Jazz Pharmaceuticals, Organon, Pfizer, Inc, Targacept Inc, and Wyeth Pharmaceuticals; is on the speaker's bureau of Astra-Zeneca, Bristol-Myers Squibb, Forest laboratories Inc, GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc, and Wyeth Pharmaceuticals; has received research support from AstraZeneca, Bristol-Myers Squibb, Cephalon Inc, Eli Lilly and Company, Forest laboratories Inc, GlaxoSmithKline, Ortho McNeil Pharmaceutical, Inc, Janssen Pharmaceutica, and Wyeth Pharmaceuticals.

DOI: 10.1097/WNF.0b013e3181ac155b

milnacipran is unaffected by food intake.[7] The peak plasma concentration is reached 0.5 to 4 hours after oral dosing, and the elimination half-life of milnacipran is approximately 8 hours.[8] Milnacipran has weak affinity[9] to plasma protein of less than 13%. Steady-state plasma level is reached within 2 to 3 days after repeated oral dosaging of 100 mg/d. Only trace amounts of active metabolites are detected in humans, and none of the metabolites of milnacipran have any pharmacological activity at levels found clinically. Milnacipran is excreted unchanged renally and is metabolized via oxidation and glucuronidation such that CYP450 isoenzymes have a minimal role. There is limited reciprocal pharmacokinetic interaction between milnacipran and CYP isoenzymes as evidenced by a number of preclinical studies using a variety of probe medications.[10,11] Accordingly clinicians may be flexible in the therapeutic combination of medications with milnacipran in clinical practice.[10,11] Preclinical studies suggest that liver dysfunction and advanced age do not warrant dose adjustment.[12] In contrast, decreased elimination of milnacipran and reduced quantity of drug recovered in urine have been correlated to the degree of renal impairment in patients with reduced creatinine clearance. A 3-fold increase in elimination half life was observed in patients with renal impairment.[7] Dose adjustment in the context of renal impairment is straightforward based on this predictable effect. In addition, research has demonstrated no cognitive or psychomotor adverse effects in healthy young volunteers who are given oral milnacipran up to 100 mg/d or in elderly volunteers who are given oral milnacipran at 75 mg/d in divided dosages.[13]

PHARMACODYNAMICS

Milnacipran inhibits the reuptake of both 5-HT and NE in vitro and in vivo with approximately equal potency, showing no effect on dopamine reuptake.[2] Preclinical data have shown that 10 and 40 mg/kg of milnacipran led to 3- to 4-fold increase in brain NE and 5-HT levels within 2 hours, which were sustained for 6 hours.[1] Long-term administration of milnacipran has been also found to maintain a significant increase in the basal synthesis of both 5-HT and NE.[1,14,15]

Milnacipran is devoid of interactions at any known neurotransmitter receptors or ion channels.[1,14] In an animal study, long-term administration of milnacipran did not alter the number of β-adrenergic receptors in the cerebral cortex, in contrast to imipramine and desipramine that decreased the binding of β-adrenoceptors. In addition, it was shown that long-term administration of milnacipran was not associated with alterations of α-1 or α-2 adrenoceptors, 5-HT1 or 5-HT2 receptors, or benzodiazepine binding sites. Hence, milnacipran seems to act exclusively presynaptically, inhibiting the uptake of 5-HT and NE.[2] In preclinical studies[8] and clinical trials,[16,17] milnacipran at dosages of 50 to 400 mg/d was associated with minimal orthostatic hypotension, anticholinergic adverse effects, and sedation as predicted by its lack of appreciable affinity for α-1 adrenergic, muscarinic, or histamine receptors.

CLINICAL DATA

Major Depressive Disorder: Brief Overview

The efficacy of milnacipran in the treatment of MDD for 6 to 24 weeks has been established in a number of randomized, double-blind, placebo-controlled clinical trials (RCTs)[17,18] and in a series of randomized, double-blind, comparator studies using TCAs (amitiptyline,[16] imipramine,[19–21] and clomipramine[22,23]) or SSRIs (fluoxetine,[24–26] fluvoxamine,[27,28] paroxetine,[29] and sertraline[30]). A meta-analysis revealed a significant difference between milnacipran (n = 227) and placebo (n = 211) in rate of response as defined by 50% reduction or more in 17-item Hamilton (54.6% and 40.6%, respectively, $P < 0.01$) and Montgomery-Åsberg Depression Rating Scale scores (52.4% and 39.8%, respectively, $P < 0.01$).[31] Individual direct comparison studies of milnacipran with TCAs and SSRIs have shown mixed results but have been limited by small sample size and heterogeneity of study methodology. Early meta-analyses of RCTs in MDD indicated that milnacipran is equivalent in efficacy and superior in tolerability compared with TCAs[32] and superior in efficacy and equivalent in tolerability compared with SSRIs.[33] However, a recent large meta-analysis comparing milnacipran to TCAs and SSRIs that included 16 RCTs (n = 2277) failed to demonstrate significant differences in achieving clinical improvement, remission, or tolerability between class and individual agents.[34] The response rates as defined by 50% reduction or more in Hamilton Depression Rating Scale scores in comparator studies with milnacipran is presented in Figure 1. Studies directly comparing milnacipran to other SNRIs (ie, duloxetine and venlafaxine) in the treatment of MDD have yet to be published.

The durability of the benefit of milnacipran in the treatment of MDD has been demonstrated in one study of 1-year duration; a significantly lower recurrence rate of 16.3% (17/104; $P < 0.05$) occurred with milnacipran treatment compared with placebo with 23.6% (26/110), without differences in tolerability between the 2 groups.[35] In addition, this study revealed superiority of long-term milnacipran treatment compared with placebo in quality of life measures such as social, communication, mobility, and social scores ($0.04 < P < 0.02$).[36]

A dose-finding study using twice-daily dosing showed the superiority of 100 and 200 mg total a day of milnacipran

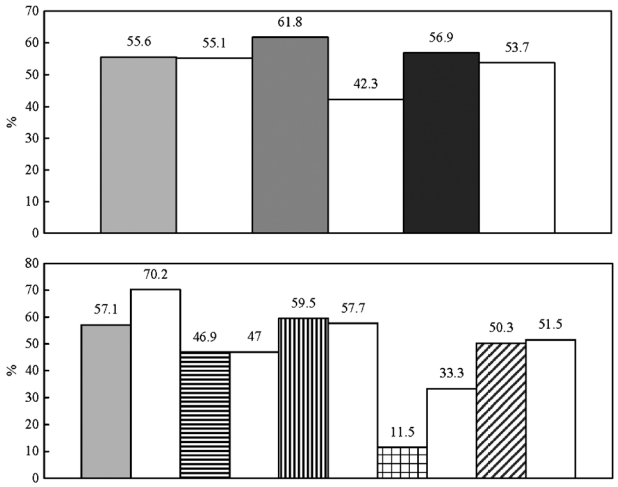

FIGURE 1. Responder rates (a ≥50% reduction in Hamilton Depression Rating Scale scores—17, 21, and 24 items) of treatment in randomized, double-blind, comparator trials of milnacipran versus tricyclic antidepressants (TCA5, IMI [n = 119/214] vs MNP [n = 122/216]; CMI [n = 34/55] vs MNP [n = 22/52]; TCAs as a class [n = 153/269] vs all MNP [n = 144/268], left to right direction on upper figure)[19–22] or selective 5-HT reuptake inhibitors (SSRIs, FVX [n = 32/56] vs MNP [n = 40/57]; FOX [n = 105/224] vs MNP [n = 158/336]; PRX [n = 91/153] vs MNP [n = 86/149]; SRT [n = 3/26] vs MNP [n = 9/27]; SSRIs as a class [n = 231/459] vs all MNP [n = 293/569], left to right direction on lower figure)[24–26,28–30] for MDD. IMI indicates imipramine; CMI, clomipramine; FOX, fluoxetine; FVX, fluvoxamine; MNP, milnacipran; PRX, paroxetine; SRT, sertraline.

compared with placebo, whereas 50 mg total a day failed to separate from placebo.[18] Although some studies[37,38] have demonstrated a linear dose-efficacy relationship, other data contradict this finding.[34]

An analysis[31] of a database of more than 3300 patients shows that overall safety and tolerability of milnacipran are superior to those of TCAs and comparable to those of SSRIs, which were in line with other large meta-analysis of RCTs for MDD.[32] Higher incidence of dysuria with milnacipran, higher frequency of nausea and anxiety with SSRIs, and higher frequency of cholinergic and cardiovascular adverse effects with TCAs were consistently reported.[31,32] Early dropout rates because of adverse events were also higher in TCA-treated patients than in milnacipran-treated patients. Data also indicate that 50 mg twice a day is better tolerated than 100 mg twice a day of milnacipran, supporting 50 mg twice a day as the preferred dose for most patients.[31]

In summary, milnacipran seems to be efficacious and tolerable in the treatment of MDD. It compares favorably to TCAs and SSRIs as described. Further research in MDD is warranted to confirm the long-term efficacy and tolerability of milnacipran and to compare milnacipran with other SNRIs.

Fibromyalgia

Overview

The American College of Rheumatology proposed a diagnostic criteria for fibromyalgia that include a history of widespread pain of at least 3 months duration and physical examination findings of pain with palpation of at least 11 of 18 specific tender points on the body.[39] The prevalence of fibromyalgia approximates 2% in the general population.[40] The definition, etiology, pathogenesis, and management of fibromyalgia remain unclear and controversial.[39] Fibromyalgia has been found to be commonly comorbid with depressive and anxiety symptoms and associated with a personal or family history of depression.[41] In addition, research reveals that psychiatric comorbidity impacts the severity and course of fibromyalgia (ie, positive correlation of mood and anxiety symptoms with functional disability in patients with fibromyalgia).[42,43]

Given the high prevalence of depressive and anxiety disorders in patients with fibromyalgia and emerging evidence supporting a modulating effect of 5-HT-NE neurotransmission on the descending pain-inhibitory pathways in the brain and spinal cord, the role of serotonergic and noradrenergic antidepressants in patients with fibromyalgia deserves considerable attention. Antidepressants inhibiting both 5-HT and NE reuptakes including TCAs and SNRIs have shown potential efficacy and direct analgesic effects in a number of RCTs in patients with fibromyalgia independent of improvement in depressive symptoms.[44–48] In a general viewpoint, the favorable safety and tolerability profile of SNRIs compared to TCAs warrants that SNRIs might be considered first-line antidepressants for fibromyalgia.

Biological Rationale: SNRI Treatment of Pain Control

Serotonin and NE are implicated in modulating descending inhibitory pain pathways in the central nervous system. A recent preclinical study has demonstrated that low doses of the SSRI paroxetine or the NE reuptake inhibitor thionisoxetine alone did not have an effect on late-phase paw-licking pain behavior in the

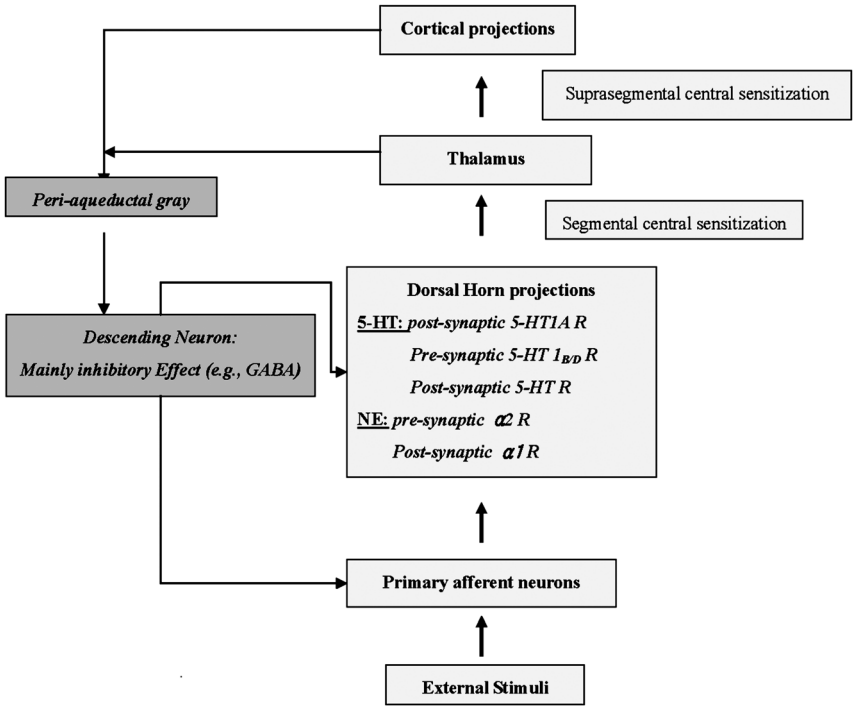

FIGURE 2. Schematic pathways of pain development and modulation. Monoamine pathways in the brain and central nervous system modulate the processing, transmission, and perception of pain signals. Bold arrow is the ascending pathway of pain input, and slim arrow is the descending pathway of the pain control. Serotonin (5-HT) and norepinephrine (NE) have been involved in the control of pain via complex modulation of various neurotransmitter receptors (Rs) resulting in different exertion of neurotransmitters release. This figure was created based on Benarroch.[75]

formalin model of persistent pain; however, when both drugs were combined, significant attenuation of this pain behavior was observed, suggesting that inhibition of both 5-HT and NE uptakes may be necessary for reduction of persistent pain mechanisms.[49]

Persistent pain results from changes in sensitivity within both ascending and descending pain pathways in the brain and the spinal cord.[50] Neuropathic pain is a type of persistent pain that arises from functional changes occurring in the pain sensory system after peripheral nerve injury. Sustained or prolonged stimulation of nociceptive afferents because of tissue damage or peripheral nerve injury has been implicated in the initiation and maintenance of central neuroplastic changes culminating in central neuronal hyperexcitability, possibly due to reduced inhibition of nociceptive neurons by neurotransmitters, such as 5-HT and NE in both spinal and supraspinal structures.[49]

The inhibitory action of 5-HT on structures of the dorsal horn may be mediated by activation of opioid-releasing interneurons. Naloxone, an opioid antagonist, attenuates the analgesic effect of intraspinal 5-HT; similarly, 5-HT antagonists interfere with analgesic effects of morphine infused in or near the spinal cord.[51]

Experimental studies have shown that 5-HT and NE given intrathecally block pain signals. By increasing levels of 5-HT and NE availabilities in key brain areas, antidepressants also have effects on modulating pain signals. This effect of antidepressants may be greatest for medications that increase availability of 5-HT and NE.

The schematic presentation of pain transmission and modulation in central and peripheral nervous system is in Figure 2.

Efficacy

The efficacy and safety of milnacipran in the treatment of adults with fibromyalgia has been reported in 2 short-term placebo-controlled RCTs including a small flexible dose, 12-week trial[44,45] and a large fixed-dose registration trial.[52] In addition, the durability of efficacy has been reported in 2 unpublished fixed-dose serial RCTs of 6-month[53] and 1-year[54] durations.

In a small short-term study,[44,45] patients were randomized to receive placebo (n = 28) or milnacipran once (n = 46) or twice daily (n = 51). The dosage was escalated for 4 weeks to a maximum of 200 mg/d followed by 8 weeks at the maximally tolerated dosage (25, 50, 100, or 200 mg/d). The primary outcome measure was the magnitude of improvement (percent change from baseline) in patients who reported daily or weekly pain scores using a handheld electronic diary (e-diary). Other efficacy measure included the visual analog scale, Gracely anchored logarithmic scale, and the Short-Form McGill Pain Questionnaire. Changes in efficacy measure scores between groups were analyzed, and differences between groups in response rates (defined as 30% or 50% improvement from baseline) for various efficacy measures were also compared. Results indicate superior efficacy of twice-daily dosing of milnacipran compared with placebo and once-daily dosing. In fact, twice-daily milnacipran dosing statistically separated from placebo on 9 of 13 measures (including continuous mean efficacy scale changes and binary response rates), whereas once-daily milnacipran dosing failed to separate on any of the 13 measures. Results for all 3 groups on these efficacy measures appear in Table 1. With regard to secondary efficacy measures, twice-daily milnacipran was superior to placebo on the Fibromyalgia Impact Questionnaire (FIQ), and both twice-daily ($P = 0.013$) and once-daily ($P = 0.008$) dosing schedules were superior to placebo on the Patient Global Improvement Change (PGIC).

Overall, the early short-term study supported the potential utility of milnacipran dosed twice a day at 200 mg/d for treating pain in patients with fibromyalgia, and results suggested that this dosing strategy may have beneficial effects on fatigue, physical function, and quality of life.[44,45] However, this 12-week RCT had some minor design and weaknesses that should be noted, as conclusions are drawn and results are translated into clinical practice. Consistent with epidemiology data indicating the preponderance of patients with fibromyalgia are women,[39,40] this study was skewed in sex representation (female, 122 [98.0%] of 125), which may limit generalization of the results to male patients. This issue was also reported in studies of duloxetine treatment of fibromyalgia.[46–48] In addition, the small sample size in the aforementioned milnacipran study yielded insufficient power to interpret data between all 3 arms. Furthermore, the intent to treat but not a completer analysis was presented.

Subsequently, a large 15-week, fixed-dose registration trial randomized 1196 patients with fibromyalgia to milnacipran at 100 mg/d (n = 399), 200 mg/d (n = 396), or placebo (n = 401) to evaluate the efficacy and tolerability of milnacipran in treating the multiple domains of fibromyalgia.[52] Primary end points were devised to determine efficacy for the indications of (1) the treatment of fibromyalgia syndrome and (2) the treatment of fibromyalgia pain specifically. Therefore, the 2 primary outcomes were (1) rates of composite responders for fibromyalgia syndrome—defined as patients concurrently experiencing clinically meaningful improvements in the following 3 domain criteria: pain (≥30% improvement, as recorded in an electronic diary); patients' global status (a rating of very much improved or much improved on the PGIC scale); and physical function (a ≥6-point improvement on the 36-item Short-Form Health Survey [SF-36)]—physical component summary [PCS] score), and (2) fibromyalgia pain composite responders—defined as those who met the pain and PGIC criteria. At end point, milnacipran treatment yielded significantly higher fibromyalgia pain composite responder rates and for fibromyalgia syndrome compared with placebo. These data appear in Table 1. In addition, both dosages of milnacipran were associated with significant improvements in secondary efficacy measures compared with placebo: weekly palm-based e-diary pain scores ($P < 0.001$); PGIC ($P < 0.001$); SF-36 mental component summary ($P < 0.05$, only 200 mg/d), and improvement in SF-36 PCS scores. Milnacipran also demonstrated superiority in improvements in FIQ ($P < 0.01$) total scores over placebo.[52] Interestingly, both dosages of milnacipran separated from placebo as early as 1 week after treatment (based on weekly palm-based e-diary pain scores) and maintained significant superiority for the rest of the study.[52]

Clauw et al[53] investigated the long-term efficacy of milnacipran in the treatment of patients with fibromyalgia (n = 888). The primary outcomes were composite responder rates similar to those used in the previous registration trial.[52] Patients were randomized to placebo (n = 223), milnacipran at 100 mg/d (n = 224), or milnacipran at 200 mg/d (n = 441) for 6 months, with data reported at 3 and 6 months of treatment.[53] Results show that for the fibromyalgia pain composite responder rates, a significant superiority of both dosages of milnacipran over placebo was found at 3 and 6 months. With respect to composite fibromyalgia syndrome responder rates, milnacipran at 200 mg/d was superior to placebo at both time points, whereas 100 mg/d was superior to placebo at 3 months but not 6 months. These data appear in Table 1. In addition, both dosages of milnacipran were

TABLE 1. A Summary of RCTs of Milnacipran in Patients With Fibromyalgia

				Outcome Measures								
				Continuous*						Binary		
	Patients	Duration	Design		MNP Twice Daily	MNP Daily†	PBO			MNP Twice Daily	MNP Daily†	PBO
Vitton et al[45]/ Gendreau et al[44]	MNP twice daily (n = 51), MNP daily (n = 46), and PBO (n = 28)	12 weeks	Flexible dosage (target dosage, 200 mg/d): MNP twice daily and daily vs PBO	DEPS	−3.0†	−2.2	−1.9	DEPR				
				WEPS	−3.1‡	−2.5	−1.1	30% R		18 (35)†	10 (22)	5 (18)
				GALS	−4.7‡	−2.9	−1.7	50% R		18 (35)†	10 (22)	4 (14)
				VAS	−2.5‡	−2.0	−0.9	WEPR				
				SF-MPQ	−2.2‡	−1.4	−0.6	30% R		20 (39)‡	13 (28)	4 (14)
								50% R		19 (37)‡	10 (22)	4 (14)
								GALS				
								30% R		23 (45)§	16 (35)	5 (18)
								50% R		19 (37)‡	13 (28)	4 (14)
								VAS				
								30% R		20 (39)†	16 (35)	6 (21)
								50% R		15 (29)†	12 (26)	6 (21)
										MNP at 100 mg/d	MNP at 200 mg/d	PBO
Claw et al[52]	MNP at 100 mg (n = 399), MNP at 200 mg (n = 396), and PBO (n = 401)	15 weeks	MNP at 100 mg/d and 200 mg/d vs PBO					Syndrome¶		24.6%‡	25.6%‖	13.4%
								Pain¶		38.6%‖	45.6%‖	25.2%
									Pain	45%‡	45%‖	27%
Claw et al[53]	MNP at 100 mg (n = 224), MNP at 200 mg (n = 441), and PBO (n = 223)	3 months (interim analysis) and 6 months	MNP at 100 mg/d and 200 mg/d vs PBO					3 months¶	Syndrome	33%‡	33%‖	17%
								6 months¶	Syndrome	33%†	32%‡	19%
									Pain	44%‡	45%‖	28%
Goldenberg et al[54]: extension study of Claw et al[53]	MNP at 100 mg (n = 48) and 200 mg (n = 401)	1 year	Maintain on 200 mg/d or rerandomized (from placebo or 100 mg/d) to either MNP at 100 or 200 mg/d				VAS: — FIQ: — PGIC: —					

There were 2 primary assessments of efficacy for syndrome and pain: (1) for syndrome, composite responder was defined as having 30% improvement or greater in pain by electronic palm-based diary, a rating of "very much improved" or "much improved" on the PGIC and 6-point improvement or greater on the SF-36 PCS score and (2) for pain, it was defined as having 30% improvement or greater in pain by electronic palm-based diary and a rating of "very much improved" or "much improved" on the PGIC. "—" represent numerical value was not provided in the original study. Blank represent not applicable.

*Mean changes from baseline. †$P > 0.05$, ‡$P < 0.05$, §$P < 0.01$, and ||$P < 0.001$. ¶Observed case analysis.

DEPR indicates daily e-diary proportion of responders; DEPS, daily e-diary pain score; GALS, Gracely Anchored Logarithmic Scale; PBO, placebo; R, reduction; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale; WEPR, weekly e-diary proportion of responders; WEPS, weekly e-diary pain score; MNP, milnacipran; PGIC, Patient Global Improvement Change.

superior to placebo at both time points on all 5 secondary efficacy measures including weekly mean of palm-based e-diary morning 24-hour recall pain scores, weekly mean of palm-based e-diary real-time pain scores, weekly palm-based e-diary recall pain scores, PGIC scores, multidimensional fatigue inventory total scores, and multiple ability self-report questionnaire total scores.

Among the completers (n = 512) of the previous unpublished, 6-month RCT,[53] 449 patients agreed to participate in the extension study[54] for an additional 6 months of treatment and were maintained at 200 mg/d of milnacipran (n = 209) or rerandomized (from placebo or 100 mg daily) to either milnacipran at 100 mg/d (n = 48) or 200 mg/d (n = 192). Efficacy measures were obtained at weeks 8, 14, 20, and 28, including the visual analog scale 24-hour pain recall, FIQ total score, and PGIC. Data are currently unpublished, and an overview was presented at the 24th Annual American Academy of Pain Medicine Meeting.[54] Patients continuing on milnacipran at 200 mg/d for an additional 6 months showed durability of analgesia for a total duration of 1 year. In addition, patients who switched from milnacipran at 100 mg/d or placebo to 200 mg/d maintained the pain relief achieved in the lead-in study and showed an additional reduction measured by FIQ and PGIC scores for the additional 6 months. The main strength of this 1-year long-term study was that patients who switched from placebo and lower dosage to milnacipran at 200 mg/d demonstrated a maintenance efficacy along with further improvements in pain and other fibromyalgia symptoms.

In summary, the efficacy of milnacipran for pain and associated symptoms of fibromyalgia has been established in short- and long-term studies of various sample size and design. Accumulated data to date support the clinical usefulness of milnacipran in patients with fibromyalgia.

Safety and Tolerability

Most adverse events (approximately 90%) in published short-term RCTs and long-term studies were rated as mild to moderate in severity and transient, usually occurring in the first 4 weeks (dose escalation period) of study.

Fibromyalgia studies with milnacipran show that rate of early discontinuation owing to treatment-emergent adverse events increases with total daily dose and decreases while dose is divided.[44,45,52–54] In once-daily dosing studies, milnacipran at 200 mg/d yielded early discontinuation rates of 24% to 28% compared with 100 mg/d yielding rates of 21.7%. Twice-daily dosing has produced early discontinuation rates varied by the milnacipran dosing strategies across the RCTs, where milnacipran twice daily at the target dosage of 200 mg/d (13.7%) and lower dosage (100 mg/d, approximately 20%) seemed more tolerable than milnacipran daily (21.7%) and higher dosage (200 mg/d, approximately ranging 24%–28%). These early dropout rates were similar or slightly higher than those of duloxetine RCTs.[46,47]

The most commonly observed adverse events across the 15-week and 6-month RCTs were nausea and headache. Other adverse events included constipation, hot flash, dizziness, palpitations, sweating, vomiting, hypertension, and increased heart rate. Laboratory findings including hepatic and cardiovascular parameters were not found to show clinically meaningful abnormalities. This adverse event profile was similar in the 1-year durability trial.[54] No cases of 5-HT syndrome have been reported in the milnacipran trials to date. Adverse events reported in 5% of patients or more in either of the milnacipran groups and twice the incidence of placebo in the 15-week and 6-month RCTs[52,53] are presented in Table 2.

Clinical Implications From RCTs of Milnacipran for Fibromyalgia

Dosing

Although an early small study suggested that milnacipran at 200 mg/d is superior to 100 mg/d, larger studies have indicated both dosages to be similarly efficacious for pain and other syndromal symptoms of fibromyalgia. Adverse events are dose related, and data support improved tolerability with 100 mg/d. This dosage trend was quite similar to the findings from duloxetine RCTs for fibromyalgia, in which dosages of 60 and 120 mg/d had a benefit, but differential tolerability was noted, with a favor to lower dosage.[46–48] Hence, it is prudent that in the treatment of fibromyalgia, the initial target dosage should be 100 mg/d, with the option of increasing to 200 mg/d based on patients' response and tolerability. If 200 mg/d is targeted, milnacipran should be divided to twice-daily dosing for better tolerability.

TABLE 2. Adverse Events Reported in 5% of Patients or More in Either the Milnacipran Groups and Twice the Incidence of Placebo

	Claw et al[52]			Claw et al[53]		
	Milnacipran			Milnacipran		
	100 mg/d	200 mg/d	Placebo	100 mg/d	200 mg/d	Placebo
Nausea	34.3	37.6	19.2	32.6	40.1	21.1
Constipation	14.3	17.9	4.0	18.3	14.3	2.7
Headache	18.0	17.7	14.5	15.6	17.7	11.7
Hot flush	11.5	14.6	1.2	9.8	10.4	2.7
Dizziness	9.5	9.1	4.2	—	—	—
Palpitation	6.5	7.6	2.5	8.0	5.7	0.9
sweating	6.3	5.8	1.2	9.8	12.5	2.2
Vomiting	6.0	5.1	2.2	4.9	8.2	1.8
Increased heart rate	5.0	5.3	0.2	5.4	7.3	2.2
Migraine	5.0	5.1	2.2	—	—	—
hypertension	6.3	3.8	1.5	5.4	4.1	2.2
Dry mouth	—	—	—	5.8	7.0	2.7

Data represent percent values; — means that no data were presented in the original paper.

Impact of Comorbid Depression on Milnacipran Effects for Fibromyalgia

The analyzed response rates between patients with and without depressive disorders were to determine whether such a diagnosis was associated with differential response of fibromyalgia pain to milnacipran. Results indicate that, statistically, greater pain improvement occurred in nondepressed patients, although this is explained by higher placebo-response rate in the depressed group as opposed to better analgesia in the nondepressed group.[47,48] In any case, the response of pain in patients with fibromyalgia who were treated with milnacipran did not seem to be because of improvement in depressive symptoms as might be theorized. The small sample size, particularly in the depressed group (n = 20/125), limits generalization[44,45]; yet, this notion is consistent with a recent meta-analysis of duloxetine trials for MDD, diabetic peripheral neuropathic pain, and fibromyalgia that demonstrated that approximately 50%, 90%, and 80%, respectively, of the observed effect on pain was a direct analgesic effect rather than an indirect antidepressant effect.[55] These findings were also in support of individual studies' path analysis results.[46–48]

Chronic Fatigue Syndrome

Fatigue is one of the most common symptoms found in both community and medical care settings and has been defined as a subjective state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest.[56] Chronic fatigue syndrome (CFS) may be another potential indication for milnacipran treatment in light of findings that milnacipran has demonstrated efficacy in reducing fibromyalgia-related fatigue by approximately 15% to 25% compared with placebo,[44,45] although the mechanism of action remains mysterious. The essential and predominant symptom of fibromyalgia, pain, is believed to stem from central sensitization and other neuronal changes. Central sensitization may also underlie fibromyalgia-associated symptoms such as fatigue, sleep disturbance, anxiety, and other psychosomatic symptoms.[57] In addition to the shared clinical features between fibromyalgia and CFS, the disorders share similar demographic and biological features such as hypothalamic-pituitary-adrenal axis dysregulation, immunological aberration, abnormal pain processing and autonomic nervous system dysfunction, and response to antidepressants involving 5-HT and NE.[58] Clinical studies of milnacipran in patients with CFS have yet to be reported, and this may be a promising area of future study.

Anxiety

Recent clinical data have shown benefit of milnacipran in the treatment of anxiety symptoms in patients with MDD, as evidenced by reduction in anxiety-specific items of depression rating scales.[17,18] In addition, preclinical research has demonstrated potential anxiolytic effects of milnacipran in animal models of anxiety.[59–61] Randomized, double-blind, placebo-controlled clinical trials of milnacipran in anxiety disorders have not been reported to date, although an open-label study supports the efficacy of milnacipran in panic disorder.[62,63] A recently published case series suggests the utility of milnacipran for anxiety symptoms in patients with schizophrenia who were treated with clozapine.[72] Overall, various evidence indicates that milnacipran may be an effective treatment for anxiety symptoms and disorders, and further research is warranted to determine the anxiolytic efficacy of milnacipran, particularly in light of copious RCTs supporting the use of other SNRIs in a wide range of anxiety disorders.[64–67]

Cognitive Function

In contrast to TCAs and some other antidepressants, milnacipran has not produced frequent sedation as an adverse event in RCTs for MDD[14,68] and fibromyalgia.[44,45,52–54] This is especially important given that fatigue and cognitive impairment (particularly deficits in concentration and memory) are common symptoms of MDD[69] and fibromyalgia.[70] A placebo-controlled study of cognition in healthy volunteers who were given milnacipran at 100 mg/d for 7 days demonstrated no effects on immediate and deferred auditory memory, immediate visual memory, sustained attention capacity, global level of awakening, central nervous system reactivity, and sensory-motor performance.[71] An additional study in healthy elderly patients older than 65 years showed significant cognitive deficits as a result of treatment with amitriptyline at 50 mg/d but not milnacipran at 75 mg/d.[13] Although controlled studies of milnacipran treatment for cognitive impairment have not been reported to date, milnacipran has demonstrated potential usefulness for treating cognitive decline in patients with post-stroke depression[72,73] and brain injury[74] in clinical trials. Future research is needed to elucidate the role of milnacipran in treating cognitive impairment from depression, fibromyalgia, and other disorders; furthermore, subsequent studies will hopefully clarify the differences between milnacipran and other treatments with regard to cognitive side effects in clinical populations. In general, milnacipran's lack of anticholinergic effects makes it comparatively benign with regard to cognitive adverse effects, particularly in the elderly.

CONCLUSIONS

Milnacipran is a safe and tolerable SNRI with relatively equipotent 5-HT and NE reuptake inhibitions that have been widely used in 22 countries for the treatment of MDD. Milnacipran has a strong body of evidence supporting its use in MDD and an emerging evidence base indicating its effectiveness for pain associated with fibromyalgia. In February 2008, a new drug application was filed with the United States Food and Drug Administration for the indication of fibromyalgia, and if approved, milnacipran will become the second SNRI after duloxetine to achieve this approval. Limited research suggests that milnacipran may be effective for anxiety disorders and anxiety symptoms of other disorders, which is consistent with the therapeutic profile of other SNRIs. A small body of evidence indicates that milnacipran may also have a role in treating fatigue and cognitive impairment, possibly via neurogenesis. These preliminary data compel future research on the role of milnacipran on a variety of disorders. Future research should also compare milnacipran with other effective antidepressants in head to head studies in MDD and fibromyalgia. Such research along with pharmacoeconomic studies clarifying the relative costs and benefits of milnacipran and other agents will assist clinicians and health care organizations seeking to devise appropriate treatment algorithms for MDD and fibromyalgia.

ACKNOWLEDGMENT

This work was supported by a grant from the Medical Research Center, Korea Science and Engineering Foundation, Republic of Korea (R13-2002-005-04001-0). This work was not supported by a manufacturer of milnacipran.

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