Milnacipran, a serotonin and norepinephrine reuptake inhibitor: a novel treatment for fibromyalgia

Milnacipran hydrochloride is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor that was recently approved by the US FDA for the treatment of fibromyalgia (FM). Evidence has accumulated suggesting that, in animal models, milnacipran may exert pain-mitigating influences involving norepinephrine- and serotonin-related processes at supraspinal, spinal and peripheral levels in pain transmission. Milnacipran has demonstrated efficacy for the reduction of pain as well as improvements in global assessments of well-being and functional capacity among treated FM patients. Its role in addressing comorbidities associated with FM, including visceral pain and migraine, has, as yet, to be investigated. Milnacipran may be of special interest for use in patients for whom hepatic dysfunction precludes the use of other agents, for example, duloxetine. It has a negligible influence on cytochrome metabolism, and therefore may be of particular benefit in patients requiring multiple concurrently prescribed medications. Milnacipran may comprise a reasonable option in the armamentarium of treatments available to manage FM.

KEYWORDS: antidepressants ■ chronic pain ■ fibromyalgia ■ milnacipran ■ serotonin and norepinephrine reuptake inhibitor

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Fibromyalgia (FM) is a syndrome characterized by chronic, widespread musculoskeletal pain and tenderness. The prevalence of FM in the general population is estimated to be 2–4%; it tends to show a female predilection, and increases with age [1,2]. Criteria established by the American College of Rheumatology (ACR) dictates that the pain must be present for at least 3 months, be associated with elicitation of 11 of 18 possible tender points and be present above and below the waist and on the right and left sides of the body [3]. In addition to pain, patients with FM experience other incapacitating symptoms, including sleep disturbances, fatigue and memory impairments. There are a number of significant comorbidities associated with FM, including irritable bowel syndrome, pelvic pain, temporomandibular joint pain and migraine [4]. Among the common psychiatric comorbidities, depression and anxiety appear to be most prevalent [5–7].

The exact pathophysiology underlying FM remains unclear. It is suggested that the symptoms of FM arise from dysfunction within the CNS, allowing for augmented pain processing. Disruptions in somatosensory processing from the periphery, amplification of peripheral sensory information at supraspinal levels and disruptions in descending spinal tracts that normally serve a pain modulatory role of information relayed from the periphery (or a confluence of such factors) have been implicated in the pathophysiology of FM [8,9].

Several pharmacological approaches have been advocated for the treatment of FM. Because of their impact on these presumptive pathophysiologic processes, antidepressants have frequently been advocated for use in the management of pain associated with FM. Among these, tricyclic antidepressants (TCAs) and their analogs have been the drugs of choice [10–12]; their efficacy has been established in prior meta-analyses [13,14]. Unfortunately, side effects limit the tolerability to, and consequently the utility of, the TCAs. The development of antidepressants such as the serotonin–norepinephrine reuptake inhibitors (SNRIs), for example, duloxetine (Cymbalta®, Eli Lilly and Company, IN, USA) and milnacipran (Savella™, Forest Pharmaceuticals, Inc., MO, USA), has made it possible to still derive analgesic benefit while avoiding many of the adverse effects typically associated with the TCAs [15,16].

Naturally, given the high co-occurrence rates, antidepressants may benefit FM patients experiencing distress from comorbid depression and/or anxiety. However, evidence has accumulated suggesting that antidepressants produce analgesic effects independent of the effects on mood. Specifically, the analgesic effects of antidepressants can be achieved earlier than the antidepressant effects can be appreciated, are often obtained at doses far lower than those

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required to achieve antidepressant effects and have been demonstrated in patients with chronic pain who are not depressed [17–19]. Therefore, antidepressants may be appropriately utilized for patients with FM, regardless of whether or not the patient is depressed.

The European League Against Rheumatism guidelines [20] suggest that antidepressants, including TCAs, duloxetine and milnacipran, as well as pregabalin and tramadol among other agents, offer the strongest evidence of efficacy in the management of FM. To date, the anticonvulsant pregabalin, functioning as an α2-δ modulator, and two SNRIs, duloxetine and milnacipran, have been approved by the US FDA for the treatment of FM.

Chemistry, pharmacodynamics & pharmacokinetics

The chemical name of milnacipran (Savella) is (±)-(1R[S],2S[R])-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride. Like duloxetine, its functions are ascribed to the inhibition of the reuptake of synaptic serotonin (5-HT) and norepinephrine (NE). A comparative analysis of human monoamine reuptake, as well as monoamine transporter binding affinities comparing milnacipran, duloxetine and TCAs amitriptyline and nortriptyline, revealed that the binding and reuptake inhibition profile observed with milnacipran more closely resembled that of the TCAs than that of duloxetine [21]. Some of the pharmacokinetic and pharmacodynamic features of milnacipran are compared with duloxetine in Table 1.

With regard to influence on the 5-HT and NE transporters, milnacipran is the most balanced of the SNRIs, but still has a slightly higher affinity for the NE transporter [22]. Nonetheless, its high affinity for both transporters suggests that it acts more like TCAs, for example, imipramine, but without the side-effect profile. In contrast, duloxetine has a slightly higher affinity for the 5-HT transporter. Unlike duloxetine, milnacipran does not have affinity for the dopamine transporter. In addition, reportedly milnacipran does not have affinity for α-adrenergic, acetylcholine histamine, peripheral 5-HT, *N*-methyl-D-aspartate or opioid receptors at therapeutic doses [23]. *In vitro*, it was demonstrated that milnacipran influenced 5-HT3, *N*-methyl-D-aspartate and acetylcholine receptors, but only at very high concentrations, in considerable excess of plasma concentration ranges achieved through customary therapeutic uses [24].

Milnacipran is rapidly and extensively absorbed from the gastrointestinal tract; its absolute bioavailability exceeds 85%. Absorption is unaffected by food intake. It has a low affinity for protein binding and a large volume of distribution [25,26].

Milnacipran is metabolized by glucuronic acid conjugation and *N*-dealkylation [22]; its metabolites are clinically inactive. Unlike duloxetine, which undergoes cytochrome P450 metabolism, milnacipran does not have significant cytochrome P450 interactions, and the metabolism of coadministered medications does not appear to be affected by concomitant milnacipran treatment [27–29]. Conversely, coadministration of carbamazepine can slightly reduce, whereas lithium and lorazepam may slightly increase, plasma levels of milnacipran, but the effects are not clinically significant [26].

The elimination half-life of milnacipran is estimated to be 8–10 h; twice-daily dosing is recommended. Steady state plasma

Table 1. Comparisons of features of the SNRIs duloxetine and milnacipran*.

	Duloxetine	Milnacipran
Influence on the 5-HT/NE transporters	5-HT > NE	NE > 5-HT
Half-life (h)	12	8
Dosing	40–60 mg/day	50–100 mg b.i.d.
Metabolism	CYP1A2 and CYP2D6	Conjugation
Active metabolites	No	No
Drug–drug interactions	Inhibits CYP2D6- and CYP1A2-dependent agents	Minimal interaction with CYP P450-dependent agents
Modifications required		
Hepatic insufficiency	No dose adjustments necessary	Avoid use
Renal insufficiency	Reduce dose in mild cases but avoid in ESRD	Reduce dose

**Data from* [22,27,53,68].
5-HT: Serotonin; CYP: Cytochrome; b.i.d.: Twice-daily; ESRD: End-stage renal disease; NE: Norepinephrine; SNRI: Serotonin–norepinephrine reuptake inhibitors.

concentrations are achieved within 2 days and milnacipran is cleared from the body within 3 days of cessation. A total of 90% milnacipran can be recovered in the urine compared with less than 5% in the feces. Since clearance of its metabolites is largely dependent on renal activity, dose adjustment in cases of severe renal insufficiency should be considered [30].

Analgesic mechanisms underlying milnacipran

The mechanisms that underlie the analgesic effects of milnacipran are thought to involve supraspinal, spinal and peripheral pain processing sites. Milnacipran, like other antidepressants, may produce pain relief by influencing NE and 5-HT neurotransmission of the supraspinal modulatory systems [31,32]. NE and 5-HT, the two neurotransmitters implicated in depression, are likewise implicated in the monoamine hypothesis of pain modulation. This model proposes that two supraspinal nuclei, one emerging from the raphe nucleus magnus (serotonergic) and the other from the locus coeruleus (noradrenergic), have axons that extend down the spinal column terminating in, and modulating, pain transmission entering the spinal dorsal horn via peripheral nerves containing pain-relaying A-δ and C-fibers [33]. Antidepressants augmenting monoamine neurotransmission from the supraspinal nuclei would be expected to enhance the inhibition of pain relayed from the periphery.

Animal studies employing microdialysis investigations confirm that milnacipran increases 5-HT and NE neurotransmitter levels within the CNS [34,35]. Electrophysiological assessments in animal models likewise support that the increased synaptic monoamine levels influence autoreceptors, which in turn alter the firing rates of the locus coeruleus and raphe nucleus [36].

In addition, some evidence has emerged suggesting that milnacipran may exert its antinociceptive effects at the spinal level. In animal models of neuropathic pain, that is ligation of the lumbar (L)5 and L6 spinal nerves, intrathecal, but not systemic (intraperitoneal), milnacipran produced reduction in pain behaviors. The analgesic effects of intrathecal milnacipran were blocked by coadministration of yohimbine (an α-2 antagonist) and methysergide (a 5-HT antagonist), suggesting that the NE and 5-HT reuptake inhibition influences of milnacipran in the spinal cord mediate its analgesic effects [37].

Finally, in an animal model of peripheral inflammatory pain (formalin-induced nociception), systemically administered milnacipran (intraperitoneal) produced antiallodynic responses. This effect was blocked by prazosin (an α-1 antagonist) and ketanserin (a 5-HT2 antagonist) [38].

As for acute visceral pain, intravenous and intrathecal milnacipran failed to demonstrate antinociceptive effectiveness in animal models, for example, colorectal or uterine cervical distention [39]. Although the effectiveness of milnacipran in acute visceral pain appears to be limited, its utility in chronic visceral pain, for example, irritable bowel and chronic pelvic pain, requires further exploration.

Additional investigations are required to elucidate the analgesic mechanisms of milnacipran. Given the complexities of chronic pain encountered in FM, it is likely that multiple pathophysiologic mechanisms, including peripheral, spinal and supraspinal processes, are involved in its genesis and perpetuation. An analgesic agent that can impact pain processing and transmission on each of these levels would be particularly advantageous.

Clinical efficacy

Several measures are advocated for assessing the efficacy and clinical outcomes of treatment interventions employed in FM. These measures include pre- and post-intervention measures of pain intensity. Pain intensity is commonly assessed using a standardized pain scale such as the visual analog scale (VAS), recorded with pen and paper and/or electronic diaries. Generally, an improvement of 30% in a standard pain assessment rating is considered to be the threshold for determining clinical efficacy [40].

In addition, functional status measures, such as assessments of physical and emotional functioning, are increasingly employed in FM research. Functional status is often assessed using scales such as the fibromyalgia impact questionnaire (FIQ) [41,42] and subscales of the 36-item short-form health survey (SF-36) [43]. The SF-36 contains both a physical and mental component, which provide valid and reliable measures of physical and emotional function, respectively, along with information regarding quality of life in patients with musculoskeletal disorders [44]. A change in the total score of 20% or more has been suggested to be clinically significant in such functional assessments [41]. The patient's subjective assessment of degree of perceived change in the severity of FM symptoms overall are often

quantified using the Patient Global Impression of Change (PGIC) scale. This scale is rated on a 7-point Likert scale ranging from 1 (being very much improved) to 7 (meaning very much worse).

The clinical meaningfulness of an investigation is called into question if it demonstrates an improvement in one measure, for example, subjective pain assessments, without commensurate improvements in patient functioning. As such, more recent investigations have employed composite responder assessments, requiring clinically meaningful improvements in several domains affected by FM.

The clinical efficacy of milnacipran has been tested in prospective, randomized, double-blind, placebo-controlled Phase II [45,46] and Phase III studies [47–50]. To date, there have been no Phase III studies comparing milnacipran with alternative pharmacological treatments.

Phase II investigation

In a 12-week double-blind, placebo-controlled Phase II trial enrolling 125 patients with FM ranging from 18–70 years of age, milnacipran-treated patients reported overall improvements in pain severity and fatigue [45,46]. Subjects were given either 200 mg milnacipran daily (q.d.), 100 mg milnacipran b.i.d. or placebo in a 3:3:2 ratio. Improvements in reported pain, fatigue and stiffness were noted among milnacipran-treated patients. The proportions of patients achieving 30 and 50% reductions in pain severity across the three conditions, using weekly electronic diary pain reports, are summarized in Table 2.

Pain ratings of patients receiving milnacipran in two daily divided doses (100 mg b.i.d.) were significantly improved compared with those of patients receiving placebo; however, pain ratings did not improve significantly for those receiving a single daily 200 mg dose compared with placebo. Attrition rates for milnacipran-treated patients were 13.7 and 21.7% for patients receiving b.i.d. and q.d. dosing, respectively, whereas that for patients receiving placebo was 3.6%. Drop-outs from the study were predominantly attributed to intolerable side effects.

The antidepressant effects of milnacipran demonstrated a trend towards improvement compared with placebo in patients with FM, but it was not statistically significant. No significant improvements were noted with milnacipran treatment in ability to sustain work, depression or anxiety. In addition, sleep did not appear to improve among FM patients given milnacipran, perhaps owing to its activating noradrenergic influences. However, no adverse sleep effects were attributed to, or reportedly exacerbated by milnacipran.

Phase III investigations

Two Phase III investigations using milnacipran were conducted in the USA [49,50]. Both studies employed a double-blind, randomized, placebo-controlled, fixed-dose trial enrolling FM patients ranging from 18–70 years of age. Milnacipran was dosed at 50 or 100 mg b.i.d.

In both investigations, the primary end point was the comparison of two composite response rates of milnacipran-treated and placebo-administered patients. The first of these was the composite pain response. Patients were deemed to be composite pain responders if they demonstrated at least a 30% reduction in baseline pain ratings as measured by the VAS in addition to conducting a self-assessment of the patient on the PGIC where they were revealed to be as 'much' or 'very much' improved compared with baseline ratings. The second dependent variable, or rather the composite syndrome response, was based upon demonstration of the above criteria along with improvement in functioning as reflected in at least a 30% improvement in the FIQ physical function score from baseline, or an improvement by 6 units from baseline ratings on the physical component summary of the SF-36.

Table 2. Proportion of fibromyalgia patients achieving pain reduction in a Phase II double-blind, randomized, placebo-controlled trial of milnacipran*.

	100 mg milnacipran b.i.d.	200 mg milnacipran q.d.	Placebo
Subjects	n = 51	n = 46	n = 28
N (%) of subjects achieving pain reduction‡			
≥30% pain reduction	20 (39%)§	13 (28%)	4 (14%)
≥50% pain reduction	19 (37%)§	10 (22%)	4 (14%)

*Data from [45].
‡Based on average weekly electronic diary pain scores.
§Significant difference when compared with placebo.
b.i.d.: Twice-daily; q.d.: Daily.

An initial Phase III study enrolling 888 patients in a study of milnacipran use in FM failed to reach statistical significance for improvement in one of the *a priori* established co-primary end points [101]. Pursuant to the aforementioned negative results, the composite responder criteria were modified and the results were published in a subsequent report [50]. The FIQ physical function criterion was eliminated since it was deemed to be insufficiently responsive to detect changes in functional status. A 6-point or greater improvement in the baseline physical function component of the SF-36 was utilized for the functional status criterion. Both composite pain responder and composite syndrome responder rates revealed significant improvements in favor of milnacipran as compared with placebo at the 3-month assessment interval, but not at the subsequent 6-month follow-up assessment interval. The proportion of patients meeting the composite response criteria across conditions is summarized in TABLE 3. The attrition rate for this study was 42% (patient withdrawals were considered nonresponders in the table provided). Discontinuation from the study was predominantly due to adverse effects in milnacipran-treated patients (10.3% in the placebo group; 27% in the 200 mg/day milnacipran group; and 19.6% in the 100 mg/day milnacipran group), and therapeutic failure was the predominant factor influencing attrition among placebo-administered patients (15.2% in the placebo group; 11.2% in the 200 mg/day milnacipran group; and 11.6% in the 100 mg/day milnacipran group).

A second Phase III investigation involving 1196 nondepressed FM patients reported more favorable results from milnacipran treatment than the aforementioned Phase III study [49,102,103]. In this 15-week trial, milnacipran-treated patients were significantly more likely to demonstrate composite response rates compared with those taking placebo. Composite responder rates across conditions are summarized in TABLE 3. Significant improvements in pain were observed as early as 1 week after treatment. Attrition rates were 34, 35 and 28% for the 100 mg/day milnacipran, 200 mg/day milnacipran and placebo conditions, respectively. As in the aforementioned study, discontinuation from the study was predominantly due to adverse effects in milnacipran-treated patients and therapeutic failure in placebo-administered patients.

A large, multinational, European study enrolling 884 FM patients randomized to receive 200 mg milnacipran/day versus placebo demonstrated significant improvements in multiple domains [48], for example, pain, sleep, fatigue and physical functioning (the latter was assessed by the FIQ physical functioning subscale and SF-36). It is noteworthy that only 77% of subjects completed the 3-month trial; the attrition rate for the milnacipran-treated group was 29.2% (127 out of 435), whereas attrition for the placebo group was 17.6% (79 out of 449). Proportions of the composite responders reflected a statistically significant improvement in favor of milnacipran-treatment over placebo (i.e., 75 out of 308 vs 54 out of 370; $p < 0.0003$).

Recently, results of another Phase III trial completed in the USA assessing the durability of milnacipran's effects was reported [47]. In this investigation, FM patients who were previously treated with 200 mg milnacipran/day for a prior 6-month study [49] were treated for an additional 6-month period. In addition, patients previously receiving 100 mg milnacipran/day or placebo were re-randomized to receive milnacipran dosed at either 100 mg/day or 200 mg/day. The authors stated that multidimensional symptom improvements were sustained for up to 1 year among patients continuing 200 mg milnacipran per day. Patients previously receiving placebo who were re-randomized to receive 200 mg/day of milnacipran demonstrated a 40% reduction in pain severity and a 22% reduction in fatigue at the first follow-up interval (8 weeks). However, importantly, the data presented lacked any statistical comparisons, so the significance of the reported effects cannot be determined. The results of the patients re-randomized to 100 mg/day were not presented. Attrition from the study was 33%, but rates of withdrawal ascribable to adverse effects versus perceived treatment failure remain unreported.

Depression as a co-variate accounting for multisymptom improvements

Milnacipran (Ixel®, Pierre Fabre Medicaments, Castres, France) is commercially available as a treatment for depression in Europe and Japan. Naturally, questions arise as to whether the benefits yielded from the aforementioned studies are attributable to an antidepressant effect, for example, patients for whom depression is alleviated may be apt to rate their pain as less severe or less incapacitating. If this were the case, a greater response to milnacipran would conceivably be achieved among FM patients with comorbid depression.

Table 3. Proportion of composite responders in two Phase III trials employing milnacipran*.

Phase III trials	100 mg milnacipran q.d.	200 mg milnacipran q.d.	Placebo
Mease* et al. *(2008)			
Subjects (n)	224	441	223
n (%) of composite syndrome responders‡			
3-month interval	44 (20%)§	85 (19%)§	27 (12%)
6-month interval	40 (18%)	73 (17%)	27 (12%)
n (%) of composite pain responders¶			
3-month interval	61 (27%)	118 (19%)§	43 (19%)
6-month interval	53 (24%)	104 (17%)	39 (17%)
Clauw* et al. *(2008)			
Subjects (n)	399	396	401
n (%) of composite syndrome responders‡	58 (15%)*	55 (14%)§	35 (9%)
n (%) of composite pain responders¶	91 (23%)*	98 (25%)§	66 (16%)

Drop-outs were considered to be nonresponders.
Patient Global Impression of Change ratings of 'very much' or 'much' improved and an above 6-point improvement on the 36-item short-form health survey.
Data from [49,50,104].
‡Greater than 30% improvement from baseline on diary pain assessments.
§Significant $p < 0.05$.
¶Greater than 30% improvement from baseline on diary pain assessments and Patient Global Impression of Change ratings of 'very much' or 'much' improved.

Analyses conducted in the previously discussed Phase II trial revealed that 100 mg milnacipran b.i.d. did not produce different outcomes for depressed and nondepressed patients [45,46]. Milnacipran generated a 50% reduction in pain severity ratings (based upon weekly electronic diary reports) among 37 and 38% of nondepressed and depressed FM patients, respectively. In contrast, for patients who were administered placebo, 33% of depressed patients and 5% of those that were not depressed demonstrated a comparable reduction in baseline pain ratings. Statistical comparisons of milnacipran-treated and placebo-administered nondepressed FM patients yielded significant differences ($p < 0.001$); however, no statistically significant differences were obtained between the two groups when depressed patients were compared, presumably owing to the greater placebo response rate among depressed patients. These data suggest that the efficacy of milnacipran in reducing pain is due to an analgesic effect rather than a potential antidepressant influence.

Two other observations in the aforementioned studies are noteworthy, as these likewise suggest that milnacipran possesses a pain-mitigating influence independent of an indirect antidepressant effect. First, in an effort to avoid the potential confounding of antidepressant influences, some investigations restricted enrollment of patients to those who were not depressed [48,49] and yet, were able to demonstrate improvement in pain. For example, subjects were excluded if they scored beyond threshold on a standardized depression inventory, such as scoring 25 points or more on the Beck depression inventory [51]. Second, pain reductions in response to milnacipran began as early as 1 week after treatment initiation [51]. Although maximal relief may not have been achieved until 9 weeks of continuous treatment, the expediential analgesic response still occurs before an antidepressant effect would be appreciated.

Safety

Milnacipran, like duloxetine, does not produce troublesome anticholinergic or α-adrenergic effects that are commonly associated with the TCAs. Milnacipran-related adverse effects encountered at least twice as often as those reported in placebo conditions included those that were noradrenergic, for example, dry mouth, sweating, increased heart rate, hypertension, hot flashes and palpitations, and those that were serotonergic, for example, nausea, constipation and vomiting [51,52]. Nausea and headache were most commonly reported. Milnacipran may exhibit

slightly more noradrenergic-related and slightly less serotonergic side effects than duloxetine [27,53], given its neurotransmitter transporter affinities. However, no direct head-to-head comparison of these agents has been conducted in this regard.

Although adverse effects were mild-to-moderate in severity, attrition rates owing to adverse effects among milnacipran-treated patients were approximately twice that associated with placebo conditions across studies [51]. Adverse effects were reversible with drug discontinuation. The dosing regimen and peak serum drug levels may be determinants of severity of adverse effects, for example, the 100 mg b.i.d regimen tended to be better tolerated than a single 200 mg q.d. dose [45,46]. Side-effect tolerability may also be influenced by the rate of milnacipran dose escalation. It is recommended that milnacipran is administered in two divided doses q.d., beginning at 12.5 mg q.d. and increased gradually to 50 mg b.i.d. at 7 days. Although the recommended dose is 50 mg b.i.d., further dose increases to 100 mg b.i.d. may be required if treatment response is suboptimal and side effects are not prohibitive [54].

Milnacipran does not influence voltage-dependent calcium, potassium or sodium ion channels in excitable tissues. As such, it is unlikely to influence cardiac functioning [55]. In animal studies comparing milnacipran with the TCAs, mild bradycardia was observed with milnacipran administration, whereas cardiac arrhythmias and subsequent death were noted among TCA-administered animals.

Milnacipran is associated with minimal blood pressure effects. In a study of 4000 patients given milnacipran, the mean blood pressure increase was less than 1 mm Hg. Minimal increases in heart rate and slight changes in the QT interval corrected for heart rate (QTc) have been associated with milnacipran [49,50,56].

Because milnacipran does not require oxidative metabolism and its pharmacokinetics are not altered by hepatic disease, no dose adjustments appear to be required for milnacipran in hepatic illness [57]. However, in a small proportion of patients, there may be slight alterations in liver function tests with use. Duloxetine has been associated with hepatitis and cholestatic jaundice, and its use in patients with pre-existing liver disease is a concern [58].

In a small percentage of patients, abrupt discontinuation of milnacipran has been associated with anxiety, and rarely, nausea and insomnia [59]. Gradual dose reductions may be required to circumvent withdrawal reactions.

Cases of human overdose of up to 2.8 g of milnacipran have demonstrated no significant sequelae [60]. To date, one fatality has been reported in association with a milnacipran overdose (at 40-times the customary serum treatment concentration) [61].

Effects of milnacipran on fetal development are unknown; it has been assigned FDA pregnancy category C. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during milnacipran therapy.

Drug interactions

Coadministration of SNRIs such as milnacipran with seroronin selective reuptake inhibitors – for example, fluoxetine and paroxetine among others, and monoamine oxidase inhibitors (MAOI's), for example, isocarboxazid (Marplan®, Oxford Pharmaceutical Services, Inc, NJ, USA), phenelzine (Nardil™, Pfizer, Inc, NY, USA), rasagiline (Azilect™, Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel), selegiline (Eldepryl™, Somerset Pharmaceuticals Inc, FL, USA and Emsam™, Bristol-Myers Squibb, NY, USA) or tranylcypromine (Parnate™, GlaxoSmithKline plc, London, UK) – is contraindicated due to concerns about serotonin syndrome. Similar concerns are raised regarding concomitant administration with serotonergic pain medication, for example, tramadol (used in cases of mild pain) or triptans (used in migraine treatment). No cases of serotonin syndrome have been reported in trials of milnacipran to date. To avoid such potentially hazardous outcomes, a sufficient medication washout period must be adhered to before initiating milnacipran treatment, for example, only beginning milnacipran 14 days after stopping an MAOI. Conversely, after patients stop taking milnacipran, they must wait at least 5 days before taking an MAOI or other serotonergic agent.

Sedation can result from concurrent use of milnacipran with over-the-counter cold and allergy medication, muscle relaxants, sedative hypnotics, anxiolytics and narcotic analgesics. Because milnacipran interferes with serotonin reuptake, there is the potential for an increase in the risk of abnormal bleeding; patients should be cautioned about its use in conjunction with NSAIDs, aspirin or other drugs affecting coagulation.

Clinical applicability

Available treatments for FM have not been particularly effective in reducing pain and disability or sustaining treatment compliance [62,63]. The recent FDA approval and availability of milnacipran offers a new option in the treatment arsenal.

Milnacipran is administered orally twice-daily; the recommended antidepressant dosing regimen is 50 mg b.i.d. The dosages employed in investigations assessing milnacipran's utility in FM have ranged from 100–200 mg q.d.. Dose reductions may be necessary for patients with renal dysfunction. In addition, lower doses may be required if intolerable side effects supervene.

It was noteworthy that only the 100 mg b.i.d. regimen, but not the 200 mg q.d. regimen, yielded significant benefits when compared with placebo [45,46]. Although the two dosing regimens were not statistically compared directly, these data suggest that milnacipran administered in divided doses may be more effective than a single q.d. dose. The divided dose allows for sustained serum drug levels and thus, sustained analgesic benefit that may not otherwise be maintained with a single q.d. dose.

As previously mentioned, attrition rates during clinical investigations were quite high – mostly attributable to adverse effects. It appears that most of these tended to occur during initial phases of the investigations when dose escalations were undertaken [45,46,49]. A majority of adverse effects were transient, resolving within 1-to-2 weeks [49,50]. It is unclear from available reports whether more gradual dose increases may be better tolerated.

Milnacipran may be of special interest for use in patients for whom hepatic dysfunction precludes the use of other agents, for example, duloxetine. In addition, patients requiring concurrently prescribed medications that rely on CYP450 metabolism may benefit from milnacipran use since it is unlikely to induce or interfere with cytochrome metabolism [64].

Shortcomings of existing research on milnacipran

There are several limitations to the research focusing on milnacipran in the treatment of pain and comorbidities associated with FM. First, in general, brief investigations prevent adequate statements regarding long-term efficacy from being made. For example, the effects on illness duration and course, and tolerability; very few studies described herein incorporated assessment intervals of 6 months or longer [65]. This is concerning as FM is a lifelong disorder requiring long-term treatment. Given the relatively short-term follow-up in the extant body of research, the optimal duration of treatment with milnacipran is, as yet, unknown.

Second, customarily, Phase III investigations are long duration trials in which one agent is compared against a standard, or at least a reasonable alternative, treatment. To date, no direct comparisons have been made comparing milnacipran against existing treatments for pain and other FM symptoms, for example, TCAs, duloxetine or other agents. As such, the ability to delineate comparative efficacies and tolerabilities are limited.

Third, direct comparisons between the dosing regimens for milnacipran were notably absent in the investigations reported herein. Rather, each milnacipran dosing regimen was compared with placebo. Without direct comparisons of dosing levels, the minimal and optimal doses for therapeutic efficacy remain a mystery.

Fourth, most studies controlled for co-administered medications. However, patients were often allowed to make use of analgesic rescue medication during the course of the trial [45,46,49,50]. Unfortunately, the influence of rescue medications on the study outcomes is not clear, for example, influencing either desired clinical benefits or untoward effects. The impact of milnacipran on the amount of rescue medication required during the course of past investigations has been unreported. Other aspects of the potential benefits of milnacipran on pain, for example, the influence of milnacipran on the number of tender points upon which the ACR diagnostic criteria are based, were not reported.

Finally, the restrictive patient inclusion/exclusion criteria employed in previous studies of milnacipran make it impossible to speculate on the generalizability of its effectiveness in several patient populations, for example, in those who are nonwhite, male and in those with distinct comorbidities such as irritable bowel, migraine and so on, or requiring multiple concurrently-prescribed medications [61]. As such, there is insufficient evidence for the effectiveness of milnacipran in less well-controlled clinical populations.

Conclusion

Fibromyalgia is a chronic, severe and disabling condition. Many patients can manage the disease with a combination of medications, exercise and other treatments [63]. There are a number of agents that have been employed to address the symptoms of FM. To date, agents that have received FDA approval for the treatment of pain and related symptoms associated with FM include duloxetine, pregabalin and most recently, milnacipran [10]. Milnacipran provides another alternative for pain and symptom relief in some FM patients.

Milnacipran is well-tolerated, and has minimal adverse effects compared with TCAs. It is safe in overdose and has a negligible influence on cytochrome drug metabolism. These features make it particularly suitable for use in FM.

Evidence suggests that milnacipran may have a role in reducing pain, fatigue and impediments to functioning associated with FM. However, its role in addressing common comorbidities associated with FM, for example, irritable bowel, pelvic pain and migraine, warrants further investigation.

Future perspective

Several investigations have advocated the use of a number of pharmacological therapies for the treatment of pain and comorbidities in FM. Direct comparison of milnacipran with other pharmacological therapies will be necessary to determine its role compared with other treatment options for FM symptoms. There is a need for studies of longer duration to investigate the long-term efficacy and side effects of treatment with milnacipran in FM. In this context, it would also be important to assess the influence of the medication on patients' quality of life and on how many patients return to normal q.d. life and work while receiving milnacipran treatment. Furthermore, trials analyzing the cost–effectiveness of milnacipran treatment should be performed. From an economic point of view, it would also be of interest to know if milnacipran reduces FM-related healthcare costs [65].

It must be kept in mind that the vast majority of studies investigated a population that did not include nonwhite and male patients. Further evidence of milnacipran's efficacy in such subgroups is required.

Future investigations attempting to identify positive and negative outcome predictors or FM subgroups would be helpful to better select medication and other treatment options for individual patients. Genetic studies may help to guide rational treatment approaches to FM, and may help to clarify whether there are subgroups of FM patients who are more likely to yield benefits from milnacipran as compared with other currently available treatment options [15,66,67].

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Executive summary

Mechanisms of action

- Milnacipran is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor.
- The exact mechanisms underlying its analgesic effects have, as yet, to be elucidated. Animal studies suggest that analgesic effects are mediated by its influences on 5-HT and NE at supraspinal, spinal and peripheral levels.

Pharmacokinetic properties

- Milnacipran has a high bioavailability, exceeding 85%.
- Absorbtion is minimally influenced by food intake.
- Milnacipran is metabolized in the liver by glucuronic acid conjugation and *N*-dealkylation and excreted as inactive metabolites by the kidneys.
- It has negligible influences on the CYP450 metabolism of other medications.
- Mild-to-moderate liver function impairment has not been shown to significantly influence the metabolism of milnacipran.
- Dose reductions are recommended for patients with moderate-to-severe renal dysfunction.

Clinical efficacy

- Significantly greater composite response rates (encompassing 30% reductions in pain ratings, improvement in self-rated patient global status and improvements in functional status) have been demonstrated among milnacipran-treated as compared with placebo-administered fibromyalgia patients.
- Data from long-term extension studies are lacking, but one study suggested that benefits in pain and functional status parameters are sustained at 1 year.
- There were no direct comparisons of milnacipran with other treatments for pain and symptoms of fibromyalgia.

Safety & tolerability

- Milnacipran is associated with a number of serotonergic (e.g., nausea) and noradrenergic (e.g., headache, sweating and palpitations) side effects.
- There are no significant safety concerns regarding its influences on cardiac functioning, blood pressure or hepatic function.

Drug interactions

- Milnacipran should not be coadministered with monoamine oxidase inhibitors due to concerns regarding precipitating of a serotonin syndrome.
- Because of its effects on serotonin and the potential increased risk of bleeding, caution is required when milnacipran is coadministered with NSAIDs, aspirin or other drugs affecting coagulation.

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