

Milnacipran for the management of fibromyalgia syndrome

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Abstract: Fibromyalgia syndrome (FMS) is a widespread pain condition associated with fatigue, cognitive dysfunction, sleep disturbance, depression, anxiety, and stiffness. Milnacipran is one of three medications currently approved by the Food and Drug Administration in the United States for the management of adult FMS patients. This review is the second in a three-part series reviewing each of the approved FMS drugs and serves as a primer on the use of milnacipran in FMS treatment including information on pharmacology, pharmacokinetics, safety and tolerability. Milnacipran is a mixed serotonin and norepinephrine reuptake inhibitor thought to improve FMS symptoms by increasing neurotransmitter levels in descending central nervous system inhibitory pathways. Milnacipran has proven efficacy in managing global FMS symptoms and pain as well as improving symptoms of fatigue and cognitive dysfunction without affecting sleep. Due to its antidepressant activity, milnacipran can also be beneficial to FMS patients with coexisting depression. However, side effects can limit milnacipran tolerability in FMS patients due to its association with headache, nausea, tachycardia, hyper- and hypotension, and increased risk for bleeding and suicidality in at-risk patients. Tolerability can be maximized by starting at low dose and slowly up-titrating if needed. As with all medications used in FMS management, milnacipran works best when used as part of an individualized treatment regimen that includes resistance and aerobic exercise, patient education and behavioral therapies.

Keywords: fibromyalgia, milnacipran, treatment

Introduction to fibromyalgia diagnosis and management

Fibromyalgia syndrome (FMS) is a disorder of chronic widespread pain (CWP) associated with fatigue, sleep disturbance, depression, anxiety, cognitive dysfunction and muscle and joint stiffness.¹ FMS affects patients worldwide, with an estimated prevalence in developed countries that ranges from 0.5% to 5.8%.² FMS can exist as a primary disorder or may occur secondarily in association with a variety of chronic medical conditions. While FMS is not an inflammatory disorder, it is commonly seen in association with inflammatory autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.^{3,4} The most widely used criteria for identifying FMS patients is the American College of Rheumatology (ACR) 1990 classification criteria.⁵ However use of the ACR criteria for FMS diagnosis is discouraged,⁶ since the ACR criteria lack sensitivity and fail to recognize associated FMS symptoms that must be addressed to optimally manage the disorder.⁷ Recently proposed FMS clinical diagnostic criteria that identify patients based on the number of somatic symptoms and painful body areas along with severity of symptoms of fatigue, sleep

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disturbance and cognitive dysfunction may eventually improve FMS diagnosis.⁸ Pending finalization of diagnostic criteria, we recommend assessment and treatment of all patients with CWP for associated FMS symptoms. These symptoms can be recalled using the “FIBRO” mnemonic, where F = Fatigue and/or Fibrofog (cognitive dysfunction), I = Insomnia (nonrestorative sleep), B = Blues (depression and/or anxiety), R = rigidity (stiffness in muscles and/or joints) and O = Ow! (pain and work difficulty).⁹ Questionnaires such as the mVASFIQ⁹ or the SIQR¹⁰ can be used to assess “FIBRO” symptoms and provide the basis for an individualized, symptom-based treatment approach to FMS management consistent with evidence-based guidelines.⁷

Three general points should be kept in mind when treating FMS patients. First, primary disorders that can mimic FMS must be ruled out before symptomatic therapies are used. These include vitamin deficiencies, anemia, and metabolic, oncologic, inflammatory or sleep disorders. Second, since the majority of FMS patients suffer from multiple medication intolerances, medications should be started individually at low dose and slowly uptitrated and/or combined. Finally, while this review focuses on pharmacologic treatment of FMS with milnacipran, medications have a limited role in FMS management. Medications work best when they are used to provide symptomatic relief so that patients can participate in nonpharmacologic modalities that provide long-term disease coping strategies including aerobic and resistance exercise, education, and cognitive behavioral therapies.

Fibromyalgia pathogenesis

While FMS was initially considered a disorder of peripheral myofascial tissue, this has been proven incorrect. FMS is a neurologic disorder caused by aberrant processing of pain and other sensory information within the central nervous system (CNS).¹¹ The concept of FMS as a centrally-mediated disorder has arisen from numerous scientific studies including functional neuroimaging of FMS patients showing that brain regions involved in pain processing are hyperactive compared to controls.^{12–14} Serotonin and norepinephrine are known to provide important inhibitory signals in regulating pain processing pathways,¹⁵ and FMS patients have reduced levels of norepinephrine and serotonin in their cerebrospinal fluid.¹⁶ Augmentation of serotonin and norepinephrine CNS activity is thought to be the mechanisms by which norepinephrine–serotonin reuptake inhibitor (NSRI) medications like milnacipran and serotonin – norepinephrine reuptake inhibitor (SNRI) medications like duloxetine decrease FMS pain. However, FMS patients are very heterogeneous

and it is unlikely that a single pathogenic mechanism is responsible for causing FMS in all patients. No single treatment has been found that is effective for all FMS symptoms,¹⁷ and individual FMS patients often respond best to different therapies. Also, the serotonin selective reuptake inhibitors (SSRIs) have shown mixed results in managing FMS.¹⁸ It is generally accepted that these mixed results are due to the fact that different SSRIs have widely varying concomitant norepinephrine reuptake inhibition (NRI) activity, and it is thought to be the NRI activity that is responsible for analgesia. Norepinephrine has an important role in pain modulation that is supported by research showing that SNRIs have analgesic effects in animal models of central pain that highly selective SSRIs lack.¹⁹ The balanced ratio of serotonin:norepinephrine reuptake inhibition provided by milnacipran is the likely reason for its analgesic properties (Table 1).^{20,21}

Overview of pharmacology, mode of action and pharmacokinetics of milnacipran

Milnacipran is one of three Food and Drug Administration (FDA)-approved medications for the management of FMS. The approved milnacipran dose is 100 or 200 mg divided twice daily. Milnacipran is characterized as an NSRI because *in vitro* studies have shown milnacipran has a three-fold greater efficacy for inhibiting norepinephrine reuptake compared to serotonin, which differentiates it from the SNRIs which are more serotonin active (Table 1).²³ However, measurement of relative reuptake inhibition is difficult and variability exists for reported values in the literature. Also, the relative reuptake inhibition observed *in vitro* may not have physiologic relevance *in vivo*. For instance, while duloxetine is considered a dual reuptake

Table 1 Relative 5-HT:NE In-vitro reuptake inhibition of SNRI-active drugs

Drug name	5-HT:NE reuptake inhibition ratio
Venlafaxine	30:1
Duloxetine	10:1
Desvenlafaxine	10:1
Amitriptyline	8:1
Milnacipran	1:1

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Abbreviations: 5-HT, serotonin; NE, norepinephrine; SNRI, serotonin–norepinephrine reuptake inhibitor.

inhibitor based on its *in vitro* activity, one study showed no effect on norepinephrine reuptake *in vivo* as determined by response to tyramine infusion in normal subjects.²⁴ Our clinical experience with dual reuptake inhibitors has been that individual FMS patients tend to respond best to a specific SNRI and the relative reuptake inhibition ratio does not appear to predict therapeutic response (ie, some patients who have no response to duloxetine do well on milnacipran and vice versa). Unfortunately, the inability to predict treatment response usually necessitates multiple therapeutic trials before an efficacious drug is found. A rational method for drug selection will likely require improved understanding of the mechanism(s) of action of dual reuptake inhibitors together with patient pharmacogenomic data.

Milnacipran has limited hepatic metabolism.²⁵ Approximately 50% of administered drug is excreted unchanged, 30% undergoes glucuronidation and 20% is oxidatively metabolized. The interaction between milnacipran and the cytochrome P450 (CYP) isoenzymes is limited, with no interaction with CYP2D6 or CYP2C19 pathways and minimal interaction with CYP1A2, CYP2C19, CYP2D6 and CYP3A4. This is in contrast to duloxetine, which is extensively metabolized by the liver and has interactions with numerous CYP isoenzymes.²⁶ The differences in CYP interactions are the reason that no dose adjustment is necessary for milnacipran use in patients with hepatic insufficiency,²⁷ whereas duloxetine use in patients with hepatic insufficiency is not recommended.²⁸ However, there have been cases of increased liver enzymes and reports of severe liver injury with milnacipran use in foreign post-marketing experience. Because of this, we recommend routine lab monitoring and discontinuation of milnacipran in patients who demonstrate evidence of liver dysfunction. Concomitant use of hepatotoxic substances with milnacipran should be avoided, and milnacipran should not be prescribed to patients with substantial alcohol use or chronic liver disease.

Milnacipran can be used without dosage adjustment in patients with mild to moderate renal insufficiency (ie, a creatinine clearance (CrCl) \geq 30 mL/min).²⁹ Milnacipran can also be used in patients with severe renal impairment (ie, a CrCl between 5 and 29 mL/min) if the dose is reduced by 50%. This is an important difference between milnacipran and duloxetine, as duloxetine use is not recommended in patients with severe renal impairment.²⁸ Also, due to its limited hepatic metabolism and lower protein binding in plasma (~13% versus >90%,

respectively), milnacipran has fewer drug-drug interactions compared with duloxetine.^{28,30}

Safety and tolerability in fibromyalgia syndrome patients

The treatment-emergent adverse events (TEAEs) seen in the milnacipran FMS trials are related to NSRI activity and are similar to those seen with the SNRIs.³⁰ Gastrointestinal disorders are the most frequent TEAEs, with nausea occurring in 35% and 39% of patients treated with 100 and 200 mg/day of milnacipran, respectively, compared to 20% of placebo-treated patients. Nervous system disorders were also commonly seen TEAEs, with headache reported by 18% of milnacipran-treated patients versus 14% of placebo controls. The noradrenergic activity of milnacipran is apparent in the increased rates of hot flushes, hyperhidrosis and palpitations reported by milnacipran treated patients versus that seen in controls (12%, 9% and 7% for milnacipran treated patients, respectively, versus a 2% rate for all these TEAEs in controls). While heart rate and blood pressure increases were seen at an increased rate in milnacipran-treated patients (6 and 3% for milnacipran treated patients versus 1% in controls for both TEAEs), these changes were mild and not deemed clinically significant on average. However, since the effect of milnacipran on blood pressure and heart rate in individual patients cannot be predicted, it is recommended that blood pressure and heart rate be regularly monitored in patients treated with milnacipran. Other common TEAEs (incidence \geq 5% and twice the placebo rate) include constipation, vomiting and dry mouth.

In placebo-controlled FMS trials, 23% of patients treated with milnacipran 100 mg/day and 26% of patients treated with milnacipran 200 mg/day discontinued prematurely due to TEAEs, compared to only 12% of patients treated with placebo.³⁰ Nausea was the most frequently cited reason for discontinuation in milnacipran treatment groups (6%), followed by palpitations (3%), and headache (2%). Milnacipran treated patients tended to have weight loss during clinical trials that was higher than that seen in placebo-treated patients, however the difference was small (0.8 versus 0.2 kg, respectively). It is likely the weight loss seen was due to the high prevalence of nausea seen in milnacipran treated patients. Nausea is a common TEAE seen with SNRI use in FMS patients, and its prevalence and severity can be lessened by having patients take milnacipran with food and through gradual dose escalation.^{31,32}

One of the milnacipran FMS trials specifically mentioned that TEAEs were dose related and typically resolved within

1 to 2 weeks of continued therapy,³³ an observation consistent with our clinical experience. The indicated dose of milnacipran for management of FMS is 100 or 200 mg divided twice daily. However, we have found that many patients have good efficacy with better tolerability when milnacipran is slowly uptitrated. We start with 12.5 mg once daily in the morning for one week, increase to 25 mg once daily in the morning for 2 weeks, and then 50 mg once daily in the morning. Some patients have good efficacy with less than the indicated dose and we do not up-titrate unless necessary. If insufficient clinical efficacy is seen but the drug remains well tolerated, we will add an evening dose with slow uptitration as above. We will discuss other tolerability observations along with a review of milnacipran efficacy in the next section.

Efficacy of milnacipran in fibromyalgia syndrome patients

To determine what evidence exists for the efficacy of milnacipran in treating FMS, we performed a search of Medline and Cochrane Library databases through September 2009 for randomized-control trials using the key words milnacipran and fibromyalgia limiting results to those in the English language. There were four published studies identified by the search,^{33–36} the results of which are summarized below and in Table 2. It should be noted that none of the milnacipran trials utilized a placebo run-in phase to exclude placebo responders, as was done in trials of pregabalin, since these run-in phases can have important implications for external validity.

Studies 1 and 2: The first two studies will be discussed together since they are separate reports of the same study.^{34,35} We will limit our discussion to results from the later report by Gendreau et al since a more conservative analysis of the data was used than that in the earlier report.³⁵ The study was a 12 week double-blind, randomized, placebo-controlled, dose-ranging, multi-center (14 sites “experienced in treating” FMS) trial performed in the US comparing milnacipran to placebo in patients with FMS. Inclusion criteria required adult patients to meet the 1990 ACR classification criteria for FMS,⁵ have a pain score of ≥ 10 on the 20-point Gracely logarithmic pain scale, and be willing to discontinue all CNS-active therapies (although stable doses of aspirin, acetaminophen and NSAIDs were allowed during the study). Exclusion criteria included psychosis; active suicidality; alcohol or substance abuse; concurrent autoimmune, inflammatory, infectious, or malignant disease; known sleep apnea; or abnormal baseline liver or kidney function tests.

The study included 125 subjects composed almost entirely of female Caucasians. The subjects recorded pain during a 2-week baseline phase and were then randomized in a 3:3:2 ratio to receive milnacipran 25 mg once daily, milnacipran 12.5 mg twice daily, or placebo with all patients receiving capsules twice daily. Milnacipran dose was uptitrated as tolerated in weekly intervals up to a maximum of 200 mg/day over 4 weeks with the ability to decrease the dose if dose-limiting toxicities (DLT) occurred. The patients then continued at the maximum tolerable dose for an additional 8 weeks. The primary endpoint was change in average daily patient self-reported pain scores over the final 2 weeks of the trial compared to the 2-week baseline period. To eliminate bias involved in asking individuals to recall symptoms and to improve compliance,³⁷ an innovative system using Palm[®]-based electronic diaries (e-diaries) was employed to measure pain level through Gracely’s anchored logarithmic scale (0 to 20).³⁸ Patients were asked to rate pain level in the e-diaries each morning, retrospectively once weekly, and in response to 4 to 6 random prompts. Patients also completed standard paper questionnaires to assess pain in monthly intervals using the McGill pain questionnaire and Gracely pain intensity scale. At the end of the study, patients completed the patient global impression of change (PGIC) scale and numerous secondary endpoints were assessed to determine the impact of once-daily and twice-daily milnacipran on fatigue, mood, physical function, sleep quality and global function as determined by the fibromyalgia impact questionnaire,³⁹ the Medical Outcomes Study Short Form 36 (SF-36),⁴⁰ the Beck depression inventory,⁴¹ the Jenkins sleep scale,⁴² and the Arizona sexual experience scale.⁴³ An intention to treat analysis with last observation carried forward was used for data analysis.

Subjects receiving milnacipran dosed twice daily reported significantly better pain relief than those receiving milnacipran once daily, but in other parameters the once-daily and twice-daily dosing regimens were similar. Thirty-seven percent of milnacipran subjects dosed twice daily reported at least a 50% reduction in pain intensity compared with only 22% of subjects receiving milnacipran once daily and 14% of those receiving placebo. There was a statistically significant difference seen when comparing the percent of subjects who rated some degree of improvement in endpoint PGIC ratings between milnacipran and placebo treatment (73% for twice daily and 77% for once-daily milnacipran treatment versus 38% for placebo). While no differences were seen for changes in FIQ global scores, milnacipran-treated subjects reported significant increases in the number

Table 2 Overview of published milnacipran fibromyalgia treatment trials

Milnacipran study	Subject number, allocation, dosing and duration	Placebo and milnacipran completion rates (%)	Mean age; mean disease duration; % female; % caucasian	Primary efficacy measure(s) and analysis	Study met primary efficacy measure?	Milnacipran effect versus placebo on improving symptoms?	% Patients significant pain improvement vs placebo	% Patients significant PGIC improvement vs placebo	Serious TEAE and drop out due to TEAE rates
Study 1: Vitton et al ³⁴	125 2:3:3 Placebo:QD;BID	Placebo 75% Milnacipran 71.1%	47 yrs; 4.15 yrs; 97%;	2-week average daily pain score by e-diary using Gracely logarithmic pain scale LOCF analysis	BID dose group only	Pain (yes), global status (yes), QOL (no), fatigue (yes), stiffness (yes), physical function (yes), sleep (no), sexual function (no)	Only BID dosing group: $\geq 30\%$ improvement: 39% BID vs 14% placebo $\geq 50\%$ improvement: 37% BID vs 14% placebo	Both BID and QD dosing groups significant: 73% BID 77% QD 38% placebo	Serious TEAE rate: 0% for all groups Drop out rates: 21.7% QD, 13.7% BID, 3.6% placebo
Study 2: Gendreau et al ³⁵	Maximum tolerated dose to 200 mg/day divided QD or BID 12 weeks		85%						
Study 3: Clauw et al ³⁶	1196 1:1:1 Placebo:100:200 Fixed dose 100 or 200 mg divided BID 15 weeks	Placebo 72.3% Milnacipran 65.5%	50.2 yrs; NR; 96.2%; 93.5%	Treatment Composite Response (Pain + Global + Function) Pain Composite Response (Pain + Global) BOCF analysis	Yes, both milnacipran groups met both composite response endpoints	Pain (yes), global status (yes), physical function (yes), fatigue (yes), sleep (no), cognition (yes)	$\geq 30\%$ improvement: 52.3% (100 mg), 54.8% (200 mg), vs 38.4% (placebo) $\geq 50\%$ improvement NR	47.5% (100 mg), 50.6% (200 mg) vs 31.8% (placebo) PGIC "much improved" or "very much improved" 23.7% 200 mg, 9.5% placebo	Serious TEAE rates: 1.3% 100 mg, 1% 200 mg, 1.5% placebo. Drop out rates: 19.5% 100 mg, 23.7% 200 mg, 9.5% placebo
Study 4: Mease et al ³³	888 1:1:2 Placebo:100:200 Fixed dose 100 or 200 mg divided BID 27 weeks	Placebo 65% Milnacipran 56%	49.5 yrs; 5.6 yrs; 95%; 94%.	Treatment Composite Response (Pain + Global + Function) Pain Composite Response (Pain + Global) Modified BOCF analysis	Pain Composite Response only in 200 mg/day group	Pain (yes), global status (yes), fatigue (yes), cognition (yes), sleep (no), sexual function (no)	$\geq 30\%$ improvement: 52.8% (100 mg), 56.2% (200 mg) vs 40.2% (placebo). $\geq 50\%$ improvement: 37% (200 mg) vs 26.2% (placebo)	27 week data not reported 15-week data: 76% (100 mg) and 78% (200 mg) vs 61% (placebo) with PGIC "much improved" to "very much improved"	Serious TEAE rates: 1.3% 100 mg, 2.5% 200 mg, 2.7% placebo Drop out rates: 19.6% 100 mg, 27% 200 mg, 10.3% Placebo

Abbreviations: BID, twice daily; BOCF, baseline observation carried forward; NR, not reported; QD, once daily; PGIC, Patient Global Impression of Change; TEAE, treatment emergent adverse event.

of days they “felt good” and the FIQ VASs for pain, fatigue and stiffness were significantly improved by milnacipran treatment along with improvements in physical function scores that neared statistical significance ($P = 0.074$). This is in contrast to results from the SF-36, Jenkins and ASEX scores which showed no significant improvements in self-reported physical function, sleep quality, or sexual function, respectively. However, it must be noted that randomization of patients with baseline comorbid depression as determined by the Mini International Neuropsychiatric Interview (MINI) was not consistent across treatment groups (placebo 32%, milnacipran twice daily 16% and once daily 7%). This may have significantly affected the results as, similar to numerous other studies,⁴⁴ the authors found depressed subjects had significantly higher placebo response rates and it is likely the differences would have been larger if depressed patients had been equally distributed.

The main importance of this study was that it proved the efficacy of milnacipran for managing FMS and that twice-daily dosing was more efficacious than once-daily dosing. It also showed that milnacipran was well tolerated, with no significant difference in dropout rates between active drug and placebo. Nearly all patients completing the trial (81% of once daily and 92% of twice-daily participants) achieved dose escalation to the maximum of 200 mg daily. These results set the stage for future phase 3 trials that ultimately led to the FDA approval of milnacipran for FMS management.

Study 3: This 15-week, multicenter (86 centers in US), double-blind, placebo-controlled, fixed-dose trial compared milnacipran 100 mg and 200 mg divided twice daily.³⁶ As in the Gendreau et al study,³⁵ subjects were required to meet the ACR 1990 criteria for FMS;⁵ in contrast, a linear rather than logarithmic VAS pain scale was used to ensure included subjects had significant pain at baseline (≥ 40 on a linear 0 to 100 VAS pain scale), making the inclusion criteria similar to that used in FMS trials of the other FDA-approved agents. Also contrary to the Gendreau et al study,³⁵ subjects with a current major depressive episode as determined by the MINI were excluded from participation, but similar exclusions included severe psychiatric illness; active suicidality; abuse of alcohol, benzodiazepines or other substances; a history of non-compliant behavior; active cardiovascular, pulmonary, hepatic, renal, gastrointestinal, or autoimmune disease; current systemic infection; active cancer; unstable endocrine disease; severe sleep apnea; prostate enlargement or other male genitourinary disorder; pregnancy or breastfeeding. As in the Gendreau et al study, patients were required to discontinue any centrally-acting medications that might interfere with the

evaluation of pain or other symptoms associated with FMS. However, contrary to the Gendreau et al study and all other FMS trials of indicated agents, patients were allowed up to 60 mg/day of hydrocodone as a rescue analgesic therapy provided it was not used during the 2-week data-collection period preceding the primary efficacy evaluation or during the 48-hour period immediately before study visits. This provision for opioid use during the study is surprising, as treatment trials used to obtain FDA approval of the other indicated FMS medications only allowed for acetaminophen as a rescue analgesic. Also, narcotic use in treating FMS is actively discouraged to prevent the development of rebound pain that can lead to dependence.

After a 2-week baseline period, subjects were randomized to receive milnacipran or placebo tablets twice daily with food. Doses were escalated over the course of 2 to 3 weeks to 50 mg twice daily (100 mg/day) or 100 mg twice daily (200 mg/day) and continued through 15 weeks total. The primary endpoints in this study were different from those used in prior FMS studies and evaluated composite response rates to investigate the ability of milnacipran to manage global FMS symptoms as well as FMS pain. FMS global composite responders were defined as subjects who simultaneously experienced clinically meaningful improvement in pain (30% or greater improvement in average morning VAS pain e-diary scores for final 2 weeks), global status (much or very much improved on the endpoint PGIC scale), and physical function (improvement of ≥ 6 points on the SF-36 physical component summary scale from baseline to week 15). FMS pain composite responders were defined as those who had improvement in pain and global status as defined above. It is important to realize these composite response outcomes are more difficult to achieve than the primary outcomes that were studied in the trials used to obtain FDA approval of the other indicated FMS medications which looked solely at reduction in pain. Secondary end points included time-weighted averages of the individual components of the composite responder analyses as well as improvement in sleep quality, cognitive function and fatigue. For the primary endpoints, missing data were handled using baseline-observation-carried forward (BOCF) methodology. BOCF is a much more conservative methodology than the more commonly used last-observation-carried forward (LOCF) method, and for this reason BOCF is now being required instead of LOCF by the FDA for approval trials. However, the study authors also reported LOCF and observed cases (OC) analyses. OC analysis only includes data from trial subjects who fully completed the trial with no missing values and is thought to better reflect the treatment

response that can be expected clinically in patients who tolerate the drug.

Primary analysis included 1196 subjects with approximately equal numbers randomized to each treatment group. Both primary endpoints were met, with a significantly greater proportion of subjects in the milnacipran treatment groups achieving FMS global (15% 100 mg/day, 14% 200 mg/day versus 9% placebo) and pain (23% 100 mg/day, 25% 200 mg/day versus 17% placebo) composite response outcome rates compared to those receiving placebo using BOCF. While the responder percentages from BOCF analysis were small, the more clinically relevant OC analyses showed about one-quarter of milnacipran treated subjects achieved FMS global composite response rates (25% 100 mg/day, 26% 200 mg/day versus 13% for placebo) and nearly half had a FMS pain composite response (39% 100 mg/day, 46% 200 mg/day versus 25% for placebo), rates similar to our clinical experience. The authors also noted that analgesic response to milnacipran began as early as one week after starting treatment. This time was during the dose-escalation phase, and this observation is consistent with our clinical experience of many patients responding to lower than indicated milnacipran doses. A published extension study indicates the efficacy of milnacipran in improving FMS symptoms may be sustainable for up to 1 year.⁴⁵ In analysis of secondary endpoints, both milnacipran doses were associated with significant improvements in fatigue but only the 200 mg/day dose improved cognitive dysfunction. There was no significant effect of milnacipran on sleep quality. This is somewhat surprising as other dual reuptake inhibitors including duloxetine have been associated with insomnia, presumably due to their noradrenergic activity. Since the majority of FMS patients have nonrestorative sleep, it is reassuring that milnacipran treatment does not appear to worsen sleep quality.

Study 4: The most recently published milnacipran study was a fixed-dose, multicenter (59 centers), randomized, placebo-control trial. Study 4 was very similar to Study 3 but lasted twice as long (27 weeks) to show the benefits of milnacipran treatment are maintained over time.³³ The strategy of performing a 3-month trial to demonstrate efficacy followed by a six month trial to show durability has now been used to gain FDA approval of all three indicated FMS medications. Inclusion and exclusion criteria were similar to those used in Study 3, except that patients were required to have baseline VAS pain scale scores ≥ 50 on a linear 0–100 scale (slightly higher than the typical ≥ 40 scores required in Study 3 and other pain studies). While milnacipran dosing was identical to that used in Study 3, Study 4 randomized fewer subjects (888)

and distributed them unequally between treatment groups using a 2:1:1 ratio between the 200 mg/day, 100 mg/day, and placebo, respectively. Primary outcomes were the same as those in Study 3, with composite responder rates used to demonstrate improvement in FMS global symptoms (simultaneous improvement in pain [30% or greater improvement in average morning VAS pain e-diary scores for final 2 weeks], global status (much or very much improved on the endpoint PGIC scale), and physical function (improvement of ≥ 6 points on the SF-36 physical component summary scale from baseline to week 27)] and improvement in FMS pain (simultaneous improvement in VAS pain e-diary and PGIC scores as defined above). Secondary endpoints were also identical to those used in Study 3 and included time-weighted averages of the individual components of the composite responder analyses as well as improvement in sleep quality, cognitive function and fatigue. In contrast to study 3 where strict BOCF analysis was used, a modified BOCF methodology was utilized for imputing missing data in Study 4, with BOCF used for patients who discontinued the trial before week 15 and LOCF used for patients who discontinued after week 15. However, as before, the study authors also reported LOCF and OC data analyses. Secondary outcomes were identical to those used in Study 3 and included changes in fatigue, sleep quality and cognitive function.

In contrast to Study 3, Study 4 did not meet its primary endpoints at 27 weeks. While a higher percentage of milnacipran treated FMS subjects achieved the predetermined FMS global composite response outcome compared to placebo (18.3% for 100 mg/day and 18.1% for 200 mg/day versus 13% for placebo), the differences were not statistically significant. The FMS pain composite outcome was met for the 200 mg/day milnacipran group, as significantly more of these subjects reached this endpoint compared with placebo (25.6% versus 18.4%, $P = 0.034$). While the 100 mg/day group had a responder rate that was higher than the rate in the 200 mg/day group (26.8% versus 25.9%, respectively), this difference failed to reach statistical significance in comparison to placebo, likely caused by lower statistical power due to the lower number of subjects in the 100 mg/day versus 200 mg/day group. Using the more clinically relevant OC comparison that limits analysis to patients who completed the trial, the 200 mg/day milnacipran treatment group met both primary outcomes, but the 100 mg/day group only met the FMS pain composite response outcome. In secondary endpoint analyses using LOCF analysis, milnacipran at 200 mg/day significantly reduced fatigue compared to placebo at both 15- and 27-week time points. While the 100 mg/day dose improved

fatigue scores at 15 weeks, statistical significance compared to placebo was lost at 27 weeks likely due to the lower number of patients in the 100 mg/day versus 200 mg/day group and a higher placebo response rate observed at the last visit. Patients treated with milnacipran at 200 mg/day had significant improvement in cognition compared to placebo at both 15 and 27 week endpoints. While the 100 mg/day dose also improved cognition, the differences were not statistically significant. As in Study 3, there were no statistically significant effects on sleep quality for the milnacipran treatment groups compared to placebo.

Forty-two percent of randomized patients prematurely discontinued the study, which is a rate higher than that seen in the other milnacipran studies. However, this was a longer study and similar high discontinuation rates have been seen in other 6 month FMS studies.⁴⁶⁻⁴⁹ Also, the rates of serious TEAEs did not differ across treatment groups. Despite these caveats, higher discontinuation rates due to TEAEs were seen in the milnacipran versus placebo arms (27% for 200 mg/day and 19.6% for 100 mg/day versus 10.3% for placebo). Gastrointestinal-related complaints were the most common TEAEs, with nausea being particularly common in all three groups (40.1% 200 mg/day, 32.6% 100 mg/day and 21.1% placebo). Higher rates of constipation and vomiting were also seen in active treatment groups, as were increased rates of headache, hyperhidrosis, hot flush, heart rate increase and palpitation. These TEAEs are typical for patients taking norepinephrine active medications, and, on average, there were no clinically relevant changes in laboratory values, heart rate or blood pressure seen in the trials. We have found that starting with a low dose of medication, stopping at the dose patients find effective, and taking milnacipran with food can limit the occurrence of these side effects in the majority of FMS patients.

Milnacipran's place in FMS management

With three FDA-approved medications for FMS management, deciding which medication to use first in individual FMS patients can be challenging since all three indicated medications have shown similar efficacy in improving FMS pain. We recommend milnacipran as the first-line medication for FMS patients who rate Fatigue and/or Fibrofog as the symptoms that are most limiting for them. This recommendation is based on our clinical experience and the fact that milnacipran is the only FDA approved FMS treatment shown to improve symptoms of fatigue and cognitive dysfunction in phase 3 clinical trials.^{33,36} Also, our clinical

experience shows that many patients who have previously failed to respond to either of the other two indicated medications can have an excellent therapeutic response to milnacipran. Despite side effects such as headache, gastrointestinal complaints, hyperhidrosis, hypertension or palpitations that can limit use in FMS patients, gradual up-titration of milnacipran starting with 12.5 mg once in the morning can maximize tolerability. However, it is important to note that the vast majority of subjects in the milnacipran trials and in our clinical practice are Caucasian women, making generalization of these recommendations to other patient populations problematic. Unfortunately, all trials of the indicated FMS drugs have primarily studied Caucasian women. New FMS trials in minorities and men are needed to determine whether these recommendations are valid for all FMS patients.

We have purposely limited the scope of our discussion of milnacipran to its role in managing FMS since that is the only FDA approved indication in the US. However, milnacipran has demonstrated clinical efficacy in treating major depressive disorder (MDD) and has been used for this indication in Europe and Japan for a decade.⁵⁰ In the treatment of MDD, milnacipran shows similar efficacy to the tricyclic antidepressants but with better tolerability.⁵¹ The relative efficacy of milnacipran in managing MDD compared to other antidepressant classes remains unknown.⁵² While not indicated in the US, we have found milnacipran to be a reasonable treatment alternative for managing FMS patients with coexisting MDD who fail duloxetine therapy.

Conclusions and key points

- The FIBRO mnemonic can be used to recall FMS symptoms including Fatigue, Fibrofog, Insomnia, Blues, Rigidity, and Ow! for pain and work disability.
- Effective FMS treatment requires an individualized program of pharmacologic and nonpharmacologic treatments (including graduated aerobic and resistance exercise) that target problematic FIBRO symptoms.
- Serotonin and norepinephrine play important roles in central pain processing, and FMS patients have reduced levels of norepinephrine and serotonin in their cerebrospinal fluid.
- Milnacipran is a balanced NSRI with demonstrated efficacy in managing global FMS symptoms and pain at doses of 100 and 200 mg divided twice daily.
- Milnacipran is associated with numerous side effects including gastrointestinal complaints, headache, hyperhidrosis, hypertension and palpitations.

- Milnacipran tolerability can be maximized by gradual uptitration and by taking milnacipran with food.
- Milnacipran may be particularly beneficial for FMS patients with significant symptoms of Fatigue, Fibrofog and/or depression.
- Milnacipran use has been linked to elevations in liver function tests and severe liver injury. We recommend regular lab monitoring and avoiding milnacipran use in patients with chronic liver disease or concomitantly with hepatotoxic substances.
- Unlike duloxetine, milnacipran can be used in patients with severe renal disease at 50% of the indicated dose.

Disclosures

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