**Drug Forecast**

**Milnacipran (Savella), a Treatment Option for Fibromyalgia**

Clayton English, PharmD; Jose A. Rey, PharmD, BCPP; and Chabely Rufin, PharmD Candidate

**INTRODUCTION**

Fibromyalgia (FM) is an idiopathic, chronic, nonlocalized pain syndrome accompanied by generalized tenderness. From 2% to 4% of people in the U.S. are affected. Although usually recognized as a disorder that predominates in middle-aged women, it can also affect men and adolescents. In addition to experiencing widespread pain and tenderness, patients may also report sleep difficulties, fatigue, anxiety, depression, paresthesias, stiffness, and an overall decline in physical function. These symptoms are distressing and may have a severe impact on quality of life.

The American College of Rheumatology uses specific criteria for diagnosing FM. The diagnosis is based on the presence of widespread pain for a period of at least three months and on the presence of 11 tender points among 18 specific anatomic sites.

The pathophysiology of FM is poorly understood. Emerging insights suggest that it is a disorder of central nervous system (CNS) pain-processing mechanisms, which results in increased nociceptive sensitivity. The augmented experience of pain is thought to be associated with either (1) excessive spinal facilitation of afferent nociceptive signaling to higher cortical pain-processing regions or (2) deficiencies in descending cortical mechanisms that dampen nociception.

Both ascending and descending nociceptive pathways are regulated through multiple neurotransmitters, including serotonin (5-HT) and norepinephrine. It is hypothesized that abnormal functioning of the noradrenergic and serotonergic systems in the ascending and descending pathways lead to the painful symptoms of FM.

Treatment options include nonpharmacological and pharmacological therapies. The most common nonpharmacological treatments are exercise, patient education, and cognitive behavioral therapy, which have shown some efficacy in randomized, placebo-controlled trials. Pharmacological therapies include a variety of antidepressants, antiepileptics, opioids, and non-steroidal anti-inflammatory agents (NSAIDs). Of the wide variety of medications available to treat FM, only three are approved by the FDA: pregabalin (Lyrica, Pfizer), duloxetine (Cymbalta, Eli Lilly), and milnacipran (Savella, Forest/Cypress Bioscience).

Milnacipran is a SNRI that inhibits the reuptake of both norepinephrine and serotonin; it also has a mild affinity for inhibiting N-methyl-D-aspartate (NMDA). Milnacipran exerts higher selectivity for norepinephrine reuptake than venlafaxine (Effexor, Wyeth) or duloxetine. The exact mechanism of milnacipran and its efficacy in FM are unknown, but it is hypothesized that the effects on regulating dysfunctional noradrenergic and serotonergic pathways contribute to its therapeutic properties. The selectivity for norepinephrine over serotonin has yet to show an overall clinical advantage, since both neurotransmitters have effects on pain modulation. Milnacipran does not affect the reuptake of dopamine, and it has no significant affinity for serotonin (5-HT1A), dopaminergic (D1–D2), opiate, benzodiazepine, and gamma-aminobutyric acid (GABA) receptors in vitro. Because milnacipran lacks affinity for adrenergic, cholinergic, and histaminergic receptors, it does not exhibit many of the expected adverse effects (AEs) seen with the tricyclic antidepressants (TCAs).

**CHEMICAL AND PHYSICAL PROPERTIES**

The chemical name of milnacipran HCl is (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopane-carboxamide HCl. Its empirical formula is C15H23ClN2O; the molecular weight is 282.8 g/mol. Milnacipran is a white to off-white crystalline powder with a melting point of 179°C. It is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and is sparingly soluble in diethyl ether.

Milnacipran is sold as orally administered, film-coated tablets in dosages of 12.5, 25, 50, and 100 mg of the active ingredient. It is also supplied in a dose titration pack for patients starting treatment. According to the manufacturer, the tablets should be stored between 59°F and 86°F.

**PHARMACOLOGY**

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Drug Forecast

oxidases (MAO-A and MAO-B) or acetylcholinesterase.6

PHARMACOKINETICS

Absorption and Distribution

The pharmacokinetic properties of milnacipran are summarized in Table 1. Following oral administration, the drug is rapidly absorbed, exhibiting maximal concentrations at two to four hours and a mean peak concentration ($C_{\text{max}}$) of 150 ng/mL after a single 50-mg dose. As a result of its favorable absorption profile, milnacipran exhibits high bioavailability of approximately 85% to 90%. First-pass elimination is limited, especially since there is low variability among subjects tested.10,11 Administration following a meal has no effect on peak plasma levels. Milnacipran exhibits low, nonsaturable, plasma protein binding (13%), which is lower than the other approved SNRIs (venlafaxine and duloxetine). Because of its low protein binding, milnacipran is free to diffuse, and it is widely distributed in the body (5.3 ± 0.4 L/kg).6,10

Metabolism and Elimination

Milnacipran is metabolized primarily through glucuronidation pathways. As it undergoes phase 2 conjugation, milnacipran forms inactive metabolites: $\text{N}$-milnacipran carbamoyl-$O$-glucuronide and $\text{d}$-milnacipran carbamoyl-$O$-glucuronide, which accounts for 20% of the excreted drug.5,12 The parent drug, not the metabolites, is responsible for milnacipran’s therapeutic effect.7 Milnacipran also undergoes $N$-dealkylation primarily through cytochrome P450 enzyme (CYP) 3A4, but this activity accounts for only about 8% of the agent’s metabolism.5,12

Milnacipran and its inactive metabolites are eliminated primarily via renal excretion, with approximately 50% to 60% of the original dose excreted in the urine as unchanged drug.15 The half-life of milnacipran is between six and eight hours. Steady-state levels are usually reached within 36 to 48 hours.5

DOSAGE

Adults6

A total of 100 mg/day is given in divided doses. The recommended dose titration schedule for milnacipran is summarized in Table 2.

The manufacturer recommends an initial dose of 12.5 mg/day given once daily on day 1. On days 2 and 3, the dose should be increased to 25 mg/day, taken as 12.5 mg twice daily. On days 4 to 7, the dose should be further increased to 50 mg/day, taken in divided doses of 25 mg twice daily. After day 7, the dose should reach 100 mg/day, taken as 50 mg twice daily. The dose may be increased to reach 200 mg/day, given as 100 mg twice daily; however, doses should not exceed 200 mg/day because of the lack of evidence for the drug’s efficacy and because of an increased risk of AEs.

Dose adjustments should be made for each patient. As commonly seen with other SNRIs, tapering of the dose is needed when the drug is discontinued. Patients should not stop milnacipran therapy abruptly because of the potential for the development of withdrawal symptoms.

Renal Insufficiency6

No dose adjustments are needed for patients with mild renal impairment (a creatinine clearance [CrCl] of 50–80 mL/minute); caution should be applied in patients with moderate renal impairment (CrCl, 30–49 mL/minute). For patients with severe renal insufficiency (CrCl, 5–29 mL/minute), the maintenance dose should be reduced by 50% to 50 mg/day in divided doses of 25 mg twice daily. Milnacipran should not be prescribed for patients with end-stage renal disease.

Hepatic Insufficiency6

No dosage adjustments are necessary for patients with hepatic impairment; however, caution should be taken in this patient population.

Elderly Patients6

In the phase 3 studies of the safety and efficacy of milnacipran for treating FM, no overall differences were observed in patients 60 years of age or older in comparison with younger patients.6 Specific trials involving milnacipran for geriatric patients with FM have not been published, although safety has been analyzed in older patients with depression. In a study comparing milnacipran with imipramine (Tofranil, Malinckrodt), milnacipran was associated with lower withdrawal rates and fewer AEs (except for nausea) in patients 65 years of age and older. Although there were fewer AEs in the milnacipran group, dry mouth was the only statistically more frequent AE seen with imipramine.11

Pregnant and Lactating Women6

Milnacipran has been designated as a Pregnancy Category C agent, implying positive fetal risks in animal studies, but studies involving humans are lacking. The manufacturer states that no adequate or well-controlled studies have been reported for pregnant women. Milnacipran should be used during pregnancy only if the potential benefits justify

<table>
<thead>
<tr>
<th>Table 1 Pharmacokinetics of Milnacipran</th>
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<tbody>
<tr>
<td><strong>Absorption and distribution</strong></td>
</tr>
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<td>Bioavailability</td>
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<tr>
<td>Volume of distribution</td>
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<td>Plasma protein binding</td>
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<td><strong>Metabolism and elimination</strong></td>
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<td>Half-life</td>
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| Data from Savella package insert.6 |

<table>
<thead>
<tr>
<th>Table 2 Dose Titration Schedule for Milnacipran</th>
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<tr>
<td><strong>Day 1</strong></td>
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<tr>
<td>12.5 mg once daily</td>
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<tr>
<td><strong>Days 2–3</strong></td>
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<tr>
<td>25 mg/day (12.5 mg twice daily)</td>
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<td><strong>Days 4–7</strong></td>
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<td>50 mg/day (25 mg twice daily)</td>
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<td><strong>After day 7</strong></td>
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<td>100 mg/day (50 mg twice daily)</td>
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| Data from Savella package insert.6 |
the potential risks to the fetus.

Controlled studies of milnacipran have not been performed in nursing mothers. Milnacipran is excreted in animals, and simultaneous nursing is therefore not recommended.

**Pediatric Populations**

No controlled studies involving milnacipran for FM have included patients younger than 17 years of age. Consequently, the drug’s safety and efficacy have not been established in this patient population.

**INDICATION**

Milnacipran is indicated for the management of FM in adults.

**CONTRAINDICATIONS AND PRECAUTIONS**

The use of milnacipran in patients with uncontrolled narrow-angle glaucoma is contraindicated. Milnacipran has been associated with an increased risk of mydriasis. Pupil dilation can restrict the flow of aqueous fluid, causing buildup behind the iris. If blockage occurs, a rapid rise in intraocular pressure can occur.

The concomitant use of milnacipran and MAO inhibitors is contraindicated because of the increased potential to cause serotonin syndrome and hypertensive crisis.

Milnacipran carries a boxed (black-box) warning for an increased risk of suicidal ideation, thinking, and behavior in children, adolescents, and young adults. This medication should not be prescribed to patients who are actively suicidal.

Reports suggest that selective serotonin reuptake inhibitors (SSRIs) and SNRIs, when used as monotherapy, can cause serotonin syndrome and neuropsychiatric syndrome (NMS)-like reactions. Clinicians should be alert to any possible symptoms relating to either reaction. Clinicians should be alert to any possible symptoms relating to either reaction. The concomitant use of milnacipran and MAO inhibitors is contraindicated because of the increased potential to cause serotonin syndrome and hypertensive crisis.

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**ADVERSE DRUG EFFECTS**

In placebo-controlled trials, the most commonly noted AE was nausea.8,14–16 Other frequently experienced side effects included constipation, hot flushes, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension.8,14–16 AEs leading to discontinuation of treatment doses of milnacipran in placebo-controlled trials consisted of nausea (6%), palpitations (3%), headache (2%), constipation (1%), increased heart rate (1%), hyperhidrosis (1%), vomiting (1%), and dizziness (1%).

In phase 3 trials, weight loss occurred at a greater rate in patients receiving milnacipran in comparison with placebo. A mean weight loss of approximately 0.8 kg was reported for milnacipran, compared with 0.2 kg for placebo.

In clinical trials, hypertension was approximately doubled in patients who received milnacipran compared with those receiving placebo. Those patients in the 100-mg treatment group were more likely to become hypertensive (19.5%) than those receiving 200 mg/day (16.6%) or placebo (7.2%). Heart rate was also reported to be increased by an average of 7 to 8 bpm with milnacipran use.

**DRUG INTERACTIONS**

Most of the milnacipran dose is metabolized predominantly through phase 2 conjugation, which reduces the possibility of interactions with drugs metabolized through CYP 450 enzymes.10 Although milnacipran is metabolized primarily through glucuronidation, the drug is a substrate and a weak inhibitor of CYP 3A4.12 This known inhibition is unlikely to produce any clinically relevant pharmacokinetic drug interactions.

Pharmacokinetic drug interactions involving CYP isoenzymes are not likely with milnacipran use, but several clinically important pharmacodynamic interactions must be considered. As previously mentioned, MAO inhibitors are contraindicated with milnacipran. Caution should be exercised with other agents such as antidepressants, antipsychotic drugs, and lithium, because these agents can precipitate 5-HT and NMS-like syndromes. Medications that increase BP and heart rate should also be used cautiously in patients receiving milnacipran because of its potential hypertensive effects.

**CLINICAL EFFICACY**

**Gendreau et al.**14

The efficacy of milnacipran for the treatment of patients with FM was evaluated in a phase 2, three-month, multicenter, randomized, double-blind comparative trial of the study drug and placebo. Adult patients received milnacipran once daily, milnacipran twice daily, or placebo for three months. This dose-escalation trial allowed maximum doses of milnacipran, up to 200 mg/day, to be tested. To be eligible for enrollment in the study, patients:

- had to be between 18 and 70 years of age.
- had to have a diagnosis of primary FM, based on the 1990 American College of Rheumatology (ACR) criteria.
- had to have a pain score of 10 or higher on a 20-point Gracely scale at baseline.
- had to have withdrawn from centrally active therapies commonly used to treat FM.

In addition, female participants were required to use contraception. Patients were excluded from the study if they:

- were actively suicidal or psychotic.
- had a substance abuse problem.
- had any concurrent autoimmune, inflammatory, infectious, or malignant disorder; sleep apnea; or prostatic hypertrophy.
- had abnormal baseline kidney and hepatic function test results.

The study consisted of a screening and washout phase, a baseline assessment, a dose-escalation phase, and a stable-dose phase. The screening and baseline phases lasted four weeks. If patients met the criteria for entering the dose-escalation phase, they were randomly assigned to one of the three study arms (milnacipran twice daily or once daily or placebo). Patients were randomly assigned by blocks of eight in a ratio of 3:3:2 for twice-daily/once-daily placebo dosing. The titration phase lasted for the first four weeks of the trial.

All patients started with 25 mg/day at week 1. Each week following week 1, personnel at the study center called patients by telephone to advise them to remain...
with the current dose, to double the dose, or to discontinue therapy based on tolerability. At the end of the titration period, patients could reach a maximum target dose of 200 mg/day, or they could have remained with a lower dose if tolerability was a problem. Patients then continued to take the stable dose for another eight weeks after they completed the titration phase.

A total of 125 patients were enrolled in the study between March 20, 2002, and December 10, 2002. The primary efficacy endpoint evaluated was the average daily pain score in an electronic diary, as recorded by the patient. Secondary efficacy measures included weekly pain scores, as recorded in the e-diary, and pain assessments via a Visual Analogue Scale (VAS), the Gracely Pain Scale, and the McGill Pain Questionnaire.

Both milnacipran groups had reduced daily e-diary pain scores (~3.0 ± 3.5 for twice-daily dosing and ~2.2 ± 2.3 for once-daily dosing). Although reductions in daily e-diary scores were higher than those reported for placebo (~1.86 ± 3.74), neither treatment group’s results were statistically significant in reducing daily pain scores when compared with placebo ($P = 0.191$ and $P = 0.635$ for twice-daily and once-daily dosing, respectively).

Twice-daily milnacipran, however, resulted in significantly lower pain scores and intensity in all secondary efficacy evaluations ($P < 0.05$) and in significantly lower weekly e-diary pain scores (~3.1 ± 3.5; $P = 0.025$) compared with placebo (~1.14 ± 3.79). The once-daily milnacipran dose did not result in a statistically significant reduction in pain scores in any primary or secondary evaluation. These observations are most likely attributed to the half-life of milnacipran.

A further analysis was conducted to determine whether comorbid depression influenced the treatment response, because milnacipran is an approved therapy in Europe for depression. Paradoxically, non-depressed patients showed significantly better improvement with milnacipran than the depressed patients did. These data are partially skewed, because most of the depressed patients with a comorbidity received placebo (32%), compared with patients using once-daily milnacipran (7%) and twice-daily milnacipran (16%).

No unexpected hazardous side effects occurred in the treatment phases of the study. During the trial, 14.4% of patients discontinued therapy before the study’s completion. Of the 14.4% who withdrew, 3.8% of patients were receiving placebo, 21.7% were receiving once-daily milnacipran, and 13.7% were receiving twice-daily milnacipran. Tolerability was better with the twice-daily dose, suggesting that higher peak levels of milnacipran were associated with increased AEs. Reasons for discontinuing the study drug were attributed primarily to headache and gastrointestinal (GI) upset. Overall, milnacipran was effective in reducing the pain of FM, but twice-daily dosing was necessary for tolerability and efficacy.

**Clauw et al.**

The efficacy and tolerability of milnacipran were evaluated in a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose trial of adults with FM. Patients received milnacipran 100 mg/day or 200 mg/day or placebo for 15 weeks. Patients were eligible for enrollment if they:

- were between 18 and 70 years of age.
- had a diagnosis of primary FM, based on 1990 ACR criteria.
- had withdrawn from centrally active therapies commonly used to treat FM.
- had discontinued treatment using transcutaneous electrical nerve stimulation (TENS), biofeedback, acupuncture, anesthetic or narcotic patches, or injections for tender and trigger points.
- had a raw score of 4 or higher on the physical function component of the Fibromyalgia Impact Questionnaire (FIQ) and 40 or more out of 100 on the mean VAS pain score.

Patients were excluded from the study if they:

- had severe psychiatric illness.
- displayed current major depressive illness based on the Mini-International Neuropsychiatric Interview or had a score higher than 25 on the Beck Depression Inventory.
- exhibited a significant suicide risk.
- were abusing alcohol, benzodiaze-...
100 mg/day and 200 mg/day achieved the primary endpoints of meeting the three criteria for a FM composite response versus placebo (milnacipran doses of 100 mg/day, \( P = 0.01 \); milnacipran doses of 200 mg/day, \( P = 0.02 \)). The number of patients experiencing more than a 30% improvement from baseline with 24-hour pain was highest with milnacipran 200 mg/day (39.9%), compared with 100 mg/day (37.3%) or placebo (28.7%).

The most frequently reported AE with the study drug was nausea, which occurred in 37.6% of patients taking 200 mg/day, in 34.3% of those taking 100 mg/day, and in 19.2% taking placebo. Other commonly reported AEs were dizziness, palpitations, hot flushes, hypertension, vomiting, tachycardia, hyperhidrosis, constipation, and migraines. Discontinuation rates attributable to AEs were higher with milnacipran than with placebo (23.7% with 200 mg/day, 19.5% with 100 mg/day, and 9.5% with placebo). Overall, milnacipran showed significant efficacy over placebo for treating FM; however, the higher dose of 200 mg/day was associated with more AEs.

**Mease et al.**

Mease and colleagues performed a randomized, double-blind study to confirm the safety and efficacy of milnacipran in patients with FM. This 27-week study compared milnacipran 100 mg/day and 200 mg/day with placebo. Eligibility requirements were as follows:

- Female and male subjects were between 18 and 70 years of age.
- Patients had a diagnosis of primary FM, based on 1990 ACR criteria. Patients were excluded from the study if they:
  - had severe psychiatric illness, a current major depressive episode, or a risk of suicide.
  - were abusing alcohol or drugs.
  - had an autoimmune disease, a systemic infection, moderate-to-severe sleep apnea, an active peptic ulcer, or inflammatory bowel disease.
  - currently had cancer or were undergoing concurrent chemotherapy.
  - had a history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease.

The 888 eligible patients from 59 centers in the U.S. were randomly assigned to receive milnacipran 100 mg/day, milnacipran 200 mg/day, or placebo in two divided doses for six months. The study involved four phases, beginning with a screening and washout phase of centrally acting therapies used for treating FM, followed by the baseline assessment phase. The next three weeks consisted of the dose-escalation phase, in which patients reached their assigned dose level. Sham dosing was implemented in the placebo patients and in the group receiving milnacipran 100 mg/day to maintain blinding. In the final phase, patients received stable doses for 24 weeks.

Baseline demographics were similar for all treatment arms. The primary efficacy measure for the treatment of FM pain was a composite response rate based on the following endpoints:

- an improvement in pain of 30% or more in VAS 24-hour morning recall
- Patient Global Impression of Change (PGIC) ratings of “very much improved” or “much improved”

At week 15, the midpoint of the study, more patients treated with milnacipran doses of 100 mg/day (27.2%; \( P = 0.056 \)) and 200 mg/day (26.8%; \( P = 0.032 \)) met the primary outcome criteria of FM pain responders compared with the placebo patients (19.3%). At the end of the study (at six months), more patients in both milnacipran groups met the criteria for response for treating FM pain (200 mg/day, 25.6%; 100 mg/day, 25.9%; and placebo, 18.4%). Although the patients receiving milnacipran 100 mg/day had the highest composite response rate for the treatment of FM pain, there was only a trend toward reaching statistical significance (\( P = 0.072 \)). Results for the 200-mg/day group differed significantly from those of the placebo group (\( P = 0.034 \)).

Improvements were observed during the study, but the rate of discontinuation associated with milnacipran use was extremely high. At week 27, 42.9% of patients receiving milnacipran 100 mg/day, 45.8% receiving 200 mg/day, and 35% of patients receiving placebo had discontinued therapy. Of the patients receiving milnacipran 200 mg/day, 27% withdrew from therapy because of AEs, compared with 19.6% taking milnacipran 100 mg/day and 10.3% receiving placebo.

Therapeutic failure was the second highest reason for discontinuing milnacipran; 11.1% of patients taking 200 mg/day stopped therapy, and 11.6% taking 100 mg/day withdrew. A higher percentage of patients receiving placebo (15.2%) experienced therapeutic failures.

Overall, milnacipran was associated with significant improvements in the treatment of pain associated with FM; however, higher doses were associated with more side effects.

**COST**

Prices of milnacipran are summarized in Table 3. The average wholesale price (AWP) of a month’s supply (12.5-mg tablets) is $122, and the price is the same for 25-, 50-, and 100-mg tablets. The titration pack is priced at $112. The prices listed may vary among institutions.

Two other medications approved for the treatment of FM— duloxetine and pregabalin—are priced similarly. Duloxetine (like milnacipran, an SNRI) costs $135 for a one-month supply; pregabalin costs $103 for a one-month supply. Prices

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**Table 3 FDA-Approved Therapies for Fibromyalgia**

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<tr>
<th>Treatment Option</th>
<th>Recommended Dose</th>
<th>Cost of a One-Month Supply</th>
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<tbody>
<tr>
<td>Milnacipran (Savella)</td>
<td>100 mg in two divided doses</td>
<td>$122</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>60 mg once daily</td>
<td>$135</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>150–450 mg in two divided doses</td>
<td>$103–$231</td>
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Data from package inserts for Savella, Cymbalta, and Lyrica.

Data from Drug Topics Red Book, 2009.
for pregabalin can vary among patients, because up to 450 mg/day can be used for treating FM. Although only three agents are approved, other medications (such as the TCAs, SSRIs, other SNRIs, muscle relaxants, benzodiazepines, and analgesics) have shown some efficacy and are currently being used for treating patients with FM. Prices may vary.

**CONCLUSION**

Milnacipran has been used for several years in Europe and Asia for treating patients with depression. It was approved in 2009 as Savella in the U.S. for patients with FM. As with older drugs used for FM, milnacipran utilizes both norepinephrine and serotonin reuptake as its primary mechanisms for treating symptoms. Pregabalin and duloxetine are also used for FM. Besides FDA-approved agents, several medications have off-label usage in therapy for FM, such as gabapentin (Neurontin, Pfizer), tramadol (Ultram, PriCara), and amitriptyline.

In January 2010, the efficacy and safety of milnacipran were called into question. Public Citizen, a non-profit consumer advocacy group, petitioned the FDA to remove the drug from the market because of its hypertensive effects and lack of long-term evidence. The average increase in systolic and diastolic BP was 3.1 mm Hg with milnacipran; almost 20% of non-hypertensive patients receiving milnacipran became hypertensive at the end of the study. The average increase in BP seen with milnacipran is comparable to that of other SNRIs on the market.

Compared with venlafaxine and duloxetine, milnacipran has the highest selectivity for norepinephrine reuptake. Although scrutiny should be used in prescribing milnacipran, it is still a valid option for FM based on the clinical evidence. Additional long-term studies of milnacipran are still needed because it is being used to treat a chronic disease state. One must consider the patient’s current medication profile, financial means, and coexisting disease states in order to select the most appropriate treatment.

**REFERENCES**