

Fibromyalgia Management and the Pharmacist:



Empowering Patients Through Education and Counseling

By understanding the challenges related to fibromyalgia management, pharmacists can directly impact the clinical outcome of patients and give the encouragement needed to take charge of their lives once again. Fibromyalgia is a chronic, multisymptom condition characterized by widespread pain. It can result in considerable disability and is a source of economic burden for both individuals and society. Savella® (milnacipran HCl), a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is approved for the management of fibromyalgia in adults.¹ The following important information is provided to help educate pharmacists on fibromyalgia in general and how Savella may help.



Frequently Asked Questions

Q What is fibromyalgia?

A Fibromyalgia is characterized by multiple symptoms, most notably widespread pain, fatigue, sleep problems, morning stiffness, cognitive impairment, and mood disturbance.² Collectively, these symptoms may force patients to make lifestyle adjustments. Fibromyalgia is also associated with a number of other comorbid conditions, such as chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, and tension or migraine headache.³ Although the exact cause of fibromyalgia is still being researched, experts believe that fibromyalgia may be associated with abnormal sensory processing in the brain and spinal cord.⁴⁻⁶



These abnormalities contribute to patients having an increased perception of pain from application of both painful and nonpainful stimuli.⁴⁻⁶

Q How is fibromyalgia diagnosed?

A Diagnosis, based upon criteria established in 1990 by the American College of Rheumatology (ACR), requires that a patient have a history of widespread, chronic pain for at least 3 months and a finding of at least 11 of 18 possible tender points.⁷ Tender points are places on the body that are especially sensitive to touch but show no signs of inflammation in the surrounding joints or muscles. To test the tender points, physicians may use the thumb of their dominant hand and apply 4 kg of pressure (about the amount of pressure to blanch the nail bed of the examiner) once to each tender point designated for approximately 4 seconds.⁷ Patients may still have fibromyalgia despite not meeting the recommended criteria. In addition, owing to the fact that chronic pain and fatigue are common symptoms associated with a number of medical conditions, diagnosis can be missed.

Q I heard that there was a treatment approved for fibromyalgia in 2009; what is it?

A In 2009, the FDA approved Savella® (milnacipran HCl), a selective serotonin and norepinephrine reuptake inhibitor (SNRI), for the management of fibromyalgia in adults. Savella is believed to inhibit the reuptake of neurotransmitters (norepinephrine and serotonin) in the brain and spinal cord that control pain processing.¹ Savella has a 3:1 greater potency for norepinephrine over serotonin, in vitro, an attribute that distinguishes Savella from other compounds that inhibit the reuptake of serotonin and norepinephrine.¹



The efficacy of Savella was established in 2 double-blind, placebo-controlled studies of 2,084 adult patients in which Savella 100 mg/day and 200 mg/day were compared to placebo. Enrolled patients met the ACR criteria for fibromyalgia (a history of widespread pain for 3 months and pain present at ≥ 11 of 18 specific tender point sites). Study 1 was 6 months in duration, and Study 2 was 3 months in duration.^{1,8,9} In clinical studies, a higher proportion of patients treated with Savella experienced simultaneous, clinically meaningful improvements in the domains of pain relief, overall fibromyalgia improvement and physical function compared with patients receiving placebo.^{1,8,9}

Q What about drug-drug interactions?

A In vitro and in vivo studies showed that Savella is unlikely to produce clinically significant pharmacokinetic drug interactions; this is of particular importance since patients with fibromyalgia may be on multi-drug regimens. Clinically important interactions may occur with MAOIs, serotonergic drugs (including other SSRIs, SNRIs, lithium, tryptophan, antipsychotics, and dopamine antagonists), triptans, catecholamines (epinephrine and norepinephrine), CNS-active drugs (including clomipramine), and select cardiovascular agents (digoxin and clonidine).¹ Savella and its metabolites are eliminated primarily by renal excretion and undergo minimal CYP450-related metabolism. Savella also has low in vitro plasma-protein binding of 13%.¹

Q What common adverse events are associated with Savella?

A In clinical trials, the most frequently occurring adverse reaction was nausea (37% vs 20% for placebo).¹ Nausea was generally mild to moderate in nature. Taking Savella with food may improve tolerability. Other frequently occurring adverse events are listed in the table. Discontinuation rates due to adverse events in clinical trials were 23% for Savella 100 mg/day, 26% for Savella 200 mg/day and 12% for placebo.¹

Treatment-Emergent Adverse Events Reported in $\geq 5\%$ and Occurring at Twice the Rate of Placebo

	Savella 100 mg (n=623) %	Savella 200 mg (n=934) %	Placebo (n=652) %
Nausea*	35	39	20
Constipation	16	15	4
Hot flush	11	12	2
Hyperhidrosis	8	9	2
Palpitations	8	7	2
Hypertension	7	4	2
Vomiting	6	7	2
Dry mouth	5	5	2
Heart rate increased	5	6	1

* In placebo-controlled trials, the most frequently occurring adverse event was nausea.

Q What is the recommended dose of Savella?

A The recommended dose of Savella is 100 mg/day (50 mg twice daily), with a 1-week titration period. Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily). In patients with severe renal impairment, the maintenance dose should be reduced by 50%. Taking Savella with food may improve tolerability. Savella is available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablets.¹

Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients.

Q Who should not take Savella?

- A** Savella is contraindicated for:
- Patients taking a monoamine oxidase inhibitor (MAOI)¹
 - Patients with uncontrolled, narrow-angle glaucoma¹

Q What underlying conditions should I be aware of before dispensing Savella?

- A**
- Hypertension, tachyarrhythmia or other cardiac diseases¹
 - Liver problems or a history of substantial alcohol use¹
 - Kidney problems, including dysuria¹
 - History of mania or seizure disorders¹
 - Bleeding disorders¹
 - Glaucoma¹

Q What other important information should be discussed with patients?

A Explain to patients that their blood pressure and pulse should be monitored at regular intervals while receiving treatment with Savella. Inform patients that they should not operate machinery or drive until they are reasonably certain that Savella treatment does not affect their ability to engage in such activities. Tell patients that they should avoid drinking alcohol while taking Savella. It is important that patients advise their physicians if they are pregnant, plan to become pregnant during therapy or are breastfeeding an infant. Inform patients being treated with Savella that they should call their physicians if they experience very high fever, rigid muscles, shaking, confusion, or rapid changes in heart rate and blood pressure. These may be signs of a rare but serious adverse event. Encourage patients to speak with their physician before stopping Savella or changing doses. Withdrawal symptoms can occur, particularly when discontinuation is abrupt.

Q When can patients begin to feel the effect of Savella?

A In clinical studies, some patients who experienced overall improvement with Savella also experienced pain reductions 1 week after they reached a stable dose (the same dose every day).¹ In clinical trials, maximal pain relief was achieved in 9 weeks.^{8,9}

Q What does Savella cost?

A Savella is a value-priced brand with a wholesale acquisition cost (WAC) of \$106.47 across all strengths (12.5 mg, 25 mg, 50 mg and 100 mg) for a 30-day supply. A titration pack containing 55 tablets for a 28-day supply is available at a WAC of \$97.60.

Q Are there any other ways that patients can alleviate fibromyalgia symptoms?

A Some of the more common and effective approaches are listed below. Inform patients that they should consult their doctor before incorporating any of these approaches.

Exercise: Regular exercise is among the more effective treatments for fibromyalgia. Pain and fatigue may make it more challenging to exercise regularly.¹⁰⁻¹²

Diet: Although no specific diet has been shown to relieve symptoms, a healthy and balanced diet can give patients more energy and help prevent other health problems.¹¹

Cognitive-behavioral therapy (CBT): CBT helps patients change the way they think, which helps change how they feel and what they do. In other words, patients are encouraged to act on a new way of thinking to help themselves feel better. During CBT, patients work with a trained therapist on a structured, time-limited basis to achieve specific patient goals. Studies of CBT in patients with fibromyalgia have shown that it can help decrease pain and fatigue, while improving function and overall mood.^{12,13}

Complementary therapies: Research on complementary treatments for fibromyalgia is limited. However, some patients find therapeutic massage can help manage stress and relieve their pain, muscle spasms, and discomfort. Other therapies that may provide relief include biofeedback, acupuncture, chiropractic treatment, and physical therapy.^{11,14}

References:

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Additional Important Safety Information

Contraindications

- Savella is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) concomitantly or within 14 days of discontinuing treatment with an MAOI. There have been reports of serious, sometimes fatal, reactions in patients started on an MAOI who were receiving or had recently discontinued a serotonin reuptake inhibitor. At least 5 days should be allowed after stopping Savella before starting an MAOI.
- Savella is contraindicated in patients with uncontrolled narrow-angle glaucoma and should be used with caution in patients with controlled narrow-angle glaucoma. In clinical trials, Savella was associated with an increased risk of mydriasis.

Warnings and Precautions

- Prescriptions for Savella should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.
- Development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs and SNRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), drugs that impair metabolism of serotonin (including MAOIs), or antipsychotics or other dopamine antagonists. The management of these reactions should include immediate discontinuation of Savella and the concomitant agent and supportive symptomatic treatment. The concomitant use of Savella with serotonin precursors is not recommended.
- SNRIs, including Savella, have been associated with cardiovascular effects, including cases of elevated blood pressure, requiring immediate treatment. In clinical trials, sustained increases in systolic and diastolic blood pressure occurred more frequently in Savella-treated patients compared to placebo. Among patients who were non-hypertensive at baseline, approximately twice as many patients receiving Savella, vs placebo, became hypertensive at the end of the study. Clinically significant increases in pulse (≥ 20 bpm) occurred more frequently in Savella-treated than placebo-treated patients. Blood pressure and heart rate should be monitored prior to initiating treatment with Savella and periodically throughout treatment. Pre-existing hypertension, tachyarrhythmias, and other cardiac diseases should be treated before starting therapy with Savella. Savella should be used with caution in patients with significant hypertension or cardiac disease. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated, and such combinations should be used with caution.

For patients who experience a sustained increase in blood pressure or heart rate while receiving Savella, either dose reduction or discontinuation should be considered.

- Savella should be prescribed with caution in patients with a history of seizure disorder or mania.
- Savella has been associated with mild elevations of ALT and AST (1 to 3 times the upper limit of normal). Rarely, reports of serious liver injury, including fulminant hepatitis, have been reported in patients treated with milnacipran. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction and should not be resumed unless another cause can be established.
- As with other SNRIs and SSRIs, withdrawal symptoms have been observed following discontinuation of milnacipran. A gradual dose reduction is recommended.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. Elderly patients may be at greater risk. Discontinuation should be considered for patients with symptomatic hyponatremia.
- SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Patients should be cautioned regarding the risk of bleeding associated with concomitant use of Savella and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- Savella can affect urethral resistance and micturition. Caution is advised in the use of Savella in patients with a history of dysuria, notably in male patients with a history of obstructive uropathies as these patients may experience higher rates of genitourinary adverse events.
- Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Use in Specific Populations

- There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions

- In clinical trials, the most frequently occurring adverse reaction was nausea (37% vs 20% for placebo). The most commonly occurring adverse reactions ($\geq 5\%$ and greater than placebo) were headache (18% vs 14%), constipation (16% vs 4%), dizziness (10% vs 6%), insomnia (12% vs 10%), hot flush (12% vs 2%), hyperhidrosis (9% vs 2%), vomiting (7% vs 2%), palpitations (7% vs 2%), heart rate increased (6% vs 1%), dry mouth (5% vs 2%), and hypertension (5% vs 2%).