MILNACIPRAN

**Brands**
- Toledomin
- Ixel
- Savella
*see index for additional brand names*

**Generic?** No

**Class**
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); antidepressant; chronic pain treatment

**Commonly Prescribed For** *(bold for FDA approved)*
- Fibromyalgia
- Major depressive disorder
- Neuropathic pain/chronic pain

**How The Drug Works**
- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Weak noncompetitive NMDA-receptor antagonist (high doses), which may contribute to actions in chronic pain
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, milnacipran can increase dopamine neurotransmission in this part of the brain

**How Long Until It Works**
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms in depression

**If It Works**
- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of fibromyalgia and chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Treatment of fibromyalgia and chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in fibromyalgia and chronic neuropathic pain may also need to be indefinite, but long-term treatment is not well-studied in these conditions

**If It Doesn’t Work**
- Many depressed patients only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer
### Notable Side Effects

- Most side effects increase with higher doses, at least transiently
- Headache, nervousness, insomnia, sedation
- Nausea, diarrhea, decreased appetite
- Sexual dysfunction (abnormal ejaculation/orgasm, impotence)
- Asthenia, sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Dose-dependent increased blood pressure
- Dry mouth, constipation
- Dysuria, urological complaints, urinary hesitancy, urinary retention
- Increase in heart rate
- Palpitations

### Life-Threatening or Dangerous Side Effects

- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Rare seizures

### Weight Gain

- Reported but not expected

### Sedation

- Occurs in significant minority

### What To Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

### Best Augmenting Agents for Side Effects

- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin or naftopidil
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia

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### Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation experience is limited compared to other antidepressants
- Benzodiazepines can reduce insomnia and anxiety
- Adding other agents to milnacipran for treating depression could follow the same practice for augmenting SSRIs or other SNRIs if done by experts while monitoring carefully in difficult cases
- Although no controlled studies and little clinical experience, adding other agents for treating fibromyalgia and chronic neuropathic pain could theoretically include gabapentin, tiagabine, other anticonvulsants, or even opiates if done by experts while monitoring carefully in difficult cases
- Mirtazapine, bupropion, reboxetine, atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression or treatment-resistant depression
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone

### Tests

- Check blood pressure before initiating treatment and regularly during treatment

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### SIDE EFFECTS

#### How Drug Causes Side Effects

- Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing urinary retention or constipation)
- Most side effects are immediate but often go away with time
Nevertheless, some patients respond better to higher doses (200–300 mg/day) than to lower doses.

- Different doses in different countries
- Different doses in different indications and different populations
- Preferred dose for depression may be 50 mg twice daily to 100 mg twice daily in France.
- Preferred dose for depression in the elderly may be 15 mg twice daily to 25 mg twice daily in Japan.
- Preferred dosing for depression in other adults may be 25 mg twice daily to 50 mg twice daily in Japan.

Thus, clinicians must be aware that titration of twice daily dosing across a 10-fold range (30 mg – 300 mg total daily dose) can optimize milnacipran’s efficacy in broad clinical use.

- Patients with agitation or anxiety may require slower titration to optimize tolerability.
- No pharmacokinetic drug interactions (not an inhibitor of CYP450 2D6 or 3A4).
- As milnacipran is a more potent norepinephrine reuptake inhibitor than a serotonin reuptake inhibitor, some patients may require dosing at the higher end of the dosing range to obtain robust dual SNRI actions.
- At high doses, NMDA glutamate antagonist actions may be a factor.

**Dosing and Use**

**Usual Dosage Range**
- 30–200 mg/day in 2 doses

**Dosage Forms**
- Capsule 25 mg, 50 mg (France, other European countries, and worldwide markets).
- Capsule 15 mg, 25 mg, 50 mg (Japan).
- Tablet 12.5 mg, 25 mg, 50 mg, 100 mg.

**How to Dose**
- Should be administered in 2 divided doses.
- Initial 12.5 mg once daily; increase to 25 mg/day in 2 divided doses on day 2; increase to 50 mg/day in 2 divided doses on day 4; increase to 100 mg/day in 2 divided doses on day 7; maximum dose generally 200 mg/day.

**Dosing Tips**
- Preferred dose for fibromyalgia may be 100 mg twice daily.
- Higher doses usually well tolerated in fibromyalgia patients.

- Once daily dosing has far less consistent efficacy, so only give as twice daily.
- Higher doses (>200 mg/day) not consistently effective in all studies of depression.

**Overdose**
- Vomiting, hypertension, sedation, tachycardia.
- The emetic effect of high doses of milnacipran may reduce the risk of serious adverse effects.

**Long-Term Use**
- Safe.

**Habit Forming**
- No.

**How to Stop**
- Taper is prudent, but usually not necessary.

**Pharmacokinetics**
- Half-life 8 hours.
- No active metabolite.
Drug Interactions
- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAO inhibitors, so do not use with MAO inhibitors or for at least 21 days after MAOIs are stopped
- Do not start an MAO inhibitor for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing milnacipran
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIIDs)
- Switching from or addition of other norepinephrine reuptake inhibitors should be done with caution, as the additive pro-noradrenergic effects may enhance therapeutic actions in depression, but also enhance noradrenergically mediated side effects
- Few known adverse pharmacokinetic drug interactions

Other Warnings/Precautions
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Can cause mild elevations in ALT/AST, so avoid use with alcohol or in cases of chronic liver disease
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use
- If patient has uncontrolled narrow angle-closure glaucoma
- If patient is taking an MAO inhibitor
- If there is a proven allergy to milnacipran

SPECIAL POPULATIONS

Renal Impairment
- Use caution for moderate impairment
- For severe impairment, 50 mg/day; can increase to 100 mg/day if needed

Hepatic Impairment
- No dose adjustment necessary
- Not recommended for us in chronic liver disease

Cardiac Impairment
- Drug should be used with caution

Elderly
- Some patients may tolerate lower doses better
- Reduction in risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardian of this risk so they can help observe child or adolescent patients
- Not well-studied

Pregnancy
- Risk Category C [some animal studies show adverse effects; no controlled studies in humans]
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence
of depression, maternal health, infant bonding) to the mother and child
• For many patients this may mean continuing treatment during pregnancy
• Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding
• Unknown if milnacipran is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
• Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
• Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
• For many patients, this may mean continuing treatment during breast feeding

Potential Advantages
• Fibromyalgia, chronic pain syndrome
• Patients with retarded depression
• Patients with hypersomnia
• Patients with atypical depression
• Patients with depression may have higher remission rates on SNRIs than on SSRIs
• Depressed patients with somatic symptoms, fatigue, and pain

Potential Disadvantages
• Patients with urologic disorders, prostate disorders
• Patients with borderline or uncontrolled hypertension

• Patients with agitation and anxiety (short-term)

Primary Target Symptoms
• Pain
• Physical symptoms
• Depressed mood
• Energy, motivation, and interest
• Sleep disturbance

Pearls
• Approved in the United States for use in pain and fibromyalgia
• Not studied in stress urinary incontinence
• Not well studied in ADHD or anxiety disorders, but may be effective
* Has greater potency for norepinephrine reuptake blockade than for serotonin reuptake blockade, but this is of unclear clinical significance as a differentiating feature from other SNRIs, although it might contribute to its therapeutic activity in fibromyalgia and chronic pain
* Onset of action in fibromyalgia may be somewhat faster than depression (i.e., 2 weeks rather than 2–8 weeks)
• Therapeutic actions in fibromyalgia are partial, with symptom reduction but not necessarily remission of painful symptoms in many patients
* Potent noradrenergic actions may account for possibly higher incidence of sweating and urinary hesitancy than other SNRIs
• Urinary hesitancy more common in men than women and in older men than in younger men
• Alpha 1 antagonists such as tamsulosin or naftopidil can reverse urinary hesitancy or retention
• Alpha 1 antagonists given prophylactically may prevent urinary hesitancy or retention in patients at higher risk, such as elderly men with borderline urine flow
• May be better tolerated than tricyclic or tetracyclic antidepressants in the treatment of fibromyalgia or other chronic pain syndromes
• No pharmacokinetic interactions or elevations in plasma drug levels of tricyclic or tetracyclic antidepressants when adding or switching to or from milnacipran

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ART OF PSYCHOPHARMACOLOGY
Suggested Reading

