Using Non-Opioid Medications: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

### Duloxetine
- Doses larger than 60 mg (up to 120 mg) of duloxetine may provide additional benefit in peripheral diabetic neuropathy but not fibromyalgia, at the expense of more adverse events. Also approved for chronic musculoskeletal pain.

### Venlafaxine
- All use for pain is considered off-label.

### SNRIs
- Better tolerated than tricyclic antidepressants, but could have troublesome adverse effects
- Similar to tricyclic antidepressants, these agents carry a black box warning for potential suicidal ideation early in therapy for children, adolescents, and young adults
- Contraindicated with monoamine oxidase inhibitors and other serotonergic agents (e.g. triptans, tryptophan as supplements, tricyclics, fentanyl, tramadol, buspirone, lithium, amphetamines, St. John’s wart) due to possible Serotonin Syndrome*

*Serotonin Syndrome = serotonergic drug use within the last five weeks and presence of tremor and hyperreflexia, spontaneous clonus, and inducible or ocular clonus with agitation or diaphoresis, or muscle rigidity and fever with inducible or ocular clonus
# Using Non-Opioid Medications: SNRIs

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<th>Drug</th>
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<td>Duloxetine</td>
<td><strong>CMP</strong>: Initiate with 30 mg/day for 1 week, increased to 60 mg/day; <strong>PDPN</strong>: Initiate and maintain with 60 mg/day</td>
<td>Nausea, dry mouth, dizziness, sedation, fatigue, insomnia, orthostatic hypotension, nausea, loss of appetite, weight loss, constipation, hyperhidrosis; bleeding. Rarely, hyponatremia, hepatotoxicity, serious skin reactions, urinary retention</td>
<td>↑ risk of SS with other serotonergic agents; ↑ risk of bleeding with NSAIDs, aspirin/anti-platelet drugs and anticoagulants</td>
<td>Bioavailability ↓ 33% in smokers; ↑ risk of falls; Caution in patients with history of mania, seizures or hypertension; monitor BP</td>
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<tr>
<td>Venlafaxine</td>
<td>All use for pain is considered off-label. Initiate with 75 mg/day in divided doses with food, titrate to 150 mg or a max of 225 mg/day in 75 mg increments in at least 4 day intervals</td>
<td>Weakness, nausea, loss of appetite, dizziness/sedation or insomnia, nervousness, dry mouth, constipation, hyperhidrosis, bleeding. Rarely, hyponatremia, serious skin reactions, interstitial lung disease</td>
<td>↑ risk of SS with other serotonergic agents; ↑ risk of bleeding with NSAIDs, aspirin/anti-platelet drugs and anticoagulants</td>
<td>Caution in patients with hypertension; monitor BP; Caution when using with other drugs that inhibit CYP3A4 or CYP2D6; ↑ sexual dysfunction</td>
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<td>Milnacipran</td>
<td><strong>Fibromyalgia</strong>: Initiate with 12.5 mg once daily to 25 mg (day 2) and 50 mg/day (days 4-7 in 2 divided doses, to a recommended dose of 100 mg/day; max = 200 mg/day</td>
<td>Nausea, loss of appetite, dizziness, dry mouth, constipation, headache, ↑ heart rate/palpitations, hyperhidrosis, bleeding. Rarely, hyponatremia, serious hepatotoxicity</td>
<td>↑ risk of SS with other serotonergic agents; ↑ risk of bleeding with NSAIDs, aspirin/anti-platelet drugs and anticoagulants</td>
<td>Dose reduction with severe renal impairment CrCl ≤ 30 ml/min; Caution in patients with hypertension and males with urinary obstruction; monitor BP</td>
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</table>

**SS** = Serotonin Syndrome; **CYP** = P450 enzyme; **CrCl** = creatinine clearance. **CMP** = chronic musculoskeletal pain; **PDPN** = painful diabetic peripheral neuropathy

Disclaimer: Information in the table obtained from FDA-approved product labeling (package insert). It is not intended to provide clinical recommendations for specific patients. Please consult the current product labeling for the most up to date information.