Brands
- Cymbalta, Xeristar, Yentreve, Ariclaim

Generic?
No

Class
- Serotonin and norepinephrine reuptake inhibitor (SNRI), antidepressant

Commonly Prescribed For
(FDA approved in bold)
- Major depressive disorder
- Generalized anxiety disorder
- Fibromyalgia
- Diabetic peripheral neuropathic pain (PDN)
- Chronic musculoskeletal pain
- Migraine prophylaxis
- Other painful peripheral neuropathies
- Cancer pain (neuropathic)
- Stress urinary incontinence

How the Drug Works
- Blocks serotonin and noradrenergic reuptake pumps, increasing their levels within hours, but antidepressant effects take weeks. Effect may be more likely related to norepinephrine receptor systems
- Preferential 5HT/NE ratio (~5–10:1)
- Weakly blocks dopamine reuptake pump (dopamine transporter)

How Long until It Works
- Fibromyalgia: as little as 2 weeks, but may take up to 3 months
- Migraine: effective in as little as 2 weeks, but can take up to 10 weeks on a stable dose to see full effect
- Tension-type headache prophylaxis: effective in 4–8 weeks
- Other painful peripheral neuropathies
- Cancer pain (neuropathic)
- Stress urinary incontinence

If It Works
- Fibromyalgia: the goal is to reduce pain intensity and symptoms, reduce use of analgesics, and improve quality of life

- Migraine: goal is 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Tension-type headache: goal is 50% or greater reduction of days with headache, duration or intensity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Diabetic neuropathy: the goal is to reduce pain intensity and reduce use of analgesics but usually does not produce remission. Continue to monitor for AEs and maintain strict glycemic control
- Depression: continue to use and monitor for AE. May continue for 1 year following first depression episode or indefinite if >1 episode of depression

If It Doesn’t Work
- Increase to highest tolerated dose
- Fibromyalgia, migraine, and tension-type headache: address other issues, such as medication overdose, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent
- Neuropathic pain: either change to another agent or add a second agent

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Fibromyalgia: SNRIs such as milnacipran and/or AEDs, such as gabapentin or pregabalin, are agents that may be useful in managing fibromyalgia. May also use in combination with natural products and nonmedication treatments, such as biofeedback or physical therapy, to improve pain control
- Migraine: for some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antihypertensives, natural products, and nonmedication treatment such as biofeedback, to improve headache control
- Neuropathic pain: AEDs, such as gabapentin, pregabalin, ocarbamazepine, and capsaicin and mexiletine are agents used for neuropathic pain. Opioids are appropriate for long-term use in some cases but require careful monitoring
Tests
- Check blood pressure at baseline and when increasing dose

<table>
<thead>
<tr>
<th>ADVERSE EFFECTS (AEs)</th>
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<tbody>
<tr>
<td><strong>How Drug Causes AEs</strong></td>
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<tr>
<td>By increasing serotonin and norepinephrine on nontherapeutic responsive receptors throughout the body. Most AEs are dose-dependent and time-dependent</td>
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<tr>
<td><strong>Notable AEs</strong></td>
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<tr>
<td>Orthostatic hypotension and syncope usually within the 1st week of use, constipation, dry mouth, sweating, diarrhea, fatigue, loss of appetite, nausea, weight loss, hypertension, headache, asthenia, dizziness, insomnia, somnolence</td>
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<tr>
<td><strong>Life-Threatening or Dangerous AEs</strong></td>
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<tr>
<td>Serotonin syndrome</td>
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<td>Hepatotoxicity</td>
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<tr>
<td>Rare activation of mania, depression, or suicidal ideation</td>
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<tr>
<td>Rare worsening of coexisting seizure disorders</td>
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**Weight Gain**
- Not unusual

**Sedation**
- Not unusual

**What to Do about AEs**
- For minor AEs, lower dose, titrate slower, or switch to another agent. For serious AEs, lower dose and consider stopping, taper to avoid withdrawal

**Best Augmenting Agents for AEs**
- Try magnesium for constipation

<table>
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<th>DOSING AND USE</th>
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<td><strong>Usual Dosage Range</strong></td>
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<td>20–120 mg/day once daily</td>
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**Dosage Forms**
- Oral capsule, delayed release: 20 mg, 30 mg, 60 mg

**How to Dose**
- Initial dose 20–30 mg take daily. Effective range 20–120 mg/day, but doses over 60 mg may not provide additional benefit except in headache prevention

**Dosing Tips**
- Start at a low dose, usually 20 mg or 30 mg, and titrate up every few days as tolerated. Low doses may be effective for pain but higher doses are often superior. Dividing doses as 2 times daily dosing may be recommended in initiating therapy for depression (e.g. 20 mg twice daily)

**Overdose**
- Serotonin syndrome, somnolence, seizures, vomiting, death can occur. No specific antidote

**Long-Term Use**
- Safe for long-term use with monitoring of blood pressure

**Habit Forming**
- No

**How to Stop**
- Taper slowly (e.g. 50% reduction every 3–4 days until discontinuation, slower if withdrawal symptoms emerge during taper or for patients with well-controlled pain disorders) to avoid withdrawal symptoms or pain disorder relapse

**Pharmacokinetics**
- Metabolized via oxidation by CYP2D6 and CYP1A2. Duloxetine is a secondary amine and a weak inhibitor of these isoenzymes. Half-life 12 hours

**Drug Interactions**
- CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion), cimetidine, and valproic acid can increase drug concentration
- Concomitant use of potent CYP1A2 inhibitors (fluvoxamine, cimetidine, quinolone antimicrobials [e.g. ciprofloxacin, enoxacin]) should be avoided
- Serotonin release by platelets is important for maintaining hemostasis. Combined use of SSRIs or SNRIs (such as duloxetine) and NSAIDs,
and/or drugs that affect anticoagulation has been associated with an increased risk of bleeding

- CYP2D6 and CYP1A2 enzyme inducers, such as rifamycin, nicotine, phenobarbital, can lower levels
- May cause serotonin syndrome when used within 14 days of MAOIs
- May increase risk of cardiotoxicity and arrhythmia when used with TCAs

Other Warnings/Precautions

- May increase risk of seizure
- Patients should be observed closely for clinical worsening, suicidality, and unusual changes in behavior in known or unknown bipolar disorder

Do Not Use

- Proven hypersensitivity to drug
- Concurrently with MAOI; allow at least 14 days between discontinuation of an MAOI and initiation of duloxetine hydrochloride or at least 5 days between discontinuation of duloxetine hydrochloride and initiation of an MAOI
- In patient with uncontrolled narrow angle-closure glaucoma
- In patients taking thioridazine
- In patients overusing alcohol (increased risk of liver failure)

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SPECIAL POPULATIONS

Renal Impairment

- Not recommended for patients with severe renal function impairment (creatinine clearance less than 30 mL/minute) or end-stage renal disease

Hepatic Impairment

- Not recommended for patients with hepatic function impairment

Elderly

- No adjustments necessary based on age (however, if very old, frail, and/or with multiple comorbidities, start with 20 mg)

Children and Adolescents

- Although duloxetine is often used off-label for children, safety and efficacy not established. Use with caution. Patient should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, in known or unknown bipolar disorder. Parents should be informed and advised of the risks

Pregnancy

- Category C. Generally not recommend for the treatment of headache or neuropathic pain during pregnancy. Neonates exposed to duloxetine or other SNRIs or SSRIs late in the 3rd trimester have developed complications necessitating extended hospitalization, respiratory support, and tube feeding. Respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying consistent with a toxic effect of the drug or drug discontinuation syndrome have been reported

Breast-Feeding

- Duloxetine is found in breast milk and use while breast-feeding is not recommended

THE ART OF PAIN PHARMACOLOGY

Potential Advantages

- Effective in the treatment of multiple pain disorders and for comorbid depression, anxiety
- Less sedation than tertiary amine TCAs (e.g. amitriptyline)
- Less hypertension than other SNRIs (venlafaxine)

Potential Disadvantages

- Patients with decreased liver function or elevated transaminases

Primary Target Symptoms

- Neuropathic pain
- Pain caused by fibromyalgia
- Headache frequency, duration, and intensity
- Chronic musculoskeletal pain

Pearls

- Number needed to treat (NNT) is 6 for 50% pain relief in fibromyalgia and PDN
- Higher potency for both serotonin and norepinephrine reuptake sites than milnacipran or venlafaxine
The presence of anxiety may be a positive predictor in treatment with duloxetine as a headache prophylaxis. May provide benefits in chronic pain similar to TCA without the antihistamine, and strong anticholinergic AEs (e.g. sedation, orthostatic hypotension, etc.)

AEs are usually dose-dependent

Dosages higher than 60 mg may provide additional therapeutic responses in the management of PDN or fibromyalgia, but may result in increased AEs

Duloxetine can precipitate mania in patients with bipolar disorder. Use with caution

Suggested Reading


