**DULOXETINE**

**Brands**  
- Cymbalta  
*see index for additional brand names*

**Generic?**  
Yes

**Class**  
- Neuroscience-based Nomenclature: serotonin norepinephrine reuptake inhibitor (SN-RI)  
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); may be classified as an antidepressant, but it is not just an antidepressant

**Commonly Prescribed for**  
*bold for FDA approved*  
- Major depressive disorder  
- Diabetic peripheral neuropathic pain (DPNP)  
- Fibromyalgia  
- Generalized anxiety disorder, acute and maintenance  
- Chronic musculoskeletal pain  
- Stress urinary incontinence  
- Neuropathic pain/chronic pain  
- Other anxiety disorders

**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  
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, duloxetine can increase dopamine neurotransmission in this part of the brain  
- Weakly blocks dopamine reuptake pump (dopamine transporter), and may increase dopamine neurotransmission

**How Long Until It Works**  
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks for depression

**If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all**  
- Can reduce neuropathic pain within a week, but onset can take longer  
- May continue to work for many years to prevent relapse of depressive symptoms or prevent worsening of painful symptoms  
- Vasomotor symptoms in perimenopausal women with or without depression may improve within 1 week

**If It Works**  
- The goal of treatment of depression and anxiety disorders is complete remission of current symptoms as well as prevention of future relapses  
- The goal of treatment of diabetic peripheral neuropathic pain and 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 diabetic peripheral neuropathic pain, 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 and anxiety disorders 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 anxiety disorders may also need to be indefinite  
- Use in diabetic peripheral neuropathic pain, 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 patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
• Other 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 for depression or biofeedback or hypnosis for pain
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
• Consider the presence of noncompliance and counsel the patient
• Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

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

- Augmentation experience is limited compared to other antidepressants and treatments for neuropathic pain
- Adding other agents to duloxetine 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 diabetic peripheral neuropathic pain and fibromyalgia and neuropathic pain could theoretically include gabapentin, pregabalin, and tiagabine, if done by experts while monitoring carefully in difficult cases
- Mirtazapine (“California rocket fuel” for depression; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Bupropion, reboxetine, nortriptyline, desipramine, maprotiline, atomoxetine (all potentially powerful enhancers of noradrenergic action for depression, but observe for activation of 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
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin, pregabalin, or tiagabine
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone for depression

**Tests**
- Check blood pressure before initiating treatment and regularly during treatment

**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 decreased appetite, increased blood pressure, urinary retention, etc.)
- Most side effects are immediate but often go away with time

**Notable Side Effects**
- Nausea, diarrhea, decreased appetite, dry mouth, constipation (dose-dependent)
- Insomnia, sedation, dizziness
- Sexual dysfunction (men: abnormal ejaculation/orgasm, impotence, decreased libido; women: abnormal orgasm)
- Sweating
- Increase in blood pressure (up to 2 mm Hg)
- Urinary retention

**Life-Threatening or Dangerous Side Effects**
- Rare seizures
- Rare induction of hypomania
- Rare activation of suicidal ideation, suicide attempts, and completed suicide
- Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24
DOUSING AND USE

Usual Dosage Range
- 40–60 mg/day in 1–2 doses for depression
- 60 mg once daily for diabetic peripheral neuropathic pain and fibromyalgia
- 60 mg once daily for generalized anxiety disorder
- 40 mg twice daily for stress urinary incontinence

Dosage Forms
- Capsule 20 mg, 30 mg, 60 mg

How to Dose
- For depression, initial 40 mg/day in 2 doses; can increase to 60 mg/day in 1–2 doses if necessary; maximum dose generally 120 mg/day
- For neuropathic pain and fibromyalgia initial 30 mg once daily; increase to 60 mg once daily after 1 week; maximum dose generally 60 mg/day
- For generalized anxiety, initial 60 mg once daily; maximum dose generally 120 mg/day

Dosing Tips
- Studies have not demonstrated increased efficacy beyond 60 mg/day
- Some patients may require up to or more than 120 mg/day, but clinical experience is quite limited with high dosing
- In relapse prevention studies in depression, a significant percentage of patients who relapsed on 60 mg/day responded and remitted when the dose was increased to 120 mg/day
- In neuropathic pain and fibromyalgia doses above 60 mg/day have been associated with increased side effects without an increase in efficacy
- Some studies suggest that both serotonin and norepinephrine reuptake blockade are present at 40–60 mg/day
- Do not chew or crush and do not sprinkle on food or mix with food, but rather always swallow whole to avoid affecting enteric coating
- Some patients may require dosing above 120 mg/day in 2 divided doses, but this should be done with caution and by experts
**Overdose**
- Rare fatalities have been reported; serotonin syndrome, sedation, vomiting, seizures, coma, change in blood pressure

**Long-Term Use**
- Blood pressure should be monitored regularly

**Habit Forming**
- No

**How to Stop**
- Taper to avoid withdrawal effects (dizziness, nausea, vomiting, headache, paresthesias, irritability)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
  ✽ If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

**Pharmacokinetics**
- Elimination half-life approximately 12 hours
- Metabolized mainly by CYP450 2D6 and CYP450 1A2
- Inhibitor of CYP450 2D6 (probably clinically significant) and CYP450 1A2 (probably not clinically significant)
- Absorption may be delayed by up to 3 hours and clearance may be increased by one-third after an evening dose as compared to a morning dose
- Food does not affect absorption

**Drug Interactions**
- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to duloxetine
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing duloxetine
- Inhibitors of CYP450 1A2, such as fluvoxamine, increase plasma levels of duloxetine, and may require a dosage reduction of duloxetine
- Cigarette smoking induces CYP450 1A2 and may reduce plasma levels of duloxetine, but dosage modifications are not recommended for smokers
  ✽ Inhibitors of CYP450 2D6, such as paroxetine, fluoxetine, and quinidine, may increase plasma levels of duloxetine and require a dosage reduction of duloxetine
- Via CYP450 1A2 inhibition, duloxetine could theoretically reduce clearance of theophylline and clozapine; however, studies of coadministration with theophylline did not demonstrate significant effects of duloxetine on theophylline pharmacokinetics
- Via CYP450 2D6 inhibition, duloxetine could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, duloxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

**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
- Rare reports of hepatotoxicity; although causality has not been established, duloxetine should be discontinued in patients who develop jaundice or other evidence of significant liver dysfunction
- 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
- Duloxetine may increase blood pressure, so blood pressure should be monitored during treatment

**Do Not Use**
- If patient has uncontrolled angle-closure glaucoma
- If patient has substantial alcohol use
- If patient is taking an MAOI
- If patient is taking thioridazine
- If there is a proven allergy to duloxetine

**Special Populations**

**Renal Impairment**
- Dose adjustment generally not necessary for mild to moderate impairment
- Not recommended for use in patients with end-stage renal disease (requiring dialysis) or severe renal impairment

**Hepatic Impairment**
- Not to be administered to patients with any hepatic insufficiency
- Not recommended for use in patients with substantial alcohol use
- Increased risk of elevation of serum transaminase levels

**Cardiac Impairment**
- Drug should be used with caution
- Duloxetine may raise blood pressure

**Elderly**
- Some patients may tolerate lower doses better
- Reduction in the 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 guardians of this risk so they can help observe child or adolescent patients
- Not studied, but can be used by experts

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- 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**
- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- 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

Suggested Reading


