# Duloxetine for major depressive disorder

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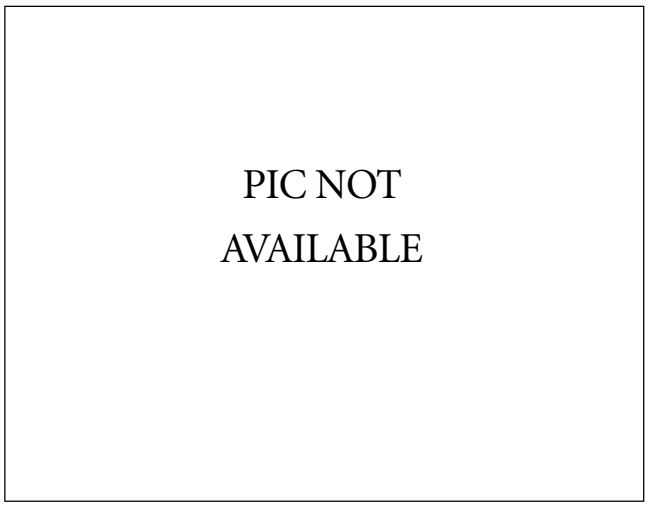
**Duloxetine (Cymbalta) is a once a day, orally administered dual serotonin and noradrenaline reuptake inhibitor that has recently been listed on the PBS for the treatment of major depressive disorder.**






## What is duloxetine?

Duloxetine (Cymbalta) is a once a day, orally administered dual serotonin and noradrenaline reuptake inhibitor that has been demonstrated to be effective for the treatment of major depressive disorder. Duloxetine can be prescribed on the PBS (restricted benefit) as 30 mg and 60 mg capsules for the treatment of major depressive disorder.

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## How effective is it?

Duloxetine has been shown to be equivalent to venlafaxine[1] in efficacy and superior to placebo[2-4] for the treatment of depression. In two clinical trials, duloxetine performed better than fluoxetine[5] and paroxetine[6] when compared with placebo for some measures in patients with major depressive disorder. Clinical trial data suggests that duloxetine has equivalent efficacy and tolerability to other first-line treatments for major depressive disorder, such as selective serotonin reuptake inhibitors (SSRIs).[5,7,8]

## How is it used?

Duloxetine is available in 30 and 60 mg capsules and is administered as a once daily dose. Most patients are treated at a dose of 60 mg/day; however, doses of up to 120 mg/day may be considered. If the patient is not currently taking other medications, duloxetine can be initiated at a dose of 60 mg/day; however, a starting dose of 30 mg/day increased to 60 mg/day after one week may be considered for patients in whom initial tolerability is a concern. Dosing can be given at any time of the day to suit the patient's preference. In some cases, patients have reported insomnia or drowsiness as a side effect of treatment, and these side effects can be minimised by choosing to dose either in the morning or the evening according to the tolerability profile.

If there are no potential drug interactions, patients currently taking antidepressant medication at low to moderate doses can be commenced on duloxetine by an immediate direct switch or by cross tapering. Directly switching to duloxetine has some advantages over cross tapering because it is easier for the patient to carry out and also for the clinician to disentangle adverse effects from withdrawal effects.

A study comparing direct switching from SSRI treatment to duloxetine and a two-week cross taper to duloxetine reported similar efficacy and tolerability for both switching techniques.[9] Patients who are receiving high doses of antidepressants should have their dose gradually reduced before switching to duloxetine. Monitoring the pulse rate and blood pressure of the patient is recommended during switching.

Duloxetine should not be commenced within two weeks of administering a monoamine oxidase inhibitor and a monoamine oxidase inhibitor should not be commenced within five days of administering duloxetine. Clearance of duloxetine is significantly reduced by CYP1A2 inhibitors, such as fluvoxamine, and to a lesser but still significant extent by inhibitors of CYP2D6. A direct switch to duloxetine

from these agents is therefore inadvisable. Duloxetine itself is a moderate inhibitor of CYP2D6 and may reduce the clearance of CYP2D6 substrates.

Duloxetine should be discontinued by gradually tapering down the dose. The dose should be reduced by half or administered on alternate days during a period of not less than two weeks. More time may be required for patients tapering down from a high dose or if discontinuation symptoms emerge with dose reduction.

## Common side effects

Duloxetine has both noradrenergic and serotonergic activity and causes side effects that are known to be associated with these mechanisms of action. The overall burden of side effects from duloxetine is equivalent to that of SSRI antidepressants. The most commonly reported side effects of duloxetine include gastrointestinal effects such as nausea, dry mouth, constipation, diarrhoea and vomiting and decreased weight and appetite, as well as fatigue, dizziness, somnolence, tremor, sweating, hot flushes, blurred vision, insomnia and sexual dysfunction. Dermatological effects such as a rash have also been reported.

Symptoms have been reported in patients who are discontinuing duloxetine and these can be minimised by dose tapering. However, duloxetine has fewer discontinuation emergent side effects than venlafaxine, despite having equivalent efficacy.[1] Treatment with duloxetine has been associated with elevated levels of alanine aminotransferase and rare cases of hepatic injury have been reported.

## Precautions

Duloxetine, as with other antidepressants, carries a black-box warning in the USA that it may increase the risk of suicide in children and adolescents. In Australia, duloxetine is not registered for use in people aged less than 18 years. Duloxetine is contraindicated in patients with hepatic impairment. Due to liver injury, consideration should also be taken when using the agent in patients with substantial alcohol use.[10] Care should be taken when duloxetine is given to patients with pre-existing medical conditions such as renal impairment. In these patients a low therapeutic dose of 30 mg/day is recommended. Blood pressure should be monitored in patients with hypertension or cardiac disease. Duloxetine may also worsen pre-existing glaucoma.

Duloxetine is classified as a Pregnancy Category B3 drug. There is a paucity of human data on the reproductive safety of duloxetine. The decision to treat a pregnant woman with duloxetine should be made on a case-by-case basis after careful consideration of all the risks and benefits.

## Conclusion

Antidepressant agents that have multiple mechanisms of action may have theoretical advantages in the management of depression. In the USA, duloxetine has been approved by the FDA for the management of generalised anxiety disorder and diabetic peripheral neuropathic pain, as well as major depressive disorder. It has also been shown to be effective in the treatment of fibromyalgia and stress urinary incontinence,[11] but further studies in this area are needed.

In Australia, duloxetine is currently approved as a treatment option for patients with major depressive disorder. It has comparable tolerability to existing agents and a potentially broader spectrum of efficacy. MT

## References

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**COMPETING INTERESTS: Dr Dodd has received honoraria for talks from Eli Lilly and research funding from Mayne Pharma, Organon, Eli Lilly, Servier, AstraZeneca, Pfizer and Novartis. Professor Berk has received grants, served on advisory boards and received honoraria for talks and presentations from Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, Pfizer, Sanofi-Synthelabo, Servier, Janssen Cilag, Lundbeck, AstraZeneca, Solvay and Wyeth.**