

## Duloxetine (Cymbalta®)

<b>Availability:</b>	<b>US: Approved in August 2004</b> <b>Canada: Released January 2008</b>
<b>Manufacturer:</b>	<b>Eli Lilly</b>
<b>Therapeutic class:</b>	<b>Antidepressant</b> <b>Serotonin and norepinephrine reuptake inhibitor (SNRI)</b>
<b>Dosage:</b>	<b>60 mg daily</b>
<b>Spectrum of activity:</b>	<b>Similar to venlafaxine (Effexor®)</b>
<b>Clinical efficacy:</b>	<b>No evidence that duloxetine works better for depressive illness compared to currently available antidepressants</b>

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### Introduction

Duloxetine is an antidepressant with dual norepinephrine (NE) and serotonin (SE) reuptake inhibition properties. It has been approved by the FDA in the US for the treatment of depression as well as for pain associated with diabetic neuropathy.<sup>1</sup> This drug may also offer new treatment options for stress urinary incontinence<sup>2-4</sup>, fibromyalgia, and chronic pain syndromes, although it has not yet been approved for these conditions thus far. The focus of this review is primarily on duloxetine's use in the treatment of depression.

### Pharmacology

Duloxetine belongs to a large class of antidepressants called reuptake inhibitors. Unlike some antidepressants that block the reuptake of just serotonin, duloxetine, similar to venlafaxine, blocks the reuptake of both norepinephrine and serotonin. As such, it is a dual acting antidepressant referred to as a serotonin and norepinephrine reuptake inhibitor (SNRI)<sup>5</sup>. Blocking the reuptake of serotonin and norepinephrine allows more of these chemicals to be available for neurotransmission. Although the exact mechanism whereby antidepressants alleviate depression remains to be proven, increasing the concentration of NE and SE is thought to trigger a series of events that ultimately leads to a decrease in depressive symptoms.<sup>6</sup>

Serotonin plays a role in controlling aggression, impulsivity, and appetite. Norepinephrine is involved in vigilance, alertness, and motivation. Serotonin also inhibits the release of norepinephrine and both neurotransmitters play a role in anxiety, mood, irritability and cognitive function.<sup>7</sup>

### Pharmacokinetics

Absorption of duloxetine begins two hours after oral administration with maximal concentration in the plasma achieved in approximately 6 hours. If it is taken in the evening rather than in the morning, there is a 3-hour delay in absorption and clearance of the drug from the plasma is increased by about 33%, resulting in potentially lower plasma concentrations. Its half-life averages about 12 hours with a range between 8 to 17 hours. Duloxetine is highly protein bound (90%) and is metabolized by cytochrome P-450 isoenzymes 2D6 and 1A2. There are at least 25 metabolites, two of which have been found to be pharmacologically active.<sup>8</sup> Duloxetine is a moderate inhibitor of CYP2D6<sup>9</sup>, but does not substantially inhibit CYP1A2.<sup>8</sup>

### Clinical Trials for Major Depression

There have been six randomized, placebo-controlled, clinical trials of duloxetine for major depression. The results are summarized in Table 1.

**Table 1: Randomized Controlled Trials of Duloxetine in Adults with Major Depression\***

(n)	Duloxetine And Comparator	Primary Outcome (LOCF) <sup>a</sup>		Rate of Remission LOCF (%)	Rate of Remission MMRM (%)	Adverse Events greater than placebo <sup>b</sup>	Reference
		Baseline HAMD <sub>17</sub>	EOS HAMD <sub>17</sub>				
173	Duloxetine 60 mg BID	18.4	9.82	43	56 <sup>b</sup>	Insomnia, asthenia	12
	Placebo	19.2	13	27	32		
	Fluoxetine 20 mg QD	17.9	n/a	30	30		
245	Duloxetine 60 mg QD	21.24	11.95 <sup>b</sup>	31 <sup>b</sup>	44 <sup>b</sup>	Nausea, dry mouth, somnolence, diarrhea, insomnia, anorexia, constipation, vomiting	10
	Placebo	21.14	15.47	15	16		
245	Duloxetine 60 mg QD	20.33	9.87 <sup>b</sup>	32	43	Nausea, dry mouth, 15 dizziness, constipation, heart-rate increase of 2.57 beats/min	
	Placebo	20.46	12.17	24	28		
353	Duloxetine 20 mg BID	18.74	16.33	35	36	80 mg: dizziness, dry mouth, anorexia, rhinitis heart rate increase of 2 beats/min. 40 and 80 mg nausea, insomnia sweating, somnolence	11
	Duloxetine 40mg BID	17.86	14.75	50 <sup>b</sup>	57 <sup>b</sup>		
	Placebo	17.2	n/a	30	25		
	Paroxetine 20 mg QD	17.83	16.32	37	34		
367	Duloxetine 40 mg BID	19.3	9.3 <sup>b</sup>	n/a	n/a	constipation sweating, sexual dysfunction somnolence	13
	Duloxetine 60 mg BID	20.0	7.9 <sup>b</sup>	n/a	n/a		
	Placebo	19.9	10.5	n/a	n/a		
	Paroxetine 20 mg QD	20.3	8.6 <sup>b</sup>	n/a	n/a		
392	Duloxetine 40 mg BID	21.3	9.2 <sup>b</sup>	n/a	n/a	constipation, sweating somnolence, sexual dysfunction	14
	Duloxetine 60 mg BID	21.4	9.0 <sup>b</sup>	n/a	n/a		
	Placebo	20.6	9.8	n/a	n/a		
	Paroxetine 20 mg QD	21.0	9.1	n/a	n/a		

<sup>a</sup>LOCF = Last observation carried forward; HAMD<sub>17</sub> = 17-item Hamilton Depression Rating Scale; EOS = End of study; MMRM = Mixed model for repeated measures

<sup>b</sup>Significantly different from placebo ( $p \leq 0.05$ ); n/a = Information not available \* Table 1 adapted with permission from reference 16

### Summary of Depression Study Results (Table 1)

Two out of the six studies<sup>10,11</sup> that used 60 to 120 mg a day of duloxetine found that the rate of remission in depression was significantly higher in the subjects receiving duloxetine than placebo when using the last observation carried forward (LOCF). All of the studies that used 60 mg/day or more of duloxetine, found greater reductions in HAMD<sub>17</sub> scores with duloxetine,<sup>10-15</sup> however, two studies<sup>13, 14</sup> did not report the rates of remission.

Duloxetine at 40 mg a day was not found to be significantly better than placebo.<sup>11</sup> One of the studies<sup>12</sup> that used 120 mg a day found a significant difference favoring duloxetine over placebo in the rate of remission when using the mixed effects model for repeated measures, but not LOCF. This was likely due to the fact that one third of the patients discontinued treatment before the end of the study. Most of the patients who stopped duloxetine did so because of adverse effects, whereas the placebo treated patients dropped out because of lack of efficacy.

### Use in peripheral neuropathic pain

Duloxetine has been approved for the treatment of diabetic peripheral neuropathic pain in the US. Results from two randomized controlled studies<sup>1,19</sup> of 1074 patients found that 58% of duloxetine-treated patients reported at least a 30%

sustained pain reduction compared with 34% of patients treated with placebo. Both 60 mg and 120 mg a day of duloxetine were found to be effective but there was no significant difference between the two doses.

### **Use in stress urinary incontinence**

Mixed or stress urinary incontinence is very common in women aged 50 years or older. Pelvis muscle training (Kegel exercises) or surgical procedures are preferred over pharmacological treatment. Duloxetine has been found to reduce the frequency of incontinence episodes by an amount significantly more than placebo<sup>2-4</sup>. Duloxetine does not have an indication for stress incontinence in the US or Canada at this time but, has approval for this indication in Europe.

### **Adverse Effects**

The most common adverse effects that occurred significantly more frequently with duloxetine than with placebo were nausea (19.9%), dry mouth (14.6%), constipation (11.4%), insomnia (9.9%), dizziness (8.9%), fatigue (8.3%), somnolence (7.1%), sweating (6.1%), decreased appetite (5.9%), vomiting (4.6%) and blurred vision (3.6%)<sup>17</sup>.

Sexual adverse effects of decreased libido, anorgasmia, erectile dysfunction occurred significantly more frequently with duloxetine than placebo<sup>17</sup>. The rate of sexual dysfunction with duloxetine was found to be comparable to paroxetine at 63% and 64% respectively.<sup>15</sup>

Hepatitis, hepatomegaly and increased levels of transaminase have been observed. Hepatic failure in a patient receiving duloxetine and mirtazapine for depression has been reported<sup>7</sup>.

### **Drug Interactions**

As with any psychotropic medication, duloxetine can interact with other centrally active drugs that affect serotonin, norepinephrine, and dopamine. Due to the similar mechanism of action and the potential for additive adverse effects such as elevated blood pressure and tachycardia, duloxetine should not be co-administered with other serotonin-norepinephrine reuptake inhibitors. Co-administration of duloxetine or venlafaxine with highly serotonergic agents such as SSRIs augments serotonin transmission, which may be synergistic on one hand, but may also result in excessive serotonin, possibly leading to serotonin syndrome. Therefore, such regimens, although tolerated by many individuals, necessitate careful monitoring. Of greater concern is the combination involving dual acting agents with MAOIs, a regimen that has the potential to cause both serotonin syndrome and hypertensive crisis. For this reason, neither duloxetine nor venlafaxine should be used with MAOIs.

Unlike venlafaxine, duloxetine is highly protein bound in human plasma, primarily to albumin and alpha-1 acid glycoprotein. In theory, two highly protein-bound drugs can compete with each other for binding sites and one drug can displace the other from the binding sites. This would lead to higher levels of unbound drug leading to both enhanced pharmacological effect and toxicity. Although there are compensatory mechanisms in the body to buffer against such events, there has been a case report citing such an interaction involving duloxetine and warfarin.<sup>33</sup> Such interactions are not expected with venlafaxine due to its low protein-binding profile.

Venlafaxine should be used cautiously with drugs that elevate blood pressure because of dose-dependent increases in blood pressure.<sup>18</sup> Duloxetine, on the other hand, has not been reported to increase blood pressure and would be the suitable dual acting agent in patients with hypertension. Unlike venlafaxine, which has not been reported to cause abnormalities in cardiac conduction, duloxetine has been shown to decrease PR and QRS intervals on the EKG at a dose of 120 mg per day.<sup>17</sup> Therefore caution and more vigilant monitoring are essential if higher doses of duloxetine are used with other drugs that potentially alter EKG, such as certain antipsychotics (eg pimozide, ziprasidone).

One study that investigated the effects of duloxetine on mental and motor function caused by alcohol found that duloxetine did not add to the impairment in these domains.<sup>34</sup> However, the use of duloxetine in patients who regularly consume large amounts of alcohol is not recommended due to additive hepatotoxic effects. Similarly, the use of duloxetine in patients who are on high-dose, chronic acetaminophen therapy should be cautioned due to risks of additive hepatotoxicity. Venlafaxine has not been reported to cause hepatotoxicity and unlike duloxetine, is not expected to exert additive hepatotoxic effects in patients susceptible to liver damage.

Duloxetine is extensively metabolized by cytochrome P450 enzymes CYP 1A2 and 2D6 prior to clearance, whereas venlafaxine is metabolized by CYP 2D6 and to a lesser degree, CYP 3A4. Pharmacokinetic interactions are possible for both drugs when co-administered with inhibitors and inducers of these enzymes. For example, the bioavailability of duloxetine is a third less in smokers compared to nonsmokers because of induction of CYP 1A2 metabolism. When used with fluvoxamine, a potent CYP 1A2 inhibitor, there are substantial changes in the pharmacokinetic profile of duloxetine: a 3-fold increase in half-life, a 5-fold increase in the bioavailability, and a 2.5-fold increase in Cmax.<sup>34</sup>

Venlafaxine does not appear to inhibit CYP isoenzymes to any significant degree. In contrast, duloxetine, in addition to being a substrate for metabolism by CYP 1A2 and 2D6, is also an inhibitor of both these enzymes. Duloxetine demonstrates dose-dependent inhibition of CYP 2D6, yet its inhibition of this enzyme is substantially less than that for fluoxetine or paroxetine and is similar to that seen with escitalopram and citalopram.<sup>35,36</sup> As a weak inhibitor of CYP 1A2, duloxetine does not affect the kinetic profile of theophylline, a prototypical substrate of CYP 1A2, even at doses of 120 mg per day.<sup>34</sup> Despite moderate inhibition of CYP 2D6 and mild inhibitory effects on CYP 1A2, the product monograph advises caution when co-administering duloxetine with tricyclic antidepressants (TCAs). This is perhaps due to the fact that plasma levels of TCAs can be increased when combined with duloxetine and furthermore, TCAs also have inherent risks for adverse effects on cardiac function.

A rational approach would be to monitor carefully and make appropriate dosage adjustments when duloxetine is co-prescribed with drugs (particularly those with narrow therapeutic windows) that are metabolized by, inducers of, or substrates of CYP 1A2 and CYP 2D6. A similar approach can be taken with venlafaxine when used with inducers and inhibitors of CYP 2D6.

**Table 2: Summary of Drug Interactions**

	<b>Duloxetine</b>	<b>Venlafaxine</b>
Pharmacokinetic	<ul style="list-style-type: none"> <li>• CYP 2D6 and CYP 1A2 substrates → increase in drug levels</li> <li>• Inhibitors of CYP 2D6 and CYP 1A2 → increase in duloxetine levels</li> <li>• Inducers of CYP 2D6 and CYP 1A2 → decrease in duloxetine levels</li> <li>• Highly protein-bound drugs → displacement from protein binding leading to toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Inhibitors of CYP 2D6 and CYP 3A4 → increase in venlafaxine levels</li> <li>• Inducers of CYP 2D6 and CYP 3A4 → decrease in venlafaxine levels</li> </ul>
Pharmacodynamic	<ul style="list-style-type: none"> <li>• MAOIs → serotonin syndrome + HTN crisis</li> <li>• Serotonergic drugs → serotonin syndrome</li> <li>• Hepatotoxic drugs → additive hepatotoxicity</li> <li>• Drugs that alter EKG → additive cardiac conduction changes</li> </ul>	<ul style="list-style-type: none"> <li>• MAOIs → serotonin syndrome + HTN crisis</li> <li>• Serotonergic drugs → serotonin syndrome</li> <li>• Drugs that increase BP → Additive increase in BP</li> </ul>

### Precautions

Since duloxetine can cause mild increases in blood pressure, patients with preexisting hypertension should have their blood pressure monitored on duloxetine. As with any antidepressant, patients should also be observed for worsening of depressive symptoms or suicidal ideation when starting therapy. However, there was no difference in the incidence of completed suicide between duloxetine (0.09%; 1 in 1139) and placebo (0.13%; 1 in 777) or in spontaneously reported suicidal ideation (0.2%; 2/1139 versus 0.3%; 2 in 777)<sup>17</sup>

### Contraindications

Duloxetine is contraindicated in patients with hepatic insufficiency including those with significant alcohol use.

### Administration

The recommended dose is 60 mg once daily, starting at 30 mg a day for tolerability in some patients and increasing to 60 mg a day within 1-2 weeks.

### Availability

Duloxetine is available in 30 mg and 60 mg delayed-release capsules.

## References

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