



*Cognitive Vitality Reports<sup>®</sup> are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Duloxetine

### Evidence Summary

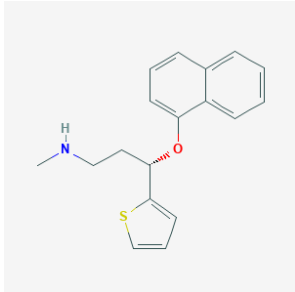
Duloxetine is approved for treating depression, anxiety, diabetic peripheral neuropathy, musculoskeletal pain, and fibromyalgia, but most people experience adverse events and it interacts with many drugs.

**Neuroprotective Benefit:** Although preclinical studies suggest neuroprotective benefit, duloxetine has had mixed and inconclusive findings with regards to cognitive effects in clinical trials, with a few showing improvement and others showing potential harm.

**Aging and related health concerns:** Duloxetine is effective in relieving pain for fibromyalgia, osteoarthritis, postoperative pain, and diabetic peripheral neuropathy.

**Safety:** Most people experience adverse events with duloxetine. Duloxetine interacts with many drugs; it should not be taken with other serotonergic drugs, as it can lead to serotonin syndrome. Abrupt discontinuation can cause "discontinuation syndrome".



<p><b>Availability:</b> Rx. Approved for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, and fibromyalgia.</p>	<p><b>Dose:</b> Most clinical trials tested 60 mg/day dose. Initial dose is often 30 mg/day and depending on the disease indication, is increased up to 120 mg/day.</p>	<p><b>Chemical formula:</b> C<sub>18</sub>H<sub>19</sub>NOS <b>MW:</b> 297.4</p>  <p>Source: <a href="#">PubChem</a></p>
<p><b>Half life:</b> mean=12 h, range of 8-17 hours (~4 hours longer in elderly women)</p>	<p><b>BBB:</b> penetrant, but a substrate of P-glycoprotein</p>	
<p><b>Clinical trials:</b> numerous meta-analyses across different disease indications; largest meta-analysis included 6,407 subjects</p>	<p><b>Observational studies:</b> none</p>	

**What is it?** Duloxetine (Cymbalta®) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), and therefore it increases the levels of serotonin and norepinephrine in the brain. Duloxetine is FDA-approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, chronic musculoskeletal pain (e.g., knee osteoarthritis and low back pain), and fibromyalgia ([DrugBank.ca](#); [MedlinePlus.gov](#)).

**Neuroprotective Benefit:** Although preclinical studies suggest neuroprotective benefit, duloxetine has had mixed and inconclusive findings with regards to cognitive effects in clinical trials, with a few showing improvement and others showing potential harm.

*Types of evidence:*

- 3 randomized controlled clinical trials
- 2 open-label clinical trials
- Numerous laboratory studies



Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have evaluated duloxetine for preventing dementia or cognitive decline.

Surgery patients: GREATER COGNITIVE DECLINE THAN PLACEBO. In a double-blind randomized controlled trial of 94 patients receiving elective repair of lumbar disc herniation, the greatest cognitive decline (as measured by MoCA) was seen in people treated with pregabalin (calcium channel blocker;  $1.83 \pm 1.31$ ) followed by the duloxetine group ( $1.16 \pm 0.82$ ), and the least decline was seen in the control group ( $0.49 \pm 0.61$ ) ([Altiparmak et al., 2018](#)). The reduction in cognitive functions was significantly greater in the pregabalin group than in the duloxetine and control groups and the mean cognitive score reduction in the duloxetine group was significantly higher than that of the control group.

Major depressive disorder: POTENTIAL COGNITIVE BENEFIT. In a double-blind randomized controlled trial of 311 elderly patients with major depressive disorder, duloxetine treatment (60 mg/day) for 8 weeks resulted in a significantly greater improvement in the composite cognitive score versus placebo (least-squares mean change from baseline to endpoint: 1.95 versus 0.76), driven by improved verbal learning and memory ([Raskin et al., 2007](#)). Compared with placebo, patients taking duloxetine had significant improvement in both verbal learning and recall tests, but not other cognitive tests. No group differences were seen for the Mini-Mental State Examination (MMSE) scores. Path analysis showed that for improvement of the composite cognitive score, there was a 90.9% direct effect ( $p=0.03$ ) and a 9.1% indirect effect through improvement in the Geriatric Depression Scale total score. In other words, the path analysis suggested that the effect of duloxetine on improvement of the composite cognitive score was mainly a direct treatment effect rather than an indirect effect through improvement of depression measures.

In a small open-label clinical trial of 21 patients with major depressive disorder and subjective cognitive dysfunction, duloxetine treatment (initial dose, 30 mg/day, followed by 60 mg/day with max dose of 120 mg/day) resulted in significant improvements in cognitive function after 12 weeks of treatment ([Greer et al., 2014](#)). Although several cognitive domains such as psychomotor speed, visual memory, decision making/response control for emotionally laden information, and verbal recognition memory were observed, due to the open-label design it is not clear whether the improvement was due to a practice effect and/or a placebo effect.



*Human research to suggest benefits to patients with dementia:*

No studies have shown benefits with duloxetine in dementia patients. A case study of an 86-year-old woman with Alzheimer's dementia who was hospitalized with depression was treated with duloxetine (60 mg/day) and brotizolam (0.5 mg/day) over 6 weeks for her depression, and no improvements were observed ([Suzuki et al., 2012](#)). The patient was also prescribed donepezil (3 mg/day) and rosuvastatin (2.5 mg/day) to treat her dementia and hypercholesterolemia, respectively. The patient showed severe disorientation and hallucination and was diagnosed with drug-induced delirium. Brotizolam was withdrawn, then donepezil was withdrawn, then rosuvastatin was withdrawn, with no improvements. Duloxetine was withdrawn last and the patient's delirium disappeared along with her EEG abnormalities. The authors speculated that duloxetine induced the delirium in this patient. Duloxetine, donepezil, and rosuvastatin are all metabolized by cytochrome P450 2D6, so drug interactions may have increased the blood concentration of duloxetine.

*Mechanisms of action for neuroprotection identified from laboratory and clinical research:*

Duloxetine crosses the blood-brain barrier and appears in the cerebral cortex at a higher concentration than the plasma ([DrugBank.ca](#)).

In a rat model of chronic cerebral hypoperfusion, duloxetine treatment attenuated neuronal damage such that the number of NeuN+ neurons in the hippocampal CA1 was comparable to that of sham-operated rats ([Park et al., 2018](#)). Duloxetine also restored phospho-mTOR and phospho-p70S6K to levels comparable to sham-treated rats, and decreased inflammation biomarkers (e.g., TNF- $\alpha$  and IL-1 $\beta$ ). mTOR, a downstream target of Akt, and phospho-mTOR have been thought to be essential for protein synthesis, cell growth, cell survival, and other cellular functions. Untreated rats with chronic cerebral hypoperfusion showed significantly decreased levels of phospho-mTOR (by 60%) and phospho-S6K (by 80-90%) in the CA1 while levels were preserved with duloxetine treatment.

Duloxetine treatment reversed the cognitive deficits and increased the neurotrophic BDNF protein expression in the medial prefrontal cortex during adulthood in mice previously exposed to social stress, to levels comparable to unstressed saline-treated mice ([Xu et al., 2016](#)).

An older study in rats also demonstrated that chronic, but not acute, treatment with duloxetine (10 mg/kg/day for 3 weeks) produces a robust increase of BDNF exon V mRNA levels in the frontal cortex ([Calabrese et al., 2007](#)). Based on subcellular fraction protein analysis, chronic treatment with duloxetine, but not with the SSRI fluoxetine, reduced mature BDNF in the cytosol, but markedly increased BDNF levels in the synaptosomal fraction. The mature BDNF was increased by 3-4-fold in the

synaptosomal fraction after chronic treatment (but not after acute) in the frontal cortex but not in the hippocampus.

APOE4 interactions: Unknown.

**Aging and related health concerns:** Duloxetine is effective in relieving pain for fibromyalgia, osteoarthritis, postoperative pain, and diabetic peripheral neuropathy.

*Types of evidence:*

- 9 meta-analyses

Duloxetine is FDA-approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, chronic musculoskeletal pain (e.g., knee osteoarthritis and low back pain), and fibromyalgia ([DrugBank.ca](#); [MedlinePlus.gov](#)).

Fibromyalgia: PAIN RELIEF. In a 2019 meta-analysis of 7 double-blind randomized controlled trials including a total of 2,642 patients with pain from fibromyalgia, duloxetine treatment (60 or 120 mg/day) for 8 weeks or longer produced greater pain relief than placebo (standardized mean difference [SMD] -0.26; 95% CI, -0.37 to -0.16) ([Lain et al., 2019](#)). The risk ratio (RR) of at least 30% pain relief was 1.31 (95% CI, 1.19 to 1.44); and the RR of at least 50% pain relief was 1.46 (95% CI, 1.28 to 1.67).

In a 2018 Cochrane meta-analysis of clinical trials testing SNRI treatment in fibromyalgia (7 of which investigated duloxetine), duloxetine and milnacipran had a clinically relevant benefit over placebo in pain relief of 30% or greater (risk difference=0.10; 95% CI, 0.08 to 0.12) and much or very much improved patient's global impression (risk difference=0.19; 95% CI, 0.12 to 0.26) ([Welsch et al., 2018](#)). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in pain relief of 50% or greater (risk difference=0.09; 95% CI, 0.07 to 0.11) or improving health-related quality of life (standardized MD=-0.20; 95% CI, -0.25 to -0.15).

Osteoarthritis: PAIN RELIEF. In a meta-analysis of 6 randomized controlled trials including a total of 2,059 patients with knee osteoarthritis, duloxetine treatment (20-120 mg/day) was significantly associated with a remarkable reduction in average pain score compared with the placebo group (weighted mean difference=-0.74; 95% CI, -0.92 to -0.57) ([Chen et al., 2019](#)). Duloxetine also had a significant effect on moderate (greater than 30% improvement; RR = 1.43; 95% CI, 1.29 to 1.59) and

substantial improvements (greater than 50% improvement; RR = 1.71; 95% CI, 1.46 to 1.99) in chronic pain. Duloxetine was effective in the management of chronic pain and loss of physical function in knee osteoarthritis.

Similarly, in a meta-analysis of 7 randomized controlled trials including a total of 2,102 subjects with osteoarthritis, those receiving duloxetine treatment (60-120 mg/day) demonstrated moderate and statistically significant effects on pain reduction (standardized MD=-0.38; 95% CI, -0.48 to -0.28) and functional improvement (standardized MD=-0.35; 95% CI, -0.46 to -0.24) over a 12- to 14- week follow-up ([Osani and Bannuru, 2019](#)).

***Postoperative pain:*** PAIN RELIEF. In a meta-analysis of 9 randomized controlled trials including a total of 574 patients undergoing surgery, duloxetine treatment (most studies tested 60 mg before surgery, then 60 mg after surgery once or for up to 2 weeks) was associated with a significant reduction in pain scores as early as 4 hours (mean difference [MD]=-0.9; 95% CI, -1.33 to -0.47) and as late as 48 hours (MD=-0.94; 95% CI, -1.56 to -0.33) postoperatively compared with placebo ([Zorrilla-Vaca et al., 2019](#)). In addition, duloxetine was associated with a significant reduction in opioid administration at 24 hours (standardized MD [SMD]=-2.24; 95% CI, -4.28 to -0.19) and 48 hours (SMD=-2.21; 95% CI, -4.13 to -0.28).

The analgesic mechanism of duloxetine is thought to be related to its ability to enhance both serotonin and norepinephrine neurotransmission in descending inhibitory pain pathways in the brain and spinal cord ([Altiparmak et al., 2018](#)). It is also known to have an antinociceptive effect through inhibition of the sodium channels.

***Neuropathic pain:*** PAIN RELIEF FOR DIABETIC NEUROPATHY. A 2014 Cochrane meta-analysis examined duloxetine treatment (60-120 mg/day) for fibromyalgia, painful neuropathy, and chronic pain; 8 randomized controlled trials including a total of 2,728 patients were included for painful diabetic neuropathy ([Lunn et al., 2014](#)). Duloxetine at 60 mg daily was effective in treating painful diabetic peripheral neuropathy in the short term, with a risk ratio (RR) for  $\geq 50\%$  pain reduction at 12 weeks of 1.73 (95% CI, 1.44 to 2.08). The authors noted that the evidence is strong and further trials are not required.

A single study included in the above Cochrane meta-analysis examined the effects of duloxetine treatment for central neuropathic pain, but the study was small (48 participants) and no therapeutic effects of duloxetine were observed in the predefined outcome measures ([Vranken et al., 2011](#)). Given



that the trial was small, the trial authors recommended that more studies of central neuropathic pain be performed.

**Major depressive disorder:** SIMILAR EFFICACY BUT LOWER TOLERABILITY COMPARED TO OTHER AGENTS. In a 2012 Cochrane meta-analysis of 16 randomized controlled trials including a total of 5,735 participants with major depressive disorder, there were no statistically significant differences in efficacy when comparing duloxetine with other antidepressants ([Cipriani et al., 2012](#)). Duloxetine did not seem to provide a significant advantage in efficacy over other antidepressants for the acute-phase treatment of major depression. In fact, duloxetine was worse than some serotonin-selective reuptake inhibitors (SSRIs; most of all, escitalopram) and newer antidepressants (e.g., venlafaxine) in terms of acceptability and tolerability.

**Safety:** Most people experience adverse events with duloxetine. Duloxetine interacts with many drugs; it should not be taken with other serotonergic drugs, as it can lead to serotonin syndrome. Abrupt discontinuation can cause “discontinuation syndrome”.

*Types of evidence:*

- 9 meta-analyses or systematic reviews
- Numerous randomized clinical trials
- 1 open-label trial
- 1 review

**Adverse reactions:** Based on Drugs.com, most people experience adverse events with duloxetine and 1 in 6 stop taking the drug because of them ([Drugs.com](#)). The most common adverse reactions are nausea (18-23%), headache (13-14%), dry mouth (11-14%), drowsiness (9-11%), fatigue (7-11%), insomnia (7-10%), constipation (9-10%), decreased appetite (6-10%), dizziness (8-9%), and vomiting (6-9%)([Drugs.com](#)). In children, adolescents, and young adults, antidepressants can increase the risk of suicidal thoughts and behavior ([US Boxed Warning](#)). SNRI antidepressants have been associated with sustained increases in blood pressure ([Drugs.com](#)). Other concerns related to adverse effects include bleeding risk, CNS depression, liver toxicity, hyperglycemia, ocular effects (e.g., may lead to an episode of narrow-angle glaucoma), orthostatic hypotension/syncope, and serotonin syndrome (see below under “Serotonin syndrome”)([Drugs.com](#)). Elderly patients or those who are hypovolemic may develop hyponatremia with duloxetine ([Smith et al., 2010](#)). There have also been reports of inappropriate antidiuretic hormone secretion in patients taking duloxetine or other SNRIs.



### ***Clinical trial findings:***

***Fibromyalgia patients:*** In a meta-analysis of 7 double-blind randomized controlled trials including a total of 2,642 patients with fibromyalgia, duloxetine treatment (60 or 120 mg/day) was associated with higher rates of nausea (26.3% vs 8.2%; RR=3.08, 95% CI, 2.44 to 3.89), constipation (14.6% vs 4.4%; RR=3.33, 95% CI, 2.31 to 4.82), excessive sweating (8.0% vs 1.4%; RR=6.28, 95% CI, 2.99 to 13.15), diarrhea (9.9% vs 4.8%; RR=2.08, 95% CI, 1.37 to 3.17), headache (14.4% vs 7.6%; RR=1.90, 95% CI 1.36 to 2.64), dry mouth (14.4% vs 4.2%; RR=3.28, 95% CI 2.23 to 4.82), somnolence (13.3% vs 5.0%; RR=2.75, 95% CI 1.89 to 4.00), and insomnia (6.8% vs 2.0%; RR=2.40, 95% CI 1.30 to 4.43)([Lain et al., 2019](#)). In the duloxetine group, 82.6% of participants had at least one adverse event compared to 69.7% in the placebo group (RR=1.17, 95% CI 1.12 to 1.23).

In a 2018 Cochrane meta-analysis of clinical trials testing SNRI treatment in fibromyalgia (7 of which investigated duloxetine), there was no difference in serious adverse events between either duloxetine, milnacipran or desvenlafaxine and placebo; however, dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo ([Welsch et al., 2018](#)). On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms.

In a 2014 Cochrane meta-analysis of clinical trials testing duloxetine (60-120 mg/day) in fibromyalgia, painful neuropathy, and chronic pain, adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect ([Lunn et al., 2014](#)). Adverse events were significantly more common with duloxetine than with placebo in 60 mg (RR=1.15; 95% CI, 1.10 to 1.20) and 120 mg doses (RR=1.19; 95% CI, 1.09 to 1.30). Doses of 60 mg and 120 mg were also associated with a significantly greater risk of cessation compared to placebo. Most adverse effects were minor, but 16% of participants stopped taking duloxetine due to adverse effects. Serious adverse events were rare.

***Osteoarthritis patients:*** In a meta-analysis of 7 randomized controlled trials including a total of 2,102 subjects with osteoarthritis, those receiving duloxetine treatment (60-120 mg/day) were 50% more likely to experience treatment-emergent adverse events compared to placebo (RR=1.53, 95% CI, 1.21 to 1.92)([Osani and Bannuru, 2019](#)). The rates of severe adverse events were not statistically different between duloxetine and placebo groups. Participants receiving duloxetine were nearly 4.5 times more likely to experience gastrointestinal adverse events (RR=4.43; 95% CI, 3.45 to 5.69), such as nausea, constipation, and dry mouth.





In a meta-analysis of 6 randomized controlled trials including a total of 2,059 patients with knee osteoarthritis, duloxetine treatment (20-120 mg/day) was associated with a significantly higher number of treatment-emergent adverse events (RR = 1.31, 95% CI, 1.20 to 1.44) and discontinuations (RR = 2.26, 95% CI, 1.63 to 3.12) compared with the placebo ([Chen et al., 2019](#)). However, similar to the study described above, the incidence of serious adverse events were not statistically different between duloxetine and placebo groups (RR = 0.92, 95% CI = 0.40 to 2.11). The duloxetine group presented with increased constipation, decreased appetite, diarrhea, dizziness, dry mouth, fatigue, excessive sweating, insomnia, nausea, and somnolence.

***Major depressive disorder:*** In a 2012 Cochrane meta-analysis of 16 randomized controlled trials including a total of 5,735 patients with depression, there was a higher rate of dropout due to any cause in the patients randomized to duloxetine compared with those randomized to escitalopram and venlafaxine (OR=1.62; 95% CI, 1.01 to 2.62 and OR=1.56; 95% CI, 1.14 to 2.15, respectively)([Cipriani et al., 2012](#)). There was also a trend suggesting that patients taking duloxetine experienced more adverse events than paroxetine (OR=1.24; 95% CI 0.99 to 1.55; p=0.06). Patients randomized to duloxetine treatment experienced a higher rate of nausea/vomiting than escitalopram (OR=1.82; 95% CI, 1.36 to 2.44), paroxetine (OR=1.46; 95% CI, 1.13 to 1.89), and desvenlafaxine (OR=1.53; 95% CI 1.00 to 2.37).

In a meta-analysis of 12 randomized controlled trials in older people (over 65) with major depressive disorder, duloxetine was associated with a significantly increased risk of dry mouth, constipation, diarrhea and dizziness, while insufficient evidence was found with respect to other adverse events ([Tham et al., 2016](#)).

***Postoperative pain management:*** In a meta-analysis of 9 randomized controlled trial including a total of 574 patients undergoing surgery, duloxetine treatment (mostly 60 mg before surgery, then 60 mg after surgery once or for longer) was associated with a statistically significant reduction in the incidence of postoperative nausea and vomiting (RR=0.69; 95% CI, 0.49 to 0.95), but no differences in pruritus (RR=1.09), dizziness (RR=1.28), or headache (RR=1.11) compared with placebo controls ([Zorrilla-Vaca et al., 2019](#)).

In a double-blind randomized controlled trial of 94 patients receiving elective repair of lumbar disc herniation, the most common adverse event was nausea (35%) in patients treated with duloxetine (60 mg, 1 hour before surgery and 12 and 24 hours after surgery)([Altiparmak et al., 2018](#)).

**Drug interactions:** Many drugs interact with duloxetine, with 98 major interactions and 419 moderate interactions ([Drugs.com](#)). Examples include cimetidine, St. John's wort, theophylline, tryptophan, amphetamines, antibiotics (ciprofloxacin, enoxacin), blood thinners (warfarin, Coumadin, Jantoven), heart rhythm medications (flecainide, propafenone, quinidine, etc.), opioids (fentanyl, tramadol), mood disorder medications (buspirone, lithium, thioridazine, etc.), and migraine medications (sumatriptan, rizatriptan, zolmitriptan, and others)([Drugs.com](#)). Duloxetine must not be taken with monoamine oxidase inhibitors as the combination could result in serotonin syndrome (see below).

Duloxetine may also interact with caffeine, which may increase the blood levels and effects of duloxetine ([Drugs.com](#)). Duloxetine may also cause liver damage, and that risk may be increased when taking it with alcohol.

**Serotonin syndrome:** Overdosage of duloxetine or interactions with other serotonergic drugs may cause serotonin syndrome, the symptoms of which include mental status changes, fast heart rate, dizziness, flushing, muscle tremor or rigidity, and gastrointestinal symptoms (nausea, vomiting, and diarrhea)([Drugs.com](#)).

**Discontinuation syndrome:** When stopping duloxetine, abrupt discontinuation can cause "discontinuation syndrome", symptoms of which include anxiety, headache, dizziness, diarrhea, abnormal sensations (e.g., pins and needles), irritability, insomnia, increased sweating, and tiredness ([Drugs.com](#)). The dose should be gradually reduced in line with the doctor's recommendation.

**Sources and dosing:** Duloxetine is an oral prescription medication approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, chronic musculoskeletal pain (e.g., knee osteoarthritis and low back pain), and fibromyalgia ([DrugBank.ca](#); [MedlinePlus.gov](#)). For depression in adults, the initial dose is 20 mg orally twice a day, with a maintenance dose of 60 mg per day (once per day or 30 mg twice daily)([Drugs.com](#)). The maximum dose is 120 mg/day for depression. For fibromyalgia, the initial dose is 30 mg/day and the maintenance doses are 30 to 60 mg/day. For adults with generalized anxiety disorder, the initial dose is 60 mg/day, and the maintenance dose is 60 to 120 mg/day. For older adults with generalized anxiety disorder, the initial dose is 30 mg/day, and the maintenance dose is 30 to 60 mg/day; the maximum dose is 120 mg/day.

**Research underway:** As of 11/25/2019, there are 68 ongoing clinical trials testing duloxetine ([ClinicalTrials.gov](#)). Most of these studies are testing duloxetine for depressive disorder, though some others are also testing it for fibromyalgia, hearing loss, schizophrenia, neuropathic pain, chemo-induced



peripheral neuropathy, acute pain, chronic pain, osteoarthritis, musculoskeletal pain, intervertebral disc degeneration, and alcohol use disorder.

**Search terms:**

Pubmed, Google: duloxetine

- + meta-analysis, + Cochrane, + apolipoprotein, + cognitive, + Alzheimer, + dementia, + cancer

Websites visited for duloxetine:

- Clinicaltrials.gov ([68 ongoing studies](#))
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- [Drugs.com](#)
- [WebMD.com](#)
- [PubChem](#)
- [DrugBank.ca](#)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (several threads: [about Cymbalta patent](#), [generic Cymbalta issues](#), [tapering off of Cymbalta](#))
- Pharmapro.com (0)

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