*Cognitive Vitality Reports® 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

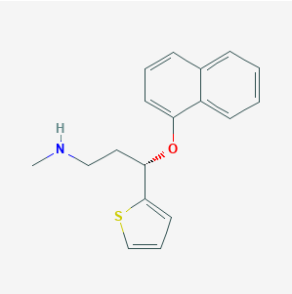
**Evidence Summary**

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:** Duloxetine has shown mixed and inconclusive findings with regards to cognitive effects in clinical trials. Benefits and/or harm may depend on many factors, including the underlying disorder and pathology.

**Aging and related health concerns:** Duloxetine is effective in relieving pain and improving other outcomes for fibromyalgia, osteoarthritis, postoperative pain, and some types of 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".

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

**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, fibromyalgia, diabetic peripheral neuropathy, and chronic musculoskeletal pain (e.g., knee osteoarthritis and low back pain) (DrugBank.ca; MedlinePlus.gov).

**Neuroprotective Benefit:** Duloxetine has shown mixed and inconclusive findings with regards to cognitive effects in clinical trials. Benefits and/or harm may depend on many factors, including the underlying disorder and pathology.

*Types of evidence:*

- A Delphi Consensus of depression in Alzheimer's disease
- 3 randomized controlled clinical trials
- 3 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±1.31) followed by the duloxetine group (1.16±0.82), and the least decline was seen in the control group (0.49±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.

In an open-label clinical study of 35 patients with first-episode drug-naïve major depression, changes in serum BDNF concentrations were compared between anti-depressant responders versus non-

responders (Yoshimura et al., 2023). The antidepressants administered were paroxetine in 15 patients, duloxetine in 11 patients, and escitalopram in 9 patients. The study found that there were no statistically significant differences between responders and non-responders in serum BDNF levels at 0, 2, 4, and 8 weeks of treatment. The responders had lower baseline serum BDNF levels compared to non-responders, and BDNF levels were significantly increased after 8 weeks. The non-responders had serum BDNF levels that were similar from baseline to week 8. Because this study did not have a placebo group, a placebo effect cannot be ruled out. These investigators are undertaking a large-scale study that includes a placebo group and a longer duration follow-up.

***Human research to suggest benefits to patients with dementia***:
A Delphi Consensus on Etiology, Risk Factors, and Clinical Management aimed to gather expert opinions on dementia and depressed patient management (Aguera-Ortiz et al., 2021). This study used a prospective, multi-center, 2-round Modified Delphi survey with 53 questions regarding risk factors, signs and symptoms, diagnosis, and treatment of depression in dementia, with a particular focus on Alzheimer's disease. The panel included 37 expert physicians in neurodegenerative diseases. One of the main findings from this survey was that regardless of the stage of dementia, depression would accelerate its course, while antidepressants would have the opposite effect. Experts unanimously considered that the gold standard antidepressants for Alzheimer's patients are those that improve cognitive function and/or have a dual or multimodal mode of action, including duloxetine, venlafaxine/desvenlafaxine, vortioxetine, tianeptine, and mirtazapine. Although antidepressants may be less effective in dementia patients compared to cognitively healthy patients, the same dosage and treatment duration should be used. Experts also noted that cholinesterase inhibitors may have a synergistic effect with antidepressants.

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 an analysis to discover repositioning opportunities using the WHO pharmacovigilance database VigiBase, drugs with anticholinesterase activities and a good safety profile were searched (Chretien et al., 2020). Of the 22 drugs with safety profiles similar to Alzheimer's medications, 4 drugs (duloxetine, clozapine, aripiprazole, and sertraline) showed a human butyrylcholinesterase inhibition rate of over 70% at $10^{-5}$ M. The most active human butyrylcholinesterase inhibitor was duloxetine, with an inhibition rate of 85% at $10^{-5}$ M and a half maximal inhibitory concentration of 1.2 µM.

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-α and IL-1β). 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.

In a mouse model of stress (induced by chronic immobilization), pretreatment with duloxetine (10 and 20 mg/kg, i.p.) 30 minutes prior to stress induction dose-dependently ameliorated anxiety-like behavior, depression-like behavior, cognitive deficits, memory disturbances, neuronal damage, and oxidative stress markers (Meejuru et al., 2021). Duloxetine pretreatment decreased oxidative stress markers (MDA) and increased anti-oxidative markers (increased glutathione, SOD, and catalase). The mechanisms of neuroprotection included increased antioxidant activity, reduced acetylcholinesterase activity, decreased glutamate toxicity, and neuroprotection.

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 and improving other outcomes for fibromyalgia, osteoarthritis, postoperative pain, and some types of peripheral neuropathy.

*Types of evidence:*

- 21 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 AND IMPROVED PHYSICAL FUNCTION.
Duloxxetine, pregabalin, and milnacipran are FDA-approved for the treatment of fibromyalgia. Amitriptyline is commonly used off-label for the treatment of fibromyalgia.

In a 2023 Cochrane meta-analysis, 176 studies with a total of 28,664 adults with chronic pain (fibromyalgia, neuropathic pain, musculoskeletal pain) were included to assess antidepressants for pain management (Birkinshaw et al., 2023). There were 59 studies of fibromyalgia, 49 studies of neuropathic pain, and 40 studies of musculoskeletal pain. There were 43 studies that tested duloxetine, 43 studies tested amitriptyline, 18 studies tested milnacipran, 11 studies tested fluoxetine, 8 studies tested paroxetine, 8 studies tested venlafaxine, and fewer than 8 studies tested other antidepressants. Across efficacy outcomes, duloxetine was consistently the highest-ranked antidepressant with moderate- to high-certainty evidence. The standard dose of duloxetine (60 mg daily, orally) was equally efficacious as a high dose (120 mg daily) for the majority of outcomes. Duloxetine (60 mg daily) showed a small to moderate effect for substantial pain relief (OR=1.91, 95% CI, 1.69 to 2.17) and reduced continuous pain intensity (standardized mean difference of -0.31, 95% CI, -0.39 to -0.24). For secondary outcomes, which included moderate pain relief, physical function, sleep, quality of life, and Patient Global Impression of

Change (PGIC), duloxetine and milnacipran were the highest-ranked antidepressants with moderate-certainty evidence, though the effect sizes were small.

In a 2023 meta-analysis of 13 randomized controlled trials including a total of 4,201 patients with chronic musculoskeletal pain (diagnosed with fibromyalgia or knee osteoarthritis), duloxetine treatment (30-120 mg daily, orally) for 10-24 weeks was significantly superior to placebo on 24-hour average pain (mean difference, -0.74, p<0.00001), quality of life, physical function, and global impressions (Ma et al., 2023). With regards to interference of pain and quality of life, the meta-analysis revealed that duloxetine was superior to placebo on general activity, mood, walking ability, normal work, interpersonal relationship, sleep, and enjoyment of life (p<0.05 for all). With regards to physical function, duloxetine significantly improved the total score of limb function, pain, stiffness, and physical function than placebo (p<0.05 for all).

In a 2022 network meta-analysis studying the comparative efficacy of amitriptyline, duloxetine, and pregabalin for fibromyalgia, pregabalin (450 mg daily) showed the highest performance for reduction of pain intensity by >30% and amitriptyline (25 mg daily) showed the highest efficacy for reduction of pain intensity by >50% (Alberti et al., 2022).

Another 2022 network meta-analysis studied the comparative effectiveness of duloxetine, pregabalin, milnacipran, and amitriptyline for the treatment of fibromyalgia (Farag et al., 2022). Duloxetine (120 mg daily) was associated with the highest improvement in pain (standardized mean difference, -0.33; 95% CI, -0.36 to -0.30) and depression (standardized mean difference, -0.25; 95% CI, -0.32 to -0.17) versus placebo. Amitriptyline was associated with reduced sleep disturbances, fatigue, and improved quality of life.

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).

The changes in norepinephrine and serotonin in the central nervous system are thought to suppress pain, which in turn may ameliorate anxiety and depression.

***Osteoarthritis***: PAIN RELIEF AND IMPROVED PHYSICAL FUNCTION
In a meta-analysis of 13 randomized controlled trials including a total of 4,201 patients with chronic musculoskeletal pain (diagnosed with knee osteoarthritis or fibromyalgia), duloxetine treatment (30-120 mg daily, orally) for 10-24 weeks was significantly superior to placebo on 24-hour average pain (mean difference, -0.74, $p<0.00001$), quality of life, physical function, and global impressions (Ma et al., 2023). The meta-analysis also revealed that duloxetine was superior to placebo on general activity, mood, walking ability, normal work, interpersonal relationship, sleep, and enjoyment of life ($p<0.05$ for all).

In a meta-analysis of 11 randomized controlled trials including a total of 1,019 patients recovering from total knee arthroplasty (for primary knee osteoarthritis), duloxetine treatment (30 or 60 mg daily) for up to 8 weeks showed a statistically significant reduction in 'pain at rest' at 3 days, 1 week, 2 weeks, and 6 weeks post-surgery (Yan et al. 2023). There was also a significant reduction in 'pain on movement' at 5 days, 1-, 2-, 4-, 6-, and 8-weeks post-surgery. Duloxetine also significantly improved physical function, range of motion of the knee (at 6 weeks), and emotional function (depression and mental health). Cumulative opioid consumption at 24 hours (but not over 7 days) was significantly lower in the duloxetine groups.

In a similar meta-analysis of 9 randomized controlled trials including a total of 806 patients who had undergone total knee or hip arthroplasty, duloxetine treatment (30 or 60 mg daily) before and after surgery reduced opioid consumption on postoperative days 2, 3, 7, and 14 (Azimi et al., 2023). Duloxetine treatment also decreased pain with activity on postoperative days 1, 3, 7, 14, and 90 ($p<0.05$ for all). The opioid-sparing effects of duloxetine needs to be weighed against the increase in somnolence and drowsiness with this drug.

In another meta-analysis of 8 randomized controlled trials of patients who had undergone knee or hip replacement, duloxetine treatment (30 or 60 mg daily) before and after surgery for up to 8 weeks significantly reduced postoperative opioid consumption at 48 and 72 hours and significantly reduced pain on days 3, 7, and week 6 (Jones et al., 2023).

In a meta-analysis of 6 randomized controlled trials including a total of 5332 patients who had undergone total knee arthroplasty, duloxetine treatment (30 or 60 mg daily) resulted in better pain score, reduced morphine consumption, and decreased length of hospital stay (Zhang et al., 2023).

Pain relief with duloxetine in people with osteoarthritis likely varies, with some patients experiencing an early analgesic effect, while normally it takes up to 6 weeks for duloxetine to become effective in osteoarthritis (Leaney et al., 2022). And there are some people who show no analgesic response to duloxetine.

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***: IMPROVEMENT IN DIABETIC NEUROPATHY AND SPINAL INJURY-INDUCED NEUROPATHY.
In a 2023 Cochrane meta-analysis, 176 studies with a total of 28,664 adults with chronic pain (fibromyalgia, neuropathic pain, musculoskeletal pain) were included to assess antidepressants for pain management (Birkinshaw et al., 2023). Of the 176 studies, 49 studies were of neuropathic pain. Forty-three studies tested duloxetine, 43 studies tested amitriptyline, 18 studies tested milnacipran, 11 studies tested fluoxetine, 8 studies tested paroxetine, 8 studies tested venlafaxine, and fewer than 8 studies tested other antidepressants. Across efficacy outcomes, duloxetine was consistently the highest-ranked antidepressant with moderate- to high-certainty evidence. The standard dose of duloxetine (60 mg daily, orally) was equally efficacious as a high dose (120 mg daily) for the majority of outcomes. Duloxetine (60 mg daily) showed a small to moderate effect for substantial pain relief (OR=1.91; 95% CI, 1.69 to 2.17) and reduced continuous pain intensity (standardized mean difference of -0.31, 95% CI, -0.39 to -0.24). For secondary outcomes, which included moderate pain relief, physical function, sleep, quality of life, and Patient Global Impression of Change (PGIC), duloxetine and milnacipran were the highest-ranked antidepressants with moderate-certainty evidence, though the effect sizes were small.

Painful diabetic peripheral neuropathy is caused by chronic hyperglycemia and is characterized by pain and nerve damage of distal lower extremities. Approximately 50% of people with type 2 diabetes develop peripheral neuropathy, of whom ~25% experience painful diabetic peripheral neuropathy, which involves tingling, shooting pain, burning pain, allodynia, hyperesthesia, and other sensations (Snyder et al., 2016). Symptoms often worsen at night and affect quality of sleep. The underlying mechanism of diabetic peripheral neuropathy is hyperexcitability in primary afferent nociceptors due to peripheral nerve damage, which in turn, leads to central sensitization (hyperexcitability in central neurons) and generation of spontaneous impulses within peripheral nerves. In central sensitization, there is lowered activation threshold, increased response to a given stimulus, and abnormal spontaneous activity. Duloxetine is approved by the FDA for treating painful diabetic peripheral neuropathy. In a 2023 meta-analysis of 7 randomized controlled trials including a total of 2,205 patients with painful diabetic peripheral neuropathy, duloxetine treatment (20 to 120 mg daily orally) for 8-12 weeks significantly improved pain compared to placebo (mean difference, -0.89, 95% CI, -1.09 to -0.69)(Wu et al., 2023). Duloxetine treatment also significantly improved quality of life, which was assessed using the Clinical Global Impression severity subscale, Patient Global Impression of Improvement scale, and European Quality of Life Instrument 5D version ($p<0.05$ for all). The authors

noted that increased noradrenaline with duloxetine may target the α2-adrenergic receptors in the dorsal horn of the spinal cord and the locus coeruleus, leading to inhibition of allodynia and hyperalgesia. Increased serotonin with duloxetine may also enhance the inhibitory effects of noradrenaline.

In a 2023 meta-analysis of 7 randomized controlled trials including a total of 645 patients, the efficacy and safety of duloxetine treatment and prevention was evaluated for chemotherapy-induced peripheral neuropathy (Chow et al., 2023). Duloxetine was statistically similar to placebo in its efficacy, both in the treatment (RR=0.92; 95% CI, 0.84 to 1.01) and prevention (RR=1.02; 95% CI, 0.87 to 1.19) of chemotherapy-induced peripheral neuropathy. One study compared duloxetine to pregabalin and found that duloxetine was inferior to pregabalin. There is currently limited evidence supporting the use of duloxetine for this type of neuropathy.

In a Bayesian network analysis and comparative efficacy study of neuropathic pain after spinal cord injury, 20 randomized controlled trials including 1,198 patients and 11 drugs were assessed for 5 outcomes: pain, risk of bias, mental health, sleep, and safety (Ling et al., 2022). BTX-A, gabapentin, pregabalin, amitriptyline, ketamine, lamotrigine, and duloxetine were effective for neuropathic pain management following spinal cord injury. Based on a network meta-analysis of pain relief at 4-week follow-up, BTX-A was ranked the highest, followed by ketamine, amitriptyline, lamotrigine, pregabalin, duloxetine, gabapentin, tramadol, levetiracetam, carbamazepine, and cannabinoids. The overall rankings accounting for safety are: BTX-A, gabapentin, ketamine, amitriptyline, pregabalin, duloxetine, lamotrigine, levetiracetam, tramadol, carbamazepine, and cannabinoids. Gabapentin, BTX-A, amitriptyline, ketamine, and lamotrigine had high pain relief efficacy and fewer adverse events, supporting them as first-line therapy for post spinal cord injury. Pregabalin and duloxetine were proposed as second-line treatment.

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 ≥ 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:*

- 19 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***:
In a 2020 meta-analysis of 17 randomized controlled trials that included various disease populations (mood disorders, fibromyalgia, chronic low back pain, etc.), duloxetine treatment (30-120 mg daily, orally) for 8-52 weeks increased heart rate by 2.22 beats/minute and diastolic blood pressure by 0.82 mmHg (Park et al., 2020). The American Heart Association guideline has reported that an increase of systolic blood pressure above 10 mmHg could clinically increase the risk of cardiovascular disease (Whelton et al., 2017). Because the levels of both serotonin and norepinephrine are increased with the use of SNRIs, hypertension, tachycardia, arrhythmias, and other adverse events are more likely than with selective serotonin reuptake inhibitors.

*Fibromyalgia patients*:
In a 2023 meta-analysis of 13 randomized controlled trials including a total of 4,201 patients with chronic musculoskeletal pain (diagnosed with fibromyalgia or knee osteoarthritis), duloxetine treatment (30-120 mg daily, orally) for 10-24 weeks did not result in a significant difference in the rate of serious adverse events compared to placebo (RR=0.81, 95% CI, 0.43 to 1.53)(Ma et al., 2023).

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 11 randomized controlled trials including a total of 1,019 patients recovering from total knee arthroplasty (for primary knee osteoarthritis), duloxetine treatment (30 or 60 mg daily) for up to 8 weeks resulted in no significant differences in the incidence of adverse events compared to controls (Yan et al. 2023).

In a meta-analysis of 9 randomized controlled trials including a total of 806 patients who had undergone total knee or hip arthroplasty, duloxetine treatment (30 or 60 mg daily) before and after surgery led to nausea, sleeplessness, dizziness, somnolence, fatigue, dry mouth, headache, constipation, hyperhidrosis, and diarrhea, but incidences of adverse events were not significantly different compared to control groups except for increased risk ratio of somnolence and drowsiness with duloxetine (RR=1.87 (95% CI, 1.18 to 2.95, p=0.007)(Azimi et al., 2023).

In a meta-analysis of 6 randomized controlled trials including a total of 5332 patients who had undergone total knee arthroplasty, duloxetine treatment (30 or 60 mg daily) did not result in significant differences in side effects (nausea, vomiting, headache, dizziness, and pruritis) compared to control groups (OR=0.89, 95% CI, 0.6 to 1.35, p=0.59) (Zhang et al., 2023).

In a Cochrane meta-analysis of 9 randomized controlled trials including a total of 2,122 patients with hip and knee osteoarthritis, one study reported a greater rate of adverse events in older participants (22.3%) compared to younger participants (7.5%), while another study reported no differences between older and younger subjects (Leaney et al., 2022).

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.

*Peripheral neuropathy*:
In a 2023 meta-analysis of 7 randomized controlled trials including a total of 2,205 patients with painful diabetic peripheral neuropathy, duloxetine treatment (20 to 120 mg daily orally) for 8-12 weeks resulted in some adverse events such as nausea, somnolence, dizziness, fatigue, constipation, and decreased appetite, but severe adverse events were rare (Wu et al., 2023). Approximately 12.6% of patients dropped out because of the adverse events symptoms. Nausea had the highest incidence rate (20.21%), followed by somnolence (12.73%), dizziness (10.10%), fatigue/malaise (8.14%), constipation (8.01%), and decreased appetite (2.89%).

*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 5/22/2023, there are 49 ongoing clinical trials testing duloxetine (ClinicalTrials.gov). These studies are testing duloxetine for depressive disorder, fibromyalgia, schizophrenia, neuropathic pain, chemo-induced peripheral neuropathy, central sensitization, acute/chronic pain, postoperative pain, low back pain, osteoarthritis, musculoskeletal pain, interstitial lung disease, and alcohol use disorder.

**Search terms:**

Pubmed, Google: duloxetine

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

Websites visited for duloxetine:

- Clinicaltrials.gov (49 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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