

# Duloxetine

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## Introduction

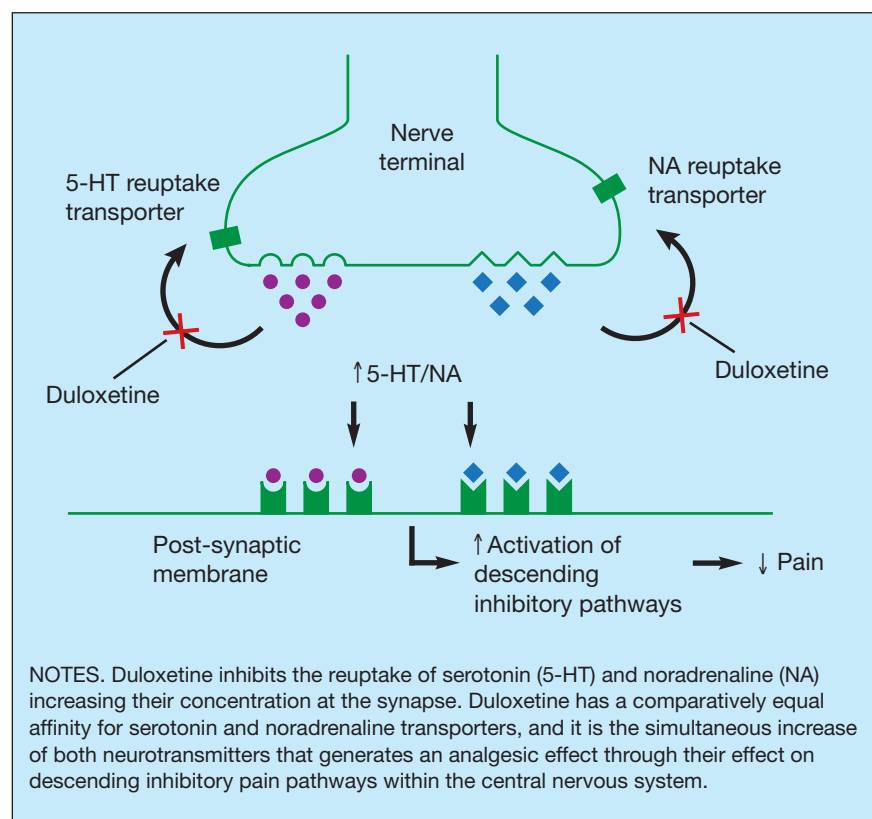
Duloxetine was initially licensed in the United Kingdom in 2004 as a treatment for urinary stress incontinence before being introduced for the treatment of major depressive disorders in 2005 as Cymbalta. The Cymbalta drug licence was subsequently extended in August 2005 to include its use in the management of diabetic painful peripheral neuropathy (PPN) making it the first antidepressant to be licensed for use in the treatment of this condition.

## Pharmacology

Figure 1 outlines the pharmacological action of duloxetine. The neurotransmitters serotonin (5-HT) and noradrenaline modulate descending inhibitory pain pathways within the central nervous system. Duloxetine inhibits the reuptake of these substances so that their concentration at the synapse is increased. Duloxetine has a comparatively equal affinity for serotonin and noradrenaline transporters, and it is the simultaneous increase of both these neurotransmitters that generates an analgesic effect.

The starting and recommended maintenance dose is 60mg daily with or without food. This may be increased up to a maximum dose of 120mg per day administered in evenly divided doses. Absorption is delayed by two hours after ingestion by the enteric coating. Duloxetine is a highly lipid soluble drug that is well absorbed with an oral bioavailability that ranges from 30% to 80% (average 50%). The plasma concentration of duloxetine displays large inter-individual variability resulting in some patients exhibiting an insufficient response to 60mg. These patients

**Figure 1.** The pharmacological action of duloxetine



may benefit from a higher dose. Maximal plasma concentration occurs at six hours with an elimination half-life of 10–12 hours.

The drug is metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP1A2. Duloxetine should not be used in combination with CYP1A2 inhibitors such as quinolone antibiotics and selective serotonin reuptake inhibitors (SSRIs). Elevated plasma concentrations of duloxetine will be generated by concomitant use of such drugs. Duloxetine is also a CYP2D6 inhibitor leading to increased levels of tricyclic antidepressants and type 1C antiarrhythmics that are also metabolised by this enzyme.

## Trials of safety and efficacy

A Cochrane review<sup>1</sup> of the use of duloxetine in the treatment of painful neuropathy and chronic pain identified three randomised studies relating to the use of the drug in the treatment of diabetic PPN.<sup>2–4</sup> All study participants were aged 18 or over with a diagnosis of PPN rated greater than 3 on the Michigan Neuropathy Screening Instrument. Participants had been diagnosed with this condition for more than six months and had a minimum weekly average pain score of 4 on an 11-point Likert scale (no pain to worst ever pain).

The first of these studies was a multicentre, double-blind study of

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457 patients randomised to treatment with placebo or duloxetine 20, 60 or 120mg daily for 12 weeks.<sup>2</sup> The later studies compared placebo with just the 60mg and 120mg doses over 12 weeks.<sup>3,4</sup> All three studies come from the same group of collaborators and were sponsored by the company that markets the drug. Data collection included spontaneously reported adverse events, hypoglycaemic events, blood pressure, heart rate, blood chemistry and haematology. Adverse effects most commonly identified in the duloxetine groups included mild or moderate nausea, somnolence, dizziness, constipation, dry mouth, sweating, decreased appetite, anorexia and weakness. Severe somnolence was more common in the group taking 120mg daily. Overall data from the three studies combined and analysed in the Cochrane review revealed that 16% of participants stopped the drug due to side effects.<sup>1</sup>

A further open-label extension of one of the original 12-week studies was carried out to look at longer-term (one year) safety and found no evidence of adverse effects of 120mg duloxetine daily on parameters of routine diabetic care including blood pressure, lipids, progression of retinopathy and nephropathy.<sup>5</sup>

Duloxetine should not be used in patients with hepatic impairment or severe renal impairment (creatinine clearance <30ml/min). It is also contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis. Abrupt discontinuation of duloxetine should be avoided as withdrawal reactions such as anxiety and depression may occur. In order to reduce this risk, the dose should be gradually reduced over a period of at least one to two weeks.

### Specific evidence for use in diabetes

The primary evidence base for the efficacy of duloxetine in diabetic PPN comes from the same three randomised, double-blind, placebo-controlled trials mentioned above.<sup>2-4</sup> The primary outcome

### Key points

- Duloxetine is an antidepressant licensed for use in painful diabetic peripheral neuropathy
- It is metabolised through the cytochrome P450 enzyme pathway
- The number needed to treat (NNT) with duloxetine 60mg daily to achieve a 50% reduction in pain for one patient is six

measure was the weekly mean of daily 24-hour average pain scores. A 30% reduction in reported pain was considered to be significant within the trials. The study by Goldstein et al. identified that a dosage of 20mg per day was insufficient to produce a significant reduction in pain.<sup>2</sup> Pooled data from all three trials were analysed by the authors of the Cochrane review, using a target of 50% reduction in pain. Their analysis shows that duloxetine 60mg daily for 12 weeks achieves 50% pain reduction with a risk ratio compared with placebo of 1.65 (95% CI 1.34–2.03) giving a number needed to treat of six (95% CI 5–10). The risk ratio for 50% pain reduction using 120mg duloxetine daily was not significantly greater (1.66, 95% CI 1.35–2.04). The effect in some patients was evident within one week of commencing treatment.

We wish to draw attention to the need for caution when prescribing duloxetine for patients with renal impairment. Patients who develop diabetic neuropathic pain often have coexisting nephropathy. In such cases it is essential to ensure that renal function is checked prior to commencing treatment.

### Discussion

The current National Institute for Health and Clinical Excellence (NICE) guideline on the treatment of neuropathic pain, and the Scottish Intercollegiate Guidelines Network (SIGN) diabetes guideline number 116 both recommend duloxetine as a first line treatment for diabetic neuropathic pain. The recommended dosage is 60mg once daily. Six patients need to be treated to achieve a 50% reduction in pain in one patient, although lesser degrees of benefit may be seen in more than one patient. Some patients may benefit from up to

120mg daily although at this dose there is an increased incidence of side effects, particularly somnolence. Duloxetine is metabolised through the cytochrome P450 pathway so the prescriber should be aware of potential drug interactions. The main clinical caution is renal failure. There is no published evidence comparing duloxetine in a randomised controlled trial setting with other drugs for diabetic PPN. As yet no long-term follow-up data are available. The primary published research relating to duloxetine in the management of diabetic PPN has been sponsored by the company that markets it. There are no high quality published data comparing the efficacy of duloxetine with other existing therapies for diabetic PPN, nor any information on cost effectiveness.

### Declaration of interest

Dr Hopkinson and Ms Harkin have no conflicts of interest to declare

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