

Duloxetine for diabetic neuropathic pain

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Duloxetine, a selective serotonin and noradrenaline reuptake inhibitor, is the first antidepressant to be licensed for the treatment of diabetic peripheral neuropathic pain.
- The recommended starting and maintenance dose is 60mg daily. Doses of up to 120mg daily are also licensed but did not confer any significant benefit in clinical trials and were less well tolerated.
- Two 12-week placebo-controlled trials have shown duloxetine to significantly improve the mean 24-hour pain severity score and increase the proportion of patients with at least a 30% reduction in pain score compared to baseline.
- Duloxetine has not been compared with established drugs used for the treatment of neuropathic pain, such as amitriptyline and other tricyclics (unlicensed), gabapentin and pregabalin (licensed), and tramadol and opioid analgesics. Its efficacy in patients unresponsive to these agents has also not been assessed. Unlike tricyclic and antiepileptic drugs, dose titration with duloxetine is not generally required.
- The most common adverse events leading to discontinuation of duloxetine in clinical trials were nausea, dizziness, somnolence and fatigue. As with other antidepressants, suicidal ideation and discontinuation symptoms have been reported with its use.
- Until comparative and long-term efficacy data become available, use of duloxetine should be reserved for patients who have failed to respond to, or are intolerant of, established therapies. Policies that encourage the use of licensed drugs when available will favour the adoption of duloxetine as a treatment for diabetic neuropathic pain, but consensus supports the first-line use of unlicensed tricyclic antidepressants for this indication.

Introduction

Duloxetine is a selective serotonin (5HT) and noradrenaline reuptake inhibitor. It was launched in the UK in September 2004 as *Yentreve*[®] for the treatment of stress urinary incontinence and in January 2005 as *Cymbalta*[®] for the treatment of major depressive episodes. The licence for *Cymbalta*[®] has now been extended to include the treatment of diabetic peripheral neuropathic pain in adults. It is the first antidepressant to be licensed for this indication, although other antidepressants, particularly the tricyclics, have been used to treat neuropathic pain for many years.

Up to 40% of people with diabetes develop neuropathy; the incidence increases with age and duration of diabetes. Neuropathy is often associated with significant burning, stabbing or tingling pain and numbness, and can result in sleep interference, depression, anxiety and severe disability. Evidence suggests that endogenous pain inhibitory mechanisms may be dysfunctional in pathological pain states such as diabetic neuropathy. Both 5HT and noradrenaline have been implicated in the mediation of endogenous analgesic mechanisms via inhibitory pain pathways in the brain and spinal cord.¹

Evidence

Efficacy of duloxetine has been demonstrated in two 12-week multicentre, double-blind, placebo controlled, fixed dose studies in adult patients with diabetic peripheral neuropathic pain.^{1,2} Both studies recruited patients with bilateral peripheral neuropathy associated with type 1 or type 2 diabetes mellitus, causing pain on a daily basis for at least six months. Patients were also required to have a mean 24-hour average pain severity score of at least four (on an 11-point Likert scale on which 0=no pain and 10=worst possible pain) and an HbA_{1c} ≤12 on screening. Exclusion criteria included current major depressive disorder, generalised anxiety disorder and alcohol or eating disorders. No indication was given in either study of the history or extent of any previous analgesic treatment.

The primary efficacy measure in both studies was the reduction in the weekly mean of the 24-hour average pain severity score from baseline to the end

Brand Name, (Manufacturer): Cymbalta[®] (Eli Lilly)

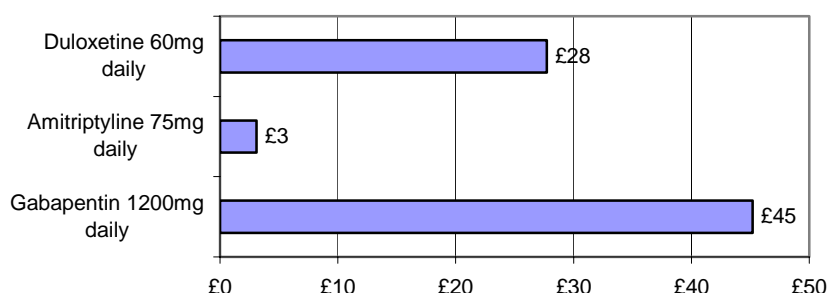
BNF Therapeutic Class: 4.3.4 Other antidepressant drugs.

Licensed Indications: Cymbalta[®] is licensed for the treatment of diabetic peripheral neuropathic pain in adults. (It is also licensed for major depressive episodes.)

Dosage and Administration: The recommended starting and maintenance dose is 60mg once daily. The dose may be increased to 120mg daily. Treatment should be reviewed after two months – additional response after this time is unlikely.

Licence extension: July 2005.

Cost Comparisons: Cost for 28 days treatment [Prices from MIMS/Drug Tariff – July 2005].



N.B. Doses shown for general comparison and do not imply therapeutic equivalence.

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of the study. Secondary efficacy measures included mean changes in worst pain and night pain severity; the Brief Pain Inventory; the Clinical Global Impression of Severity and Patient Global Impression of Improvement scales; the short-form McGill Pain Questionnaire; measures of allodynia (pain on brush stroking); and average daily intake of paracetamol. The studies also assessed rates of treatment response, where response was defined as a $\geq 30\%$ reduction from baseline in the 24-hour average pain severity score, and a sustained response as a $\geq 30\%$ reduction in score from baseline at a visit at least two weeks prior to the end of the study with a reduction in pain score of $\geq 20\%$ at every visit in between.

The first study, a phase II trial, compared duloxetine 20mg once daily, 60mg once daily and 60mg twice daily with placebo in 457 patients (in press).¹ After 12 weeks treatment the weekly mean 24-hour average pain severity score was reduced by 2.36, 2.89, 3.24 and 1.91, respectively. Patients on duloxetine 60mg and 120mg daily had statistically significant greater improvement in pain severity scores compared to those on placebo at week one ($p < 0.001$), and at each subsequent weekly visit until study end. Duloxetine 20mg daily was not significantly more effective than placebo at any visit. The proportion of patients in the placebo and duloxetine 20mg, 60mg or 120mg groups achieving a response was 47%, 51%, 64% and 65%, respectively; 33%, 46%, 56% and 56%, respectively, achieved a sustained response.

In the second study, a phase III trial, duloxetine 60mg daily, 60mg twice daily and placebo were compared in 334 subjects (poster).² Mean change in the 24-hour average pain severity score between the active and placebo groups was significantly different from week one onwards; at study end there was a change in scores of approximately -2.7, -3.1 and -1.5, respectively, from baseline ($p < 0.001$ vs. placebo).

In both studies, improvements in the 24-hour pain severity score were considered to be largely due to a direct effect on pain, and not to indirect improvements in depressive and anxiety symptoms as assessed by Beck Depression Inventory scores.

Most secondary endpoints in the two studies were significantly improved in patients on duloxetine 60mg once or twice daily, compared to those on

placebo. See table in appendix II for details.

In a 52-week open-label extension to the phase II trial, patients were randomised to receive duloxetine 60mg twice daily or routine care.³ The main objective was to assess long-term safety, but the study also assessed quality-of-life (QoL). Of the ten domains measured in the SF-36 Health Survey, a statistically significant difference in favour of duloxetine was noted only in that for bodily pain. The European Quality of Life Survey indicated patients' QoL deteriorated on routine care but did not change in those receiving duloxetine.

Safety

Approximately 14% of the 568 patients on duloxetine in the two key studies discontinued treatment because of an adverse event compared to 7% of the 223 patients on placebo. Nausea (3.5% vs. 0.4%), dizziness (1.6% vs. 0.4%), somnolence (1.6% vs. 0%) and fatigue (1.1% vs. 0%) were the most common events leading to discontinuation and considered to be drug related.⁴

In a 28-week open-label safety study, 63% of 449 patients randomised to duloxetine 120mg daily completed the study. Mean changes in heart rate, blood pressure, lipid levels and HbA_{1c} were noted; some of the changes were statistically significant but described as clinically unremarkable.⁵ Pooled data from trials of duloxetine in the treatment of depression indicate that its cardiovascular effects are similar to those of fluoxetine and paroxetine.⁶

In the 52-week extension study, 14.4% of patients on duloxetine reported serious adverse events compared to 19.1% on routine care; 14.0% vs. 9.6%, respectively, discontinued therapy because of adverse events.³ There were no significant differences between groups in the number of hypoglycaemic events, changes in HbA_{1c} or in the progression of neuropathy, nephropathy or retinopathy.

Place in Therapy

Diabetic neuropathy is often associated with pain unresponsive to conventional first-line analgesics and drugs such as antidepressants, certain antiepileptic drugs (AEDs), tramadol and opioids, are commonly used to manage such pain. Although a number of these agents are unlicensed for this indication, their use is supported by a considerable body of

evidence and by reputable professional bodies.^{7,8}

Tricyclic antidepressants are generally considered first-line treatment for neuropathic pain. Typically the number needed to treat (NNT) is about 2. SSRI antidepressants have also been used but evidence of efficacy is conflicting. AEDs are often used when diabetic neuropathic pain has not responded to tricyclics. Gabapentin and pregabalin are licensed for this indication; the NNT for gabapentin is 3.8. Carbamazepine is also used and has an NNT of 3.3.^{7,8,9}

Duloxetine is the first antidepressant licensed for the treatment of diabetic neuropathic pain, and unlike tricyclics, AEDs and opioids, does not generally require dose titration. These factors may be used to promote the drug. However, duloxetine has not been compared with the tricyclics and AEDs and its efficacy has only been assessed in short-term studies. Although there are no data demonstrating efficacy in patients not responding to established therapies, its use should probably be reserved for such patients until evidence of comparative and long-term efficacy is available.

The generally accepted practice of not using unlicensed drugs when licensed products are available will favour the adoption of duloxetine for the treatment of peripheral neuropathic pain. However, current consensus and evidence support the first-line use of unlicensed tricyclic antidepressants for this indication.

Appendix I: Bibliography Appendix II: Table of Key Clinical Trials

Risk Management Issues:

Duloxetine is associated with discontinuation symptoms and treatment should be withdrawn gradually.

Suicide ideation and behaviour have been linked with antidepressant use and a small number of cases have been reported with duloxetine when used in the treatment of urinary incontinence.¹⁰ Causality has not been established.

Produced for the UK Medicines Information Service

by Christine Proudlove, North West Medicines Information Centre, Pharmacy Practice Unit,
70 Pembroke Place, Liverpool L69 3GF. Tel: 0151 794 8117 Email: druginfo@liv.ac.uk

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Appendix I

Bibliography

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Appendix II: Table of key clinical trials evaluating duloxetine in diabetic neuropathic pain

Study	Trial Design	Trial Population	Efficacy Outcomes (change from baseline to end of study)				
				Placebo n=115	Duloxetine 20mg/d n=115	Duloxetine 60mg/d n=114	Duloxetine 120mg/d n=113
Ref. 1	Phase II, double-blind, randomised, placebo-controlled 12-week, fixed dose study conducted in USA, Puerto Rico, Canada and Argentina.	457 adults, mean age 60.1 years, with bilateral peripheral neuropathy caused by type 1 or type 2 diabetes. Pain present on a daily basis for at least 6 months. Subjects had a mean pain score of ≥ 4 (on an 11 point Likert scale) on the 24-hour average pain severity score and a HbA1c of ≤ 12 . Exclusion criteria included a diagnosis of major depression, generalised anxiety disorder, alcohol or eating disorder.	Primary outcome:				
			Weekly mean of 24-hour average pain severity (SE)	-1.91 (0.22)	-2.36 (0.21)	-2.9*** (0.22)	-3.2*** (0.23)
			Secondary outcomes:				
			Response [§] (% of patients)	47	51	64**	65**
			Sustained response ^{\$\$} (% of patients)	33	46	56***	56***
			24-hour worst pain score (SE)	-2.09 (0.24)	-2.78* (0.23)	-3.31*** (0.24)	-3.72*** (0.24)
			Night pain score (SE)	-2.2 (0.23)	-2.48 (0.22)	-2.91* (0.23)	-3.45*** (0.24)
			Brief Pain Inventory – • Mean pain severity • Interference with general activity	-2.04 -1.72	-2.25 -1.87	-2.81** -2.43*	-3.07*** -2.54**
			Clinical Global Impression of severity (SE)	-0.83 (0.12)	-1.28* (0.11)	-1.42*** (0.12)	-1.7*** (0.12)
			Patient Global Impression of Improvement (SE)	+2.91 (0.12)	+2.68 (0.12)	+2.21*** (0.12)	+2.24** (0.12)
			SF McGill Total Score (SE)	-5.39 (0.66)	-7.23* (0.67)	-8.25*** (0.65)	-9.18*** (0.64)
			Average paracetamol daily dose	335.25mg	178.27mg	74.11mg*	80.06mg*
Ref. 2 Ref. 10	Phase III double-blind, randomised, placebo-controlled 12-week, fixed dose study conducted in USA and Puerto Rico.	334 adults, mean age 60.7 years, with bilateral peripheral neuropathy caused by type 1 or type 2 diabetes. Pain present on a daily basis for at least 6 months. Subjects had a mean pain score of ≥ 4 (on an 11 point Likert scale) on the 24-hour average pain severity score and a HbA1c of ≤ 12 . Exclusion criteria included a diagnosis of major depression, generalised anxiety disorder, alcohol or eating disorder.	NB: most figures for this study are derived from graphs				
			Primary outcome:				
			Weekly mean of 24-hour average pain severity		-1.5	-2.7***	-3.1***
			Secondary outcomes:				
			Response (% of patients)		42	63*	69*
			24-hour worst pain score		-2.2	-3.3***	-3.7***
			Night pain score		-2.1	-3.5*	-3.8***
			Brief Pain Inventory – Mean pain severity Interference with general activity		-1.8 -2.0	-2.6*** -2.6	-3.0*** -2.7*
			Clinical Global Impression of severity			P<0.05 vs. placebo	P<0.05 vs. placebo
			Patient Global Impression of Improvement			P<0.05 vs. placebo	P<0.001 vs. placebo
			SF McGill Total Score			P<0.05 vs. placebo	P<0.001 vs. placebo
			Average paracetamol daily dose				P<0.001 vs. placebo

* P<0.05 ** P<0.01 ***P<0.001

§ Response = $\geq 30\%$ reduction from baseline in the 24-hour average pain severity score

\$\$ Sustained response = $\geq 30\%$ reduction in score from baseline at a visit at least two weeks prior to study endpoint with a reduction in pain score of $\geq 20\%$ at every visit in between.

SE = standard error