

Duloxetine for depression

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

Summary

Duloxetine (Cymbalta®), a selective serotonin and noradrenaline reuptake inhibitor (SNRI), has been marketed for the treatment of major depressive episodes. It belongs to the same class of antidepressants as venlafaxine.

Two published 9-week trials indicate that duloxetine at a dose of 60mg daily is associated with significant improvements in symptoms of major depressive disorder compared with placebo, as measured by changes in the HAM-D₁₇ score.

A small number of trials have included the SSRIs fluoxetine and paroxetine as active comparators to demonstrate non-inferiority of duloxetine, but none of these trials employed the licensed dose of duloxetine.

The most commonly reported adverse effects of duloxetine are nausea, dry mouth and constipation. As with similar preparations, duloxetine has been associated with suicidal ideation and a discontinuation syndrome.

Duloxetine is marketed as Cymbalta® to treat depression. It is also licensed as Yentreve® for the treatment of moderate to severe stress urinary incontinence. The presentation and licensed dosage differs for the two indications.

Introduction

Duloxetine, a selective serotonin and noradrenaline reuptake inhibitor (SNRI), was launched for the treatment of major depressive episodes in January 2005, under the trade name Cymbalta®. It has also been licensed for moderate to severe stress urinary incontinence under the trade name Yentreve (see NMP November 2004), and Cymbalta is now licensed for the treatment of diabetic peripheral neuropathic pain in adults.

Evidence

The submission to the licensing authority for the treatment of depression included six placebo-controlled trials, which assessed the efficacy of duloxetine administered over a dose range of 40mg to 120mg daily for a period of eight to nine weeks. From these trials a dose of 60mg daily was found to be the optimal therapeutic dose.^{1, 2, 3} On the basis of these trials, the Committee for Medicinal Products for Human Use (CHMP) concluded that duloxetine had demonstrated statistical superiority over placebo as measured by improvements in the 17-item Hamilton Depression Rating Scale (HAM-D₁₇) total score.⁴ Two of these six trials have been fully published and are reviewed below.^{5, 6}

Both nine week studies compared duloxetine 60mg daily with placebo and were of randomised, double blind, parallel-group design (see Appendix II). All patients met the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) confirmed by the Mental health Needs Index (MINI) interview. Baseline severity of depression was defined by the patients' scores on the HAMD₁₇ and the Clinical Global Impression - Severity of Illness (CGI-S).

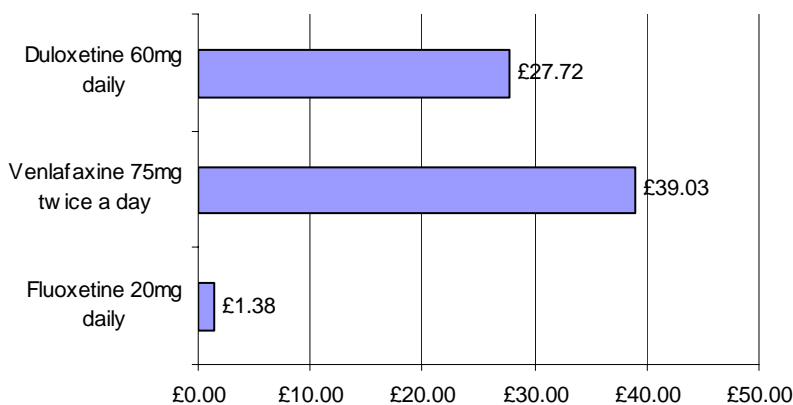
The primary efficacy parameter was the HAMD₁₇ total score. Secondary measures included the Visual Analogue Scale (VAS) for pain, physician assessed CGI-S scale and the Patient Global Impression - Improvement (PGI-I) scale. The Quality of Life in Depression Scale (QLDS) was also measured. The studies were designed to have an 80% power to detect a difference of 2.73 points in the HAMD₁₇ total score in a sample size of 240 patients, assuming a standard deviation of 7 and two-sided significance level of 0.05. The intention-to-treat (ITT) population was used in the efficacy analysis.

Of the 267 patients enrolled in the first study⁵, 128 were randomised to duloxetine and 139 to placebo. Major depressive disorder (MDD) symptoms were significantly reduced by duloxetine compared with placebo, although the difference was less than 2.73 points on the HAM-D₁₇ total score. The estimated

Brand Name, (Manufacturer): Cymbalta, (Eli Lilly)
BNF Therapeutic Class: 4.3.4 'other antidepressant drugs'
Licensed Indications: Treatment of major depressive episodes.
Dosage and Administration: The starting and recommended maintenance dose is 60mg once daily, with or without food.
Marketed: January 2005

Cost Comparisons:

Cost for 28 days treatment [Prices from eMIMS July 2005].



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

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probabilities of response and of remission of depression were also higher with duloxetine than with placebo (65% vs. 42%, $p=0.004$ and 43% vs. 28%, $p=0.064$ respectively). Patient measures of global improvement and quality of life were significantly improved with duloxetine treatment. These are the best predictors of patient satisfaction and long term compliance with treatment.

Of the 245 patients in the second study⁶, 123 received duloxetine and 122 placebo. Compared to placebo, significant improvements in major depressive symptoms were seen after two weeks in the duloxetine group, which continued throughout the trial. The estimated probabilities of response and of remission of depression were also higher with duloxetine treatment than with placebo (62% vs. 29%, and 44% vs. 16%, $p<0.001$ for both). Patients and clinicians global assessment of depression were significantly improved with duloxetine, as were the patients' self assessed quality of life.

Pain and depression often co-exist in clinical practice. Although the populations in the above trials were not selected on the basis of having painful physical symptoms and had low levels of pain at base line, both trials reported that duloxetine resulted in improvements in painful physical conditions. Improvements were noted early in the trial but were not consistently maintained to study end. Greater improvement in pain scores was associated with a higher estimated probability of remission after accounting for changes in the core emotional symptoms of depression (measured by HAMD₁₇).^{5, 6}

A longer-term, unpublished study⁷ was powered to look at time to relapse. Patients who had responded to 12 weeks of therapy with duloxetine 60mg were randomised to duloxetine 60mg daily ($n=136$) or placebo ($n=142$) for 26 weeks (continuation phase). The estimated probability of relapse by 182 days was 19.7% (duloxetine) and 38.3% (placebo) ($p=0.004$).

A head to head study has been performed between duloxetine and venlafaxine in the treatment of MDD. The results showed no significant difference between the two medications on the primary global benefit-risk analysis. It should be noted that the exclusion criteria includes lack of response of current episode of MDD to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for at least 4 weeks.⁸

Three of the six trials noted above as being included in the licensing submission

included the selective serotonin reuptake inhibitors (SSRIs) paroxetine or fluoxetine to demonstrate non-inferiority of duloxetine.^{9,2,3} As the trials did not use the licensed dose of duloxetine, the value of the comparison is limited.

Safety

The most commonly reported adverse events in clinical trials were nausea, dry mouth and constipation ($\geq 10\%$). The majority of adverse events were mild/moderate, occurred early on in therapy and subsided as therapy was continued. Other adverse events included reduced appetite and weight, insomnia, anorgasmia, dizziness, increased sweating, erectile dysfunction and delayed ejaculation.¹⁰ Numerically but not clinically significant increases in ALT, AST and CPK were seen infrequently in duloxetine-treated patients. Urinary hesitation may occur during treatment with duloxetine.

In the 8-week clinical trials the heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Depression is thought to be associated with an increased risk of suicidal thoughts, self-harm, and suicide, persisting until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored.

When discontinuing treatment after a patient has taken duloxetine for more than one week the dose should be tapered over no less than two weeks in order to reduce the risk of discontinuation symptoms. The dose should be halved or administered on alternate days. Discontinuation symptoms include dizziness, nausea, insomnia, headache and anxiety.

Duloxetine should not be used with monoamine oxidase inhibitors (MAOIs), SSRIs, tricyclic antidepressants or St Johns Wort, due to risk of serotonin syndrome. Concomitant use with potent CYP1A2 inhibitors such as ciprofloxacin should be avoided as combination results in elevated plasma concentrations of duloxetine.

Place in Therapy

The place of duloxetine in the treatment of depression is unclear, but there is little to recommend it over established antidepressants for which there is greater experience in use. The trials that

included an active SSRI as comparator were not powered or designed to evaluate any differences in efficacy, but to show non-inferiority between them and duloxetine.

Duloxetine was not included in the most recent NICE guidance on the management of depression, as it was not licensed at the time of writing. The current guidance recommends the SSRIs as first-line antidepressants in routine care. The guidance also recommends that the SNRI, venlafaxine, should only be used in treatment resistant depression in patients who have not responded adequately to two previous antidepressants, and be initiated, and supervised by, specialist mental health medical practitioners or GPs with a special interest in mental health.

As duloxetine is also an SNRI, and there is a lack of data to differentiate it from venlafaxine or to compare it to SSRIs, it might be prudent to restrict the use of duloxetine to those situations in which venlafaxine use might be considered. This may leave duloxetine as the main SNRI that could be prescribed by GPs. However, there are no data to support the use of duloxetine in treatment-resistant depression.

For duloxetine, blood pressure monitoring is only recommended in patients with known hypertension or cardiac disease. Any effects that duloxetine had on the QT interval in the trials did not differ significantly from those seen with placebo; post-marketing data is needed to confirm whether treatment with duloxetine is not associated with cardiac problems.

The full London New Drugs Group document (Feb 05) can be found via [NeLM](#).

**[Appendix I: Bibliography](#)
[Appendix II: Table of Clinical Trials](#)**

Risk Management issues

Duloxetine is also licensed for the treatment of moderate to severe stress urinary incontinence in women, under the trade name Yentreve. The recommended dose of Yentreve is 40mg twice daily. The recommended dose of Cymbalta is 60mg daily. It may be prudent to prescribe duloxetine by trade name to reduce any potential prescribing or dispensing errors.



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Appendix I

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Appendix II: Table: Key results from the trials of duloxetine

Treatment	Key results			
Trial design: Randomised, double blind, placebo controlled, parallel group 9-week trial in 267 patients. ⁵				
	HAMD₁₇	PGI –I	CGI-S	QLDS
Duloxetine 60mg	-10.46	2.59	-1.74	-9.54
Placebo	-8.29	3.00	-1.51	-7.04
	p=0.024 mixed effect model repeated measures (MMRM) analysis p=0.048 last observation carried forward (LOCF)	p=0.014 MMRM analysis	p=0.150 (not significant) MMRM analysis	p=0.032 MMRM analysis
Overall pain - The baseline scores were 25.8 on a 100-point VAS scale. Duloxetine significantly reduced the severity compared to placebo at weeks 2-5 (p≤0.05). Duloxetine also produced significantly greater baseline-to-endpoint improvement on the VAS for overall pain severity (LOCF, p=0.037).				
Back pain - Duloxetine significantly reduced the severity compared to placebo at weeks 1-3 (p≤0.05).				
Trial design: Randomised, double blind, placebo controlled, parallel group 9-week trial in 245 patients. ⁶				
	HAMD₁₇	PGI –I	CGI-S	QLDS
Duloxetine 60mg	-10.91	2.48	-1.87	-8.64
Placebo	-6.05	3.27	-0.97	-4.55
	p < 0.001 (MMRM)	p=<0.001 (MMRM)	p=<0.001 (MMRM)	p=0.001 (LOCF)
Pain scores Duloxetine produced significantly greater improvement than placebo in 5 of the 6 measures (overall pain, back pain, shoulder pain, interference with daily activities and amount of time in pain whilst awake) at least once during treatment (by weeks two and three). At week 9 duloxetine was statistically significantly superior to placebo (p<0.001) for reducing back pain and marginally superior for improving overall pain (p=0.055), headaches (p=0.065), shoulder pain (p=0.083) and time in pain whilst awake (p=0.069). Duloxetine was not superior to placebo in improving interference with daily activities (p=0.220).				
Trial design: Randomised, double blind, placebo controlled, 26-week. Total of 278 patients. ⁷				
	HAMD₁₇	Probability of relapse by 182 days		
Duloxetine 60mg	2.92	p<0.001	19.7%	p=0.004
Placebo	7.82		38.3%	
Trial design: Randomised, double blind, 8 – week acute phase study, followed by a 6-month continuation phase in 367 patients. ⁹				
	HAMD₁₇	Discontinuations at 6 months	Median time to loss of response	
Duloxetine 120mg	-12.1 (0.05) p≤0.001	6.7%	84 days	
Duloxetine 80mg	-11.0 (0.5) p≤0.001	4.3%	63 days	
Paroxetine 20mg	-11.7 (0.5) p≤0.001	2.9 %	77days	
Placebo	-8.8 (0.5)	6.9%	83.5 days	
Trial design: Randomised, double blind, placebo controlled, 8-week trial in 353 patients. ²				
	HAMD₁₇	Response rate at endpoint	Remission rate at endpoint	
Duloxetine 40mg	-2.43 (95% CI -4.66, -0.19), p=0.034	Placebo: 31% Duloxetine 40mg: 44%, p=0.083 vs. placebo	Placebo: 30% Duloxetine 40mg: 35%, p=0.045 vs. duloxetine 80mg	
Duloxetine 80mg	-3.62, (-5.86, -1.38), p=0.002	Duloxetine 80mg: 51%, p=0.009 vs. placebo	Duloxetine 80mg: 50%, p=0.008 vs. placebo	
Paroxetine 20mg:	-1.23 (-3.48, 1.04), p=0.285	Paroxetine: 40%, p=0.204 vs. placebo	Paroxetine: 37%, p=0.091 vs. duloxetine 80mg	
Trial design: Randomised, double blind, 8 – week study in 167 patients. ³				
HAMD₁₇				
Duloxetine 120mg: -9.73 p=0.009		Placebo: -6.61	Fluoxetine 20mg: -7.75	