

NEW DRUG EVALUATION

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DULOXETINE FOR DEPRESSION

Duloxetine is an antidepressant that inhibits the reuptake of noradrenaline and serotonin. It significantly reduced depression severity and improved quality of life scores in two short-term placebo-controlled trials in patients with at least moderately severe depression. Adverse effects, notably nausea, are common but often transient. Since there is limited published evidence for its long-term efficacy and safety and direct head-to-head comparisons with other antidepressants are lacking, its use is not currently recommended.

What is it?

Duloxetine (Cymbalta,[®] Eli Lilly) is an antidepressant that selectively inhibits the reuptake of the neurotransmitters noradrenaline and serotonin.¹ The dose of duloxetine for the treatment of a major depressive disorder is 60 mg daily. It is also licensed for the treatment of stress incontinence under the brand Yentreve,[®] for which the dose is 20 - 40 mg twice daily.

How effective is it?

Two 9-week, randomised, double-blind, placebo-controlled trials have evaluated duloxetine 60 mg a day in the treatment of major depressive disorders, MDD (Hamilton Depression Rating Scale, HAMD, score ≥ 15).^{2,3} The primary endpoint in both trials was the change in HAMD score from baseline. Secondary endpoints included response ($\geq 50\%$ improvement in HAMD score) and remission (HAMD score ≤ 7) rates.

In the first trial (n=245),² duloxetine significantly reduced the overall HAMD score from baseline compared with placebo (-10.91 vs. -6.05, respectively $p < 0.001$) the difference becoming statistically significant after two weeks. The response (45% vs. 23%, $p < 0.001$) and remission (31% vs. 15%, $p = 0.003$) rates were also significantly greater than with placebo.

In the second trial (n=267),³ duloxetine also significantly reduced the HAMD score from baseline compared to placebo at seven weeks (-10.46 vs. -8.29, respectively $p = 0.024$). Although statistically significant, this difference was less than the 2.73 points the study was powered to detect. The response rate (50% vs. 35% with placebo, $p = 0.017$) but not the remission rate (32% vs. 24% with placebo, $p = 0.212$) was significantly greater with duloxetine.

Changes in quality of life scores were evaluated as secondary end-points in both trials. In several of these disease-specific measures, significant improvements were seen with duloxetine compared with placebo. However, consistent improvements in the physician assessed CGI-S (clinical global impression – severity of illness) scale were not demonstrated.

Two pooled analyses of these trials have been published.^{4, 5} The first assessed the onset of effect for duloxetine, although the original studies were not designed to measure this.⁴ The median time to sustained 30% improvement in HAMD was 35 days for duloxetine-treated patients while that for placebo-treated

patients could not be estimated since less than half of the patients met the criteria by the end of the trial. Due to a lack of active comparator, it is difficult to draw conclusions regarding the time to onset of effect.

The second assessed the mean changes from baseline in Visual Analogue Scale (VAS) pain outcomes.⁵ Duloxetine treated patients demonstrated significantly greater improvement in overall pain ($p = 0.016$), back pain ($p = 0.002$) and shoulder pain ($p = 0.021$) at week 9 compared with placebo. However baseline VAS scores within these groups were relatively low (28.6 and 25.8 on a 100 point scale).^{2,3}

Three further studies have been published that support the findings that duloxetine is efficacious for the treatment of major depressive disorder.^{6,7,8} They included a selective serotonin reuptake inhibitor, SSRI (fluoxetine or paroxetine) but were not designed or powered to make a direct comparison with duloxetine. These studies did not use the licensed dose of duloxetine as a comparator (mainly using doses higher than 60mg a day).

How safe is it?

The most common adverse event associated with duloxetine treatment is nausea. In short-term trials this occurred in 30-46% of patients compared with 9-12% treated with placebo.^{3,4} Other side-effects include dry mouth (14%), constipation (11%), insomnia (10%), dizziness (9%), diarrhoea (8%), fatigue (8%), somnolence (7%), increased sweating (6%), decreased appetite (6%), blurred vision (4%), hot flushes (2%) and sexual function disorders (4-2%).⁹ Most adverse reactions usually started early in therapy, and most tended to subside even as therapy was continued.⁹ Similar results have been seen in a 52-week open-label trial (n=1,279) comparing duloxetine 80mg daily with 120mg daily.¹⁰

Urinary hesitation occurred in fewer than 1% of men.⁹ Abrupt discontinuation of treatment may be associated with dizziness, nausea, insomnia, headache and anxiety.⁹ There is little clinical experience of overdose but no fatalities have been reported; ingestion of up to 1400 mg has been recorded.⁹

What other options are there?

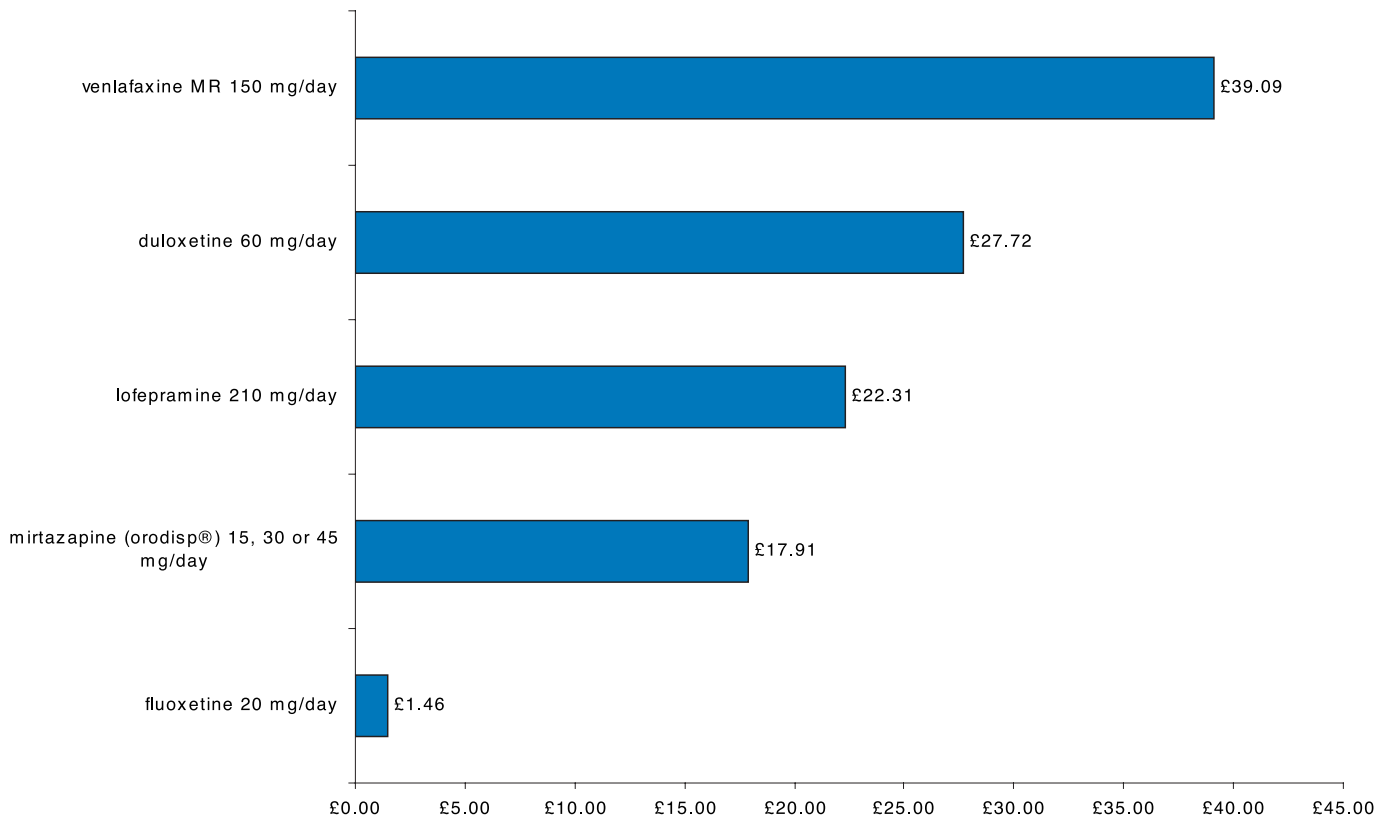
NICE guidelines state that when a drug is required for the treatment of moderate to severe depression, the first choice is an SSRI.¹¹ If initial treatment is not successful and antidepressant therapy is still indicated, options include an alternative SSRI or mirtazapine; consideration should also be given to moclobemide, reboxetine and a tricyclic antidepressant other than dosulepin.

When should duloxetine be used?

Duloxetine has not been compared directly at the licensed dose with other antidepressants in published trials. There is limited evidence of long-term safety and efficacy particularly in patients greater than 75 years of age and those with severe MDD. Therefore, its role in the management of depression cannot currently be defined.

How much does it cost?

Cost for 28 days treatment (prices from eMIMS May 2005/Drug Tariff May 2005)



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

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KEY RCT-randomised controlled trial, R-review, G-guideline

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