

# NEW DRUG EVALUATION

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## DULOXETINE

Duloxetine is a dual serotonin and noradrenaline re-uptake inhibitor licensed for the treatment of stress urinary incontinence. In short-term studies in women with moderate to severe incontinence, duloxetine produced a modest reduction in the frequency of incontinence episodes and a small improvement in quality of life scores. It has not been compared with surgical interventions, which offer high long-term rates of efficacy. The commonest adverse effect of duloxetine is nausea, which causes discontinuation in 5% of patients. The role of duloxetine is currently unclear, but may be an option for women awaiting surgery.

### *What is it?*

Duloxetine is a dual serotonin and noradrenaline re-uptake inhibitor, which increases the tone of the urethral sphincter by stimulating the nervous system in the sacral spinal cord.<sup>1</sup> It is licensed for the treatment of moderate to severe stress urinary incontinence (SUI) in women.<sup>2</sup> The recommended dose is 40 mg twice daily.<sup>2</sup> It is expected that duloxetine will also be licensed in the UK in the next couple of months for the treatment of major episodes of depression.

### *How effective is it?*

Duloxetine has been evaluated in four double-blind randomised placebo-controlled studies,<sup>3-6</sup> each of 12 weeks duration; a meta-analysis of these is currently available in abstract form.<sup>7</sup> These studies had a common protocol and included women experiencing at least 4 incontinence episodes per week, no increased urinary frequency, and in whom urge symptoms did not predominate. The primary endpoints were the median reduction in incontinence episode frequency (IEF) and the incontinence quality of life questionnaire (I-QoL), a 100-point scale.

The meta-analysis included 1913 women aged 22-83 years. The mean baseline IEF was 16.9 per week, representing moderate to severe SUI. The median reduction in IEF associated with duloxetine was 52% compared with 33% with placebo ( $P < 0.001$ ). This is equivalent to approximately one less incontinence episode every other day compared with placebo.<sup>1</sup>

I-QoL score increased by a mean of 9.2 in patients taking duloxetine compared with 5.9 with placebo.<sup>7</sup> Though the difference is statistically significant, the

clinical importance of a 3.3-point difference in a 100-point scale is uncertain.

A double-blind placebo-controlled study involving 109 women with SUI showed that duloxetine was safe and effective in the management of women with SUI awaiting surgery.<sup>8</sup>

In a study available only as an abstract, duloxetine 80 mg/day was compared with pelvic floor muscle training (PFMT), alone and in combination, in 201 women with SUI (median IEF 18.3 - 22.1).<sup>9</sup> After 12 weeks the mean reduction in IEF were 29% for placebo, 35% for PFMT alone, 57% for duloxetine and 57% for duloxetine and PFMT. Both arms including duloxetine were statistically significantly more effective than PFMT alone or placebo.

### *How safe is it?*

The commonest adverse effect associated with duloxetine is nausea (23% of patients vs. 3.7% with placebo).<sup>10</sup> Most cases (94%) occurred during the first 4 weeks; 18% were severe and 5% of women with nausea discontinued treatment.<sup>10</sup> Other common adverse effects occurring significantly more frequently than with placebo included dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%) and diarrhoea (5.1%).<sup>10</sup>

Discontinuation of treatment with duloxetine was significantly more frequent than with placebo (20.5% vs. 3.9%); this was primarily due to adverse effects, notably nausea.<sup>10</sup>

## What other options are there?

There are no other pharmacological treatments for SUI. Alternative strategies include PFMT and surgery.

PFMT is superior to no treatment or placebo but its efficacy compared with other treatments is unclear; reported discontinuation rates range from 12 to 41%.<sup>11</sup>

NICE guidance recommends that surgery should only be considered after a period of conservative treatment from a specialist therapist has been offered and rejected, or has failed.<sup>13</sup> The most successful procedure is Burch colposuspension, which has a one-year continence rate of 85 - 90%. Tension-free vaginal tape is similarly effective and is associated with a shorter hospital stay.<sup>12,13</sup>

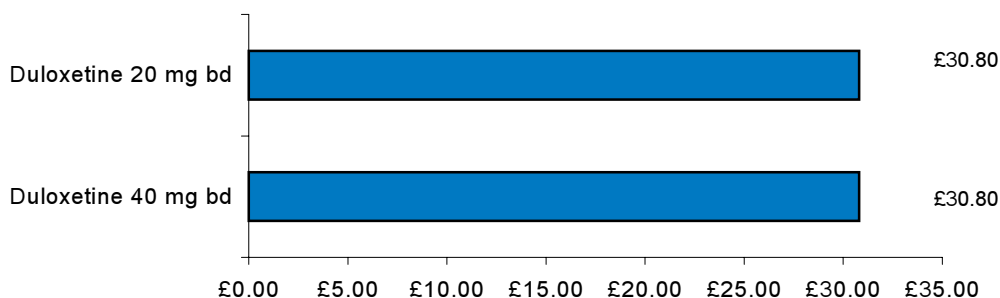
## When should it be used?

The role of duloxetine is uncertain. It is less effective than established surgical interventions, achieving continence in about 10% of women<sup>4</sup>. It produces a small reduction in the frequency of incontinence episodes in most women and only a small improvement in quality of life.

It has not been evaluated for longer than 3 months in placebo-controlled trials or demonstrated in women with mild SUI (IEF < 14 per week). In these women, it may provide no benefit beyond that afforded by more conservative behavioural interventions.<sup>2</sup> One possible application is to reduce incontinence in women awaiting surgery.

## How much does it cost?

### Cost for 28 days treatment (prices from MIMS/BNF December 2004)



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KEY RCT - randomised controlled trial, CT-controlled trial, G-guideline, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

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