An evaluation of the cost-effectiveness of duloxetine as a treatment for women with moderate-to-severe stress urinary incontinence

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared five different options for the treatment of moderate-to-severe stress urinary incontinence (SUI). The options compared were:

- current standard treatment in the authors' setting;
- duloxetine alone as first-line treatment;
- duloxetine in combination with pelvic floor muscle training (PFMT) as first-line treatment;
- duloxetine alone as second-line treatment after the use of PFMT; and
- duloxetine in combination with PFMT as second-line treatment after PFMT.

Standard treatment consisted of PFMT and surgery. The four types of surgery considered the analysis were colposuspension, tension-free vaginal tape, injectables and traditional slings. Duloxetine, the only medicinal treatment in the authors' setting, is a combined serotonin and noradrenaline re-uptake inhibitor.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The target population comprised women with moderate-to-severe SUI (i.e. with 14 or more incontinence episodes a week). No further inclusion or exclusion criteria were reported.

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from sources published between 2002 and 2005. The cost data were derived from sources published in 2004 and 2005. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, augmented by authors' assumptions.
Modelling
The authors constructed a Markov model using Tree-Age software to evaluate the cost-effectiveness of the treatment options. It took the postponement of costs and benefits due to delayed access of SUI services (e.g. outpatients, surgery and PFMT) into account. The time horizon of the model was 2 years and each cycle was 3 months in duration.

Outcomes assessed in the review
There were many different clinical parameters in the model. Those relating specifically to duloxetine were the average percentage reductions in incontinence episode frequency (IEF) in patients who:
- continue duloxetine treatment after 12 weeks of duloxetine alone;
- discontinue duloxetine treatment after 12 weeks of duloxetine alone;
- continue duloxetine after 12 weeks when taken in combination with PFMT;
- discontinue duloxetine after 12 weeks when taken in combination with PFMT;
- have successful or failed outcome with surgery or PFMT (drug as first- and second-line); and
- have successful or failed outcome with PFMT (when drug and PFMT as first- and second-line).

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Overall, the authors used eight primary references as sources of effectiveness evidence.

Methods of combining primary studies
Some estimates of effectiveness were based on a published meta-analysis. The overall surgery success rate was based on the weighted average of the success rate of the four main types of surgery. Further results from individual primary studies were not combined.

Investigation of differences between primary studies
The authors do not appear to have investigated differences between the primary studies.

Results of the review
The results of the review were reported in full detail. However, they are too numerous to be reported here.

The average percentage reduction in IEF in patients who:

continue duloxetine after 12 weeks' duloxetine alone was 55%;

discontinue duloxetine after 12 weeks' duloxetine alone was 42%;

continue duloxetine after 12 weeks' combination treatment (duloxetine plus PFMT) was 76%;

discontinue duloxetine after 12 weeks' combination treatment (duloxetine plus PFMT) was 42;

have successful surgery was 100%; and

have a successful outcome with PFMT (drug and PFMT first-line and drug and PMFT second-line) was 47%.

Methods used to derive estimates of effectiveness
The authors made assumptions to derive some estimates of effectiveness.

Estimates of effectiveness and key assumptions
The authors assumed that the average percentage reduction in IEF was 55% after a failed surgery outcome, 21% after a failed PFMT outcome, and 55% after a successful outcome with PFMT (drug first- and second-line).

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The utility values were either obtained from the literature or were based on authors' assumptions. The authors made assumptions on the basis of data published in the literature. It was reported that utility values were based on the utility of full dryness, which was derived from the literature, multiplied by the corresponding reduction in IEF for each treatment outcome. The estimates were based on the assumption that there is a linear relationship between IEF reduction and utility gain. The benefits were discounted at a rate of 3.5%.

Direct costs
Health service costs were included in the analysis. These covered the first outpatient attendance and visit, the cost of urodynamics, surgery, general practitioner consultation, pelvic floor exercises (PFEs), PFMT training, duloxetine (3 months) and discontinuing duloxetine. The costs and the quantities were reported separately. The cost data were derived from official published sources, with the exception of the PFE leaflet (which the authors assumed to be zero). The quantities of resources used were derived from the model. As the time horizon of the model was 2 years, the costs were appropriately discounted at a rate of 3.5%.

Statistical analysis of costs
The costs appear to have been treated deterministically.

Indirect costs
The indirect costs were not included in the analysis.

Currency
UK pounds sterling (£).
**Sensitivity analysis**

The authors conducted a sensitivity analysis to investigate the robustness of the results to variability in the model parameters. A one-way sensitivity analysis was carried out. The parameters investigated were IEF reduction for failed and for successful surgery, IEF reduction in PFMT failure and PFMT success, and utility associated with full continence. Low and high values were used and reported according to the authors’ judgement. In addition, a two-way sensitivity analysis was carried out using the same parameters and altering the time horizon from 2 to 5 years. A probabilistic sensitivity analysis was also conducted using distributions of model parameters. The distributions used were reported in full.

**Estimated benefits used in the economic analysis**

In the baseline analysis (2-year time horizon), the following benefits were reported.

When duloxetine alone as first-line therapy was compared with standard treatment, the utility gain was 0.0434 for standard treatment and 0.0544 for duloxetine.

When duloxetine alone as second-line therapy was compared with standard treatment, the utility gain was 0.0436 for standard treatment and 0.0518 for duloxetine.

When duloxetine (first-line therapy) plus PFMT was compared with standard treatment, the utility gain was 0.0409 for standard treatment and 0.0909 for duloxetine.

When duloxetine (as second-line therapy) plus PFMT was compared with standard treatment, the utility gain was 0.0399 for standard treatment and 0.0599 for duloxetine.

**Cost results**

In the baseline analysis (2-year time horizon) the following costs were reported.

When duloxetine alone (first-line therapy) was compared with standard treatment, the cost was 620.20 for standard treatment and 717.10 for duloxetine.

When duloxetine alone (second-line therapy) was compared with standard treatment, the cost was 613.90 for standard treatment and 539.50 for duloxetine.

When duloxetine (first-line therapy) plus PFMT was compared with standard treatment, the cost was 617.50 for standard treatment and 910.20 for duloxetine.

When duloxetine (second-line therapy) plus PFMT was compared with standard treatment, the cost was 618.30 for standard treatment and 500.70 for duloxetine.

**Synthesis of costs and benefits**

An incremental cost-effectiveness analysis was performed.

When first-line use of duloxetine alone was compared with standard treatment, it resulted in an incremental cost-effectiveness ratio (ICER) of 8,730. When first-line duloxetine plus PFMT was compared with standard treatment, it resulted in an ICER of 5,854.

Second-line use of duloxetine alone or in combination with PFMT proved to be more effective and less costly (dominant strategies) than standard treatment.

The results of the sensitivity analyses were reported under the assumption of a willingness-to-pay of 30,000 per QALY.

The only parameters that the results were sensitive to were the PFMT effectiveness rates. When duloxetine alone was used as first-line treatment, it was not cost-effective under any assumption except the case where a lower value of...
PFMT success and a high value of utility were used.

The probabilistic sensitivity analysis demonstrated that there was a 90% probability that all treatment options would be cost-effective at 2 years in comparison with standard treatment.

The real-life clinical practice scenario resulted in an ICER of 22,122 when duloxetine is used as first-line therapy and an ICER of 14,906 when used as second-line therapy, compared with standard treatment.

**Authors’ conclusions**

When adopting a "willingness to pay" threshold of 30,000 per quality-adjusted life-year (QALY) gained, duloxetine used as first-line therapy over a 2-year time horizon proved to be cost-effective. When used as second-line therapy, it was more effective and less costly than standard treatment.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators was fully justified. Standard treatment represented current practice in the authors' setting. On the other hand, duloxetine constituted the only pharmaceutical option for the treatment of women with moderate-to-severe SUI in the authors' setting. You should decide if this represents a widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not indicate that a systematic review of the literature was undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. In most cases, the authors appear to have used data from the available studies selectively. In addition, the impact of differences between the studies was not taken into account when estimating effectiveness. The authors made some assumptions to derive various estimates of effectiveness. Although in some cases they justified their assumptions with reference to the medical literature and real life clinical practice, they did not provide any justification for the majority of their choices of assumptions. However, the authors did conduct a number of sensitivity analyses relating to the efficacy estimates. These analyses improve both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates.

**Validity of estimate of measure of benefit**

The authors used QALYs as the measure of benefit in the economic analysis. They reported the source of the utility estimates.

**Validity of estimate of costs**

Although not stated clearly, the perspective of the NHS appears to have been adopted in the economic analysis. All the relevant categories of costs were included. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. The cost data were derived from official published sources. The price year was not reported, which hinders future reflation exercises. The costs and benefits were appropriately discounted, and an extensive sensitivity analysis was carried out to test the robustness of the estimates used.

**Other issues**

The authors did not compare their findings with those from published studies. However, this might have been due to a lack of published studies in this particular research area. The authors directly addressed the issue of generalisability of the results to other settings. The study enrolled women with moderate-to-severe SUI and this was reflected in the authors' conclusions. The authors do not appear to have presented their results selectively. However, had they calculated ICERs comparing all the interventions in ascending order of effectiveness, then duloxetine used as first-line therapy over a 2-year time horizon would have been shown to have had a worse ICER than that actually calculated by the authors.
The main limitations reported by the authors referred to assumptions made for key parameters used in the model. The assumptions were made under the hypothesis of best practice, which may lead to an overestimation of effectiveness. The authors also mentioned that the extension of the time horizon to more than 2 years does not provide robust results.

**Implications of the study**

The authors did not make explicit recommendations for changes in policy or practice, or the need for further research. However, the discussion highlighted areas where more research-based information could be useful.

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