Economic evaluation of duloxetine for the treatment of women with stress urinary incontinence: a Markov model comparing pharmacotherapy with pelvic floor muscle training

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 four strategies for the treatment of women with stress urinary incontinence (SUI). The strategies compared were:

pelvic floor muscle training (PFMT);
duloxetine alone;
the use of duloxetine after an inadequate response to PFMT; and
no treatment. Duloxetine is a serotonin and norepinephrine re-uptake inhibitor that acts on the sacral spinal cord.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
As this was a modelling study, the target population comprised a cohort of 1,000 women aged 50 years and older who suffered from unspecified SUI and presented to the general practitioner (GP) for treatment. No further inclusion or exclusion criteria were reported.

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

Dates to which data relate
The demographic and effectiveness data were derived from sources published between 1990 and 2003. The data on resource use were derived from sources published between 1991 and 2003, while the cost data were mainly derived from a source published in 2000. All costs were reported for the price year 2002.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, augmented by expert opinion.

Modelling
The authors constructed a Markov model, using spreadsheet modelling with Microsoft Excel (Windows 2000), to estimate the cost-effectiveness of the four strategies compared. The health states included in the model were:

- no SUI, defined as zero incontinence episodes (IEs) per week;
- mild SUI, defined as 1 to 9 IEs per week;
- moderate SUI, defined as 10 to 25 IEs per week;
- severe SUI, defined as 26 or more IEs per week; and
- death.

It was reported that, in each health state, patients were divided into those who received treatment and those who did not. The time horizon of the model was 5 years and the length of each cycle was 3 months.

**Outcomes assessed in the review**

The following transition probabilities were reported for PFMT and duloxetine.

- The initial cohort distribution of prevalence of SUI states (mild, moderate and severe).
- The success rate of PFMT and duloxetine during the first cycle, as defined by the following possible transitions: probability of moving from mild SUI to no SUI, from moderate to mild SUI, from moderate SUI to no SUI, and from severe SUI to moderate, mild, or no SUI.
- The probability of non-response in each of the SUI health states during the 1st and subsequent cycles.
- The dropout rates during the 1st and subsequent cycles when the patient was in the following states: no SUI with no change, worsening from no SUI to mild SUI, mild SUI with no change, worsening from mild to moderate SUI, moderate SUI with no change, worsening from moderate to severe SUI, and severe SUI with no change.
- The mortality rates according to age group (50 to 54 years, 55 to 59 years, 60 to 64 years, 65 to 69 years, 70 to 74 years and 75 to 79 years).
- The transition probabilities for letting the disease take its natural course, without treatment being administered.

**Study designs and other criteria for inclusion in the review**

Inclusion and exclusion criteria for study designs to be included in the review were not reported. The authors reported that a large survey and several randomised controlled trials (RCTs) were included in the review to assess outcomes. For example, the natural course of SUI was derived from a large survey (n=1,956), an RCT was used to assess the rates of treatment success with PFMT, and a double-blind, placebo-controlled trial was used to assess the rates of treatment success with duloxetine.

**Sources searched to identify primary studies**

The authors searched MEDLINE (from 1966 through March 2003), ERIC (from 1966 to March 2003), and CINAHL (from 1982 to March 2003) for primary studies. The search terms were reported. The review was restricted to literature written in the English language.

**Criteria used to ensure the validity of primary studies**

No criteria were reported. Recent studies were preferred to older ones in cases where more than one study was available.
Methods used to judge relevance and validity, and for extracting data
An advisory board consisting of “leading experts in the Netherlands” was used to validate the model structure, model assumptions, the definition of the study population, and the outcome parameters.

Number of primary studies included
Overall, the authors used 9 primary studies as sources of effectiveness evidence.

Methods of combining primary studies
The authors used narrative methods (e.g. weighted means) to combine the results from primary studies. In addition, all methods applied to calculate transition probabilities were explicitly reported.

Investigation of differences between primary studies
Differences between the primary studies do not appear to have been investigated in detail.

Results of the review
The results of the review were too numerous to report in this abstract. The most important drivers were as follows.

Initial cohort prevalence was 23.3% for mild SUI, 44.2% for moderate SUI and 32.5% for severe SUI.

The mean treatment success probabilities during the first cycle for the following disease progressions were:

- from mild SUI to no SUI, 0.451 for PFMT and 0.099 for duloxetine;
- from moderate to mild SUI, 0.498 for PFMT and 0.521 for duloxetine;
- from moderate to no SUI, 0.049 for PFMT and 0 for duloxetine;
- from severe to moderate SUI, 0.375 for PFMT and 0.511 for duloxetine;
- from severe to mild SUI, 0.229 for PFMT and 0 for duloxetine; and
- from severe to no SUI, 0 for both treatment options.

The mean non-response to treatment probabilities during the 1st cycle were:

- for no SUI patients, 0.851 in the PFMT group and 0.786 in the duloxetine group;
- for mild SUI patients, 0.400 in the PFMT group and 0.686 in the duloxetine treatment group;
- for moderate SUI patients, 0.304 in the PFMT group and 0.265 in the duloxetine treatment group; and
- for severe SUI patients, 0.247 in the PFMT group and 0.275 in the duloxetine group.

Further outcomes were reported in detail in the paper.

Methods used to derive estimates of effectiveness
It was stated that some estimates of effectiveness were based on expert opinion.

Estimates of effectiveness and key assumptions
It was assumed that the probability of PFMT training cessation would decline linearly after each cycle.
The success rate of duloxetine was only estimated for the first cycle, owing to the assumption that the maximum treatment effect would be achieved after 3 months of treatment.

The treatment discontinuation rate was only applied during the 1st cycle, after which it was assumed to be constant and equal to 0.01%.

The effectiveness of duloxetine, when used after inadequate response to PFMT, was assumed to be equal to the success rate of PFMT during the first cycle and to the success rate of duloxetine during subsequent cycles.

**Measure of benefits used in the economic analysis**
Due to a lack of severity-specific health utility estimates, the number of IEs was used as the measure of benefit in the economic analysis. The total expected number of IEs over the 5-year time horizon was estimated using the IE frequency per week, as derived from the model. The health benefits were discounted at an annual rate of 4%.

**Direct costs**
The health service costs included in the analysis were GP visit, PFMT visit, duloxetine (including pharmacist fee), relevant travel and incontinence pads. The costs and the quantities were reported separately in great detail for each treatment group. The quantities of resources used were derived from the literature, while the costs were derived from either official published sources (e.g. the Dutch Manual for Cost Research) or actual data (e.g. pharmacists’ cost data on incontinence pads). All costs were appropriately adjusted and reported for the price year 2002. As the time horizon of the model was 5 years, discounting was appropriately conducted (annual rate of 4% rate).

**Statistical analysis of costs**
It appears the unit costs have been treated deterministically.

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

**Currency**
Euros (EUR).

**Sensitivity analysis**
The authors carried out various sensitivity analyses to investigate the robustness of the model results to variability in the model parameters. The parameters investigated in the one-way sensitivity analyses were age (55 to 75 years), IE frequency per week (minimum values of 1, 10 and 26, and maximum values of 9, 25 and 40, per respective SUI state), discount rate (0% instead of 4% in the base-case analysis), initial distribution of prevalence of SUI states (49% for mild SUI, 32% for moderate SUI and 19% for severe SUI).

In addition, the authors conducted probabilistic sensitivity analyses in which the impact of variability in the input parameters on the incremental cost-effectiveness ratio (ICER) was investigated. The parameters assigned probability distributions were treatment success, natural course of the disease, quantities of incontinence pads used and IE frequency per week. The authors used Monte Carlo simulation and, for each analysis, 1,000 iterations were run. Various threshold values of willingness-to-pay for each additional benefit were used, and the results were used to plot cost-effectiveness acceptability curves. For each strategy, the net monetary benefit was estimated by subtracting the costs from the effect, multiplied by the willingness-to-pay threshold value, for 1,000 simulations.

**Estimated benefits used in the economic analysis**
The estimated benefits were reported per patient (50 years of age) over a 5-year time horizon.
No treatment resulted in 2,829 IEs, PFMT in 2,174 IEs, duloxetine after PFMT in 1,820 IEs, and duloxetine alone in 2,556 IEs.

**Cost results**
The cost results were reported per patient (50 years of age) over a 5-year time horizon.

No treatment incurred a 5-year cost of EUR 1,070 per patient, PFMT EUR 1,088 per patient, duloxetine after PFMT EUR 2,437, and duloxetine alone EUR 2,822.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was performed.

When PFMT was compared with no treatment, the ICER was EUR 0.03 per IE avoided. When duloxetine after PFMT was compared with PFMT, the ICER was EUR 3.81 per IE avoided. Duloxetine alone was dominated when compared with duloxetine after PFMT (i.e. duloxetine alone was more costly and less effective).

The one-way sensitivity analyses demonstrated that the majority of the results were most sensitive to a discount rate of 0% (i.e. PMFT became the dominant strategy in comparison with no treatment and with duloxetine strategies). The results were also sensitive to different initial prevalence distributions as PFMT became the least costly strategy. Probabilistic sensitivity analyses demonstrated that the duloxetine strategy alone was dominated by all other strategies. Assuming a willingness-to-pay value of EUR 2.3 per IE, the probability that PFMT was cost-effective was 100%. At a higher value this probability decreased, with an increase in the probability that duloxetine after inadequate PFMT response was cost-effective. The threshold value was EUR 3.65 per IE avoided since, below this value, PFMT had a greater probability of being cost-effective and, above this value, duloxetine after PFMT had a greater probability of being cost-effective. Overall the probability that any of the other treatment options (i.e. no treatment or duloxetine alone) was cost-effective was insignificant for all values considered.

**Authors’ conclusions**
The analysis demonstrated that pelvic floor muscle training (PFMT) represented the most cost-effective treatment option for women aged 50 years or older with stress urinary incontinence (SUI). As there is no benchmark for the acceptable cost per incontinence episode (IE) avoided, it is up to policy-makers to determine whether the ratio of EUR 3.81 per IE avoided for women treated with PFMT would be acceptable.

**CRD COMMENTARY - Selection of comparators**
PFMT appeared to represent standard practice in the authors' setting. Although pharmacologic therapy is not approved in the authors' setting (the Netherlands), data in the literature suggest that duloxetine is effective in decreasing the frequency of IEs. You should decide if this represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The demographic data were derived from national statistical sources. However, as a systematic review was not undertaken, the epidemiological and effectiveness data were selectively taken from the literature. Some estimates of effectiveness were derived from a narrative synthesis. The authors did not investigate the impact of differences between the primary studies when estimating effectiveness. In addition, some estimates of effectiveness were based on expert opinion and on authors' assumptions. The authors did not provide any justification for their choice of assumptions, or any information about the methods used to obtain the experts’ opinions. On the other hand, the authors did carry out several sensitivity analyses relating to the efficacy estimates. These may 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 IEs as the measure of benefit in the economic analysis. These were derived from the literature and were analysed in the model. However, this kind of measure does not enable comparisons with the results from other health interventions.

Validity of estimate of costs
Although it was reported at the outset that the analysis was conducted from a societal perspective, the indirect costs were not included in the analysis. Beyond this omission, all categories of health service costs were included in the analysis and the unit costs and resource quantities were reported and analysed separately. This will enable the analysis to be easily reworked for other settings. The quantities of resources used were taken from the literature and estimates used in the base-case analysis were investigated in extensive sensitivity analyses. However, the cost data were treated deterministically and no sensitivity analysis was conducted to assess the robustness of the estimates used; this might introduce uncertainty into the results. Inflation adjustments, the price year and discounting were all appropriately reported.

Other issues
The authors compared their findings with those from other studies and, in general, found them to be in agreement. The issue of the generalisability of the results to other settings was directly addressed and the restricted generalisability of the results was explicitly pointed out. The results of the analysis do not appear to have been presented selectively. The study considered women aged 50 years and older with SUI and this was reflected in the authors' conclusions.

The authors reported a number of limitations to their study. These were mainly related to the limited information available in the literature and to the assumptions on which the model was based. Given the limited data available around the natural course of the disease, the severity of SUI and relevant outcome parameters, the transition probabilities for duloxetine strategy, and the authors' assumptions about the side effects of duloxetine, it was concluded that the analysis had most probably resulted in an underestimation of treatment success. In addition, the interpretation of the results in terms of cost-effectiveness was difficult as there is no established threshold for the cost per IE avoided. On the other hand, severity-specific health utility data were not available and a cost-utility analysis could not, therefore, be performed.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice. However, they called for further economic evaluation of duloxetine especially for patients referred to surgical treatment. The discussion highlighted areas where more research-based information is necessary.

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