Cost-effectiveness of new treatments for overactive bladder: the example of tolterodine, a new muscarinic agent. A Markov model

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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 use of tolterodine as a second-line therapy to alleviate the symptoms of an overactive bladder, when first-line therapy has failed. The comparator was no therapy.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised patients with overactive bladder for whom first-line therapy had failed. The study sample was patients who had participated in three clinical trials. The authors did not provide further details about these patients. Those patients who had incomplete data in the trials were excluded from the study.

Setting
The setting of the study was not specified but it appeared to relate to primary care. The economic study was carried out in Sweden.

Dates to which data relate
The effectiveness data were taken from two studies published in 1997 and a third unpublished study. The utility weights were obtained from a willingness-to-pay survey published in 1997. The date of resources use was not defined. The price year was 1997.

Source of effectiveness data
The effectiveness data were collected from a review of published and/or completed studies.

Modelling
A Markov model was used to estimate the benefits and costs. The model compared tolterodine with no treatment.

Outcomes assessed in the review
The transition probabilities for the Markov states were estimated from the effectiveness data. Markov states were defined according to the severity of symptoms, where severity was assessed on the frequency of voids and leaks (number of micturitions per day and leakages per day). The participants were classified into the following states: state 1 (frequency: less than 9), state 2 (frequency: 9 to less than 12), state 3 (frequency: 12 to less than 15), state 4 (frequency: }
15 to less than 18), state 5 (frequency: 18), and drop-outs from therapy.

**Study designs and other criteria for inclusion in the review**
The three studies included in the review were placebo-controlled, clinical trials with open long-term extensions. The authors did not state whether there were any inclusion or exclusion criteria for the review.

**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**
Three primary studies were included in the review.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
The authors stated that the three primary studies had identical designs, but did not report the methods used to investigate any differences in the results between them.

**Results of the review**
The cohort of patients passed through 12 months of treatment in the Markov model.

In cycle 1 (baseline or no treatment), there were 0.0680 patients in state 1, 0.3196 in state 2, 0.2799 in state 3, 0.1592 in state 4, 0.1733 in state 5, and 0 dropouts.

By 3 months, there were 0.3413 patients in state 1, 0.2855 in state 2, 0.0971 in state 3, 0.0665 in state 4, 0.0662 in state 5, and 0.1434 dropouts.

By 12 months, there were 0.2789 patients in state 1, 0.2334 in state 2, 0.0794 in state 3, 0.0544 in state 4, 0.0541 in state 5, and 0.2999 dropouts.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the quality-adjusted life-year (QALY). The utility rates for the Markov states were obtained by a linear regression analysis of the correlation between the urinary symptoms and the EuroQol (EQ-5D) scores in a Swedish willingness-to-pay survey. The utility for each Markov state was calculated using the mid-point of the symptom range in the different states. The mean utility of the cohort at baseline was assigned to the dropout state. The EQ-5D score is a generic valuation matrix. The authors reported that the EQ-5D was shown to discriminate between people with and without symptoms of overactive bladder. The authors did not report any other details about the survey or the appropriateness of the valuation instrument used.
**Direct costs**
The resources and costs were not reported separately. The authors did not report which direct costs were included in the analysis. However, they did report that in the treatment states, costs were based on drug usage, incontinence pad usage and two visits to the general practitioner. It was unclear whether these costs were estimated for both the tolterodine and control arms. The authors reported that the costs for dropouts were estimated as pad costs only. The quantities and costs associated with pad usage were estimated from actual data. The source of the cost data was not specified. The cost year was 1997. Discounting was not carried out because of the short timeframe of the study.

**Statistical analysis of costs**
There was no statistical analysis of costs.

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

**Currency**
Swedish kroner (SEK). The costs were reported in both SEK and US dollars ($). The conversion rate was $1 = 7.6 SEK.

**Sensitivity analysis**
Sensitivity analyses were performed.

A one-way sensitivity analysis examined the effect of different rates of dropout from treatment with tolterodine.

The model was run over a second year to verify whether the cost-effectiveness ratio was maintained over a longer period of time.

The basic model assigned the mean cost and utility of the cohort at baseline to patients who withdrew from treatment. An alternative model was also run, which assumed that there was one dropout state corresponding to each treatment state.

**Estimated benefits used in the economic analysis**
The utilities applied to each Markov state were as follows: 0.742 for state 1, 0.712 for state 2, 0.676 for state 3, 0.640 for state 4, 0.598 for state 5, and 0.672 for drop-out. The number of months spent in state 1 was considered as controlled or basically normal. The side effects of the treatment were not included in the economic analysis. The authors did not report any differences in life expectancy for the 12 month timeframe of the model. The total utility (QALY) for the 12 month period was 0.6977 for tolterodine and 0.6728 for no treatment.

**Cost results**
The mean total costs of one year’s treatment with tolterodine were 8,595 SEK ($1,131). The mean total cost of no treatment was 3,286 SEK ($342).

**Synthesis of costs and benefits**
The incremental cost of tolterodine was 5,309 SEK and the incremental utility was 0.0249. The extra cost to achieve an additional QALY with tolterodine, compared with receiving no treatment, was 213,042 SEK ($28,032).

The incremental cost of tolterodine was 5,309 SEK. The incremental number of months in state 1 (controlled or normal) was 2.8549. The extra cost for an additional month spent in state 1 when using tolterodine, compared with receiving no treatment, was 1,860 SEK ($215).
Sensitivity analyses:

The rate of drop-outs was varied to 15, 20, 35, 40 and 50%. The incremental cost-utility ratios were: 211,111 SEK at 15% drop-out, 211,466 SEK at 20% drop-out, 213,042 SEK at 35% drop-out, 214,812 SEK at 40% drop-out, and 216,757 SEK at 50% drop-out. The incremental cost-effectiveness ratios were: 1,807 SEK at 15% drop-out, 1,821 SEK at 20% drop-out, 1,879 SEK at 35% drop-out, 1,903 SEK at 40% drop-out, and 1,959 SEK at 50% drop-out.

When the model was run for a second year, the incremental cost-utility ratio was 205,233 SEK and the incremental cost-effectiveness ratio was 1,856 SEK.

For the alternative model, the incremental cost-utility ratio was 233,164 SEK and the incremental cost-effectiveness ratio was 1,761 SEK.

**Authors’ conclusions**

The authors concluded that the incremental cost-utility ratio for tolterodine, when compared with no treatment, was within the range of what is generally accepted as cost-effective in most studies.

**CRD COMMENTARY - Selection of comparators**

The authors reported that a large proportion of patients failed or dropped-out from first-line pharmacological therapy for the symptoms of overactive bladder. In addition, many of these were not treated after failure or drop-out. You should decide whether no treatment is a common practice for patients who fail first-line therapy in your own setting.

**Validity of estimate of measure of effectiveness**

There was insufficient information provided on how the review of the literature was conducted. There was no detailed description of the methods used to search the literature or the sources searched. In addition, the authors did not provide details of the methods used to assess the validity of the identified studies or to extract the data from these studies. The authors reported that they used three identical multinational controlled clinical trials to compare tolterodine with placebo. One of these trials was unpublished.

The authors did not provide a detailed description of the primary studies included, in terms of the methods used to select the patients and the patient sample, and whether a randomisation procedure was used. They also did not report on the power of the individual or combined studies to detect statistically significant differences, or the results of the trials. These factors made it difficult to assess the validity of the data used in the model. The authors defined states of the model according to data from a willingness-to-pay survey. These data were used to verify that the individual states represented discrete differences in health that were important to the patients. The authors did not report the methods used to validate whether the structure of the model, in terms of the sequence of events, adequately reflected routine practice. You should consider whether the structure of the model, and the definition of the states included, reflect practice in your setting.

Only three months of effectiveness data were available from the clinical trials. The authors assumed that there were no further treatment effects after this point, in order to estimate the outcomes and costs at 12 months for the tolterodine arm. They also assumed that patients in the control group would not move between the initial health states over the 1 year timeframe. These assumptions required the additional assumption that there is no progression or remission of the condition in either the treatment or control groups. The authors also assumed that the patients in both groups did not seek alternative methods of dealing with the symptoms.

Sensitivity analyses were used to test the robustness of the results to changes in the drop-out rate, and to extrapolate the 3-month data to 2 years rather than 12 months. However, the authors did not report whether sensitivity analyses were used to investigate the effect of variations in the transition probabilities used for either the treatment or control groups, or the use of a shorter timeframe (e.g. modelling over 3 or 6 months), on the results. You should consider whether the assumptions and data used are realistic and valid for the question addressed in your own setting.
Validity of estimate of measure of benefit
The authors reported that the willingness-to-pay survey in Sweden found that the symptoms of incontinence have considerable impact on the quality of life of patients with overactive bladder. Therefore, the choice of QALYs seems to have been appropriate for assessing the benefits of treatment. The authors also reported that the EQ-5D score was shown to discriminate between people with and without symptoms of overactive bladder.

The model included the impact of side-effects or adverse events, in so far as they resulted in patients discontinuing treatment. The drop-outs were assigned the mean utility of the cohort at baseline, or entry to the model. This could have underestimated the utility of patients who discontinued treatment because the disease had resolved. However, it could have overestimated the utility of patients who discontinued due to the detrimental effects of adverse events on their health status and/or those who then progressed to worse health states following the discontinuation of treatment. In the sensitivity analysis, the authors included one drop-out state for each health state at the point of drop-out. The next lowest utility value was used for the drop-out state. For example, if patients in state 1 discontinued treatment they were assigned the utility of state 2. This could also have under- or overestimated utility as for the discontinuation of treatment. However, the results of the model did not appear to be sensitive to these changes.

Validity of estimate of costs
Not all the resource use and price data were reported separately. The authors noted that the cost of tolterodine was not known at the time of the analysis and that they used the expected, rather than the actual, market price of the drug. However, they did not report the dose of tolterodine used in the analysis, or the source of the data used to estimate the dose. The patterns of incontinence pad usage from the multinational clinical trials were adjusted to those for Swedish patients in the trial. The authors did not report the number of pads used in the trial or the model, or the price per pad.

The authors noted that the cost analysis was limited to general practitioner visits, tolterodine and pads. The cost of additional treatment of symptoms, or the treatment of side-effects, was not included. The patients who discontinued treatment were assigned the mean costs of pads for the cohort at baseline. This may have underestimated the cost of discontinuation. The pad usage was extrapolated from the 3-month clinical trial data to the 1-year timeframe of the model. No sensitivity analyses testing the robustness of the results to variations in resource use or price estimates were reported. The costs were not discounted, which was appropriate given the 1 year timeframe of the study.

Other issues
The authors commented that the model may have underestimated quality of life in these patients over time, as they became accustomed to the improvement of their symptoms and abandoned coping mechanisms. However, the real change in utility may have been less than that estimated in the model, as patients may have had more severe symptoms and co-morbidities. There was little information on the patients in the three clinical studies. In addition, the authors noted that there was little published information about the quality of life or costs of treatment for people with overactive bladder symptoms. This means that, at the time of the analysis, it was not possible to compare the results with other studies. The authors did not discuss the extent to which the results of the analysis were generalisable to other settings.

The authors noted that the results were generated by a model using several assumptions, and should be treated with caution. They also noted that tolterodine was still under investigation at the time of analysis, and that further data can only be gathered once it is on the market.

Implications of the study
The treatment of overactive bladder with a well-tolerated pharmacological treatment, such as tolterodine, was cost-effective. The authors also concluded that treatment with tolterodine was as cost-effective as other interventions, which they did not give any details of. Further long-term research is needed to confirm the results.

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