Cost-effectiveness analysis of extended-release formulations of oxybutynin and tolterodine for the management of urge 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
Four treatments for patients with urge incontinence were examined. The specific treatments were oxybutynin extended-release (Oxy-ER), tolterodine extended-release (Tol-ER), oxybutynin immediate-release (Oxy-IR) and tolterodine immediate-release (Tol-IR).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with urge incontinence associated with an overactive bladder.

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 studies published between 1999 and 2001. The costs and most resource use data were estimated from a database published in 2000. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies.

Modelling
Empirical models (equations and functions) were used to extrapolate drug efficacy over a 1-year time horizon. Patient-level data obtained from clinical trials were found to be characterised by negative binomial distributions. Two equations were found to fit mean weekly number of episodes of urinary incontinence with time and variance with time. Persistence was estimated from the proportion of patients who remained on their initially prescribed drug, with an exponential function found to fit the data best.

Outcomes assessed in the review
The outcomes estimated from the literature were treatment efficacy (in terms of the weekly number of incontinent episodes) and persistence (which referred to patients remaining on their initial drug treatment).
Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify the primary studies. The following inclusion criteria were used:

randomised, actively controlled trials (comparing Oxy-ER with Oxy-IR, Tol-IR and/or Tol-ER; or Tol-ER with Oxy-IR and/or Tol-IR);

patients with urge urinary incontinence as defined by the International Continence Society;

the total number of weekly incontinent episodes recorded as an end point;

fixed dose or dose titration (not forced dose escalation);

patients and investigator blinded to treatment allocation.

Treatment effectiveness came from three clinical trials, while persistence data were obtained from the IMS MediPlus UK dataset. One trial compared Oxy-ER 10 mg/day with Tol-IR 2 mg twice daily in 378 patients over a 12-week period. A second trial compared Tol-ER 4 mg daily with Tol-IR 2 mg twice daily in 1,529 patients, again over 12 weeks. The third trial compared Oxy-ER (median dose 10 mg/day) and Oxy-IR (median dose 15 mg/day) in 105 patients over a median time period of approximately 5 weeks. Details of the three clinical trials, in terms of the patient population and results, were reported.

Sources searched to identify primary studies
The primary studies were identified by searching the Cochrane Controlled Trials Register, MEDLINE and EMBASE using broad search strategies (oxybutynin and tolterodine in free text search) and by contacting pharmaceutical companies. The searches were run from the earliest date available (e.g. 1966 for MEDLINE and 1988 for EMBASE).

Criteria used to ensure the validity of primary studies
The validity of the primary studies was ensured by the inclusion of randomised, double-blind clinical trials.

Methods used to judge relevance and validity, and for extracting data
The use of clinical trials ensured a high internal validity of the primary estimates.

Number of primary studies included
Four primary studies provided the clinical evidence.

Methods of combining primary studies
The combined effect of treatment and persistence was calculated, starting from patient-level data that were entered into specific equations. The trial that compared Oxy-ER and Tol-IR was used as the reference (baseline drug efficacy) against which the others were compared. This trial was chosen because it included two drugs also investigated in the other two trials.

Investigation of differences between primary studies
Adjustments for baseline differences in patient populations between studies were made.

Results of the review
The total number of incontinent episodes per week was:
26.3 (standard deviation, SD=18.5) for Oxy-IR and 29.3 (SD=24.2) for Oxy-ER in one trial,
28.4 (SD=17.8) for Oxy-ER and 28.0 (SD=18.3) for Tol-IR in a second trial (reference trial), and
23.2 for Tol-IR versus 22.1 for Tol-ER in the third trial.

The efficacy and persistence data were then reported as coefficients and variables of the equations used to derive the combined estimates.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the annual number of incontinence-free weeks. This was estimated from the equations used to combine the primary estimates obtained from the literature. The annual number of incontinence episodes was also reported.

**Direct costs**
The analysis of the costs was carried out from the perspective of the NHS. It included direct medical costs of drugs, appliances, containment products, staff and overheads. The unit costs were presented separately from the quantities of resources used, and a very detailed list of cost categories was provided. NHS costs and resources used came from the Continence Foundation, which relied on typical NHS sources. The drug costs were estimated from the British National Formulary. All costs were inflated to 2001 values using inflation indices. Discounting was not relevant as the costs were incurred during one year.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not taken into consideration.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
The issue of uncertainty in the proportion of patients who discontinued therapy was initially addressed by considering three scenarios alternative to the base-case analysis. In the first scenario, all patients who discontinued therapy reverted to baseline-disease characteristics. In the second scenario, patients who discontinued therapy adopted the disease characteristics observed in a cohort of patients receiving placebo. In the third scenario, all patients continued with therapy for the duration of the analysis (full persistence). Subsequently, several univariate sensitivity analyses were carried out on key parameters. The sources of the alternative ranges were not stated.

**Estimated benefits used in the economic analysis**
The annual number of incontinence-free weeks was 7.5 with Oxy-IR, 11.1 with Oxy-ER, 9.6 with Tol-IR and 10.9 with Tol-ER.

The annual number of incontinence episodes was 997 with Oxy-IR, 780 with Oxy-ER, 819 with Tol-IR and 766 with Tol-ER.

**Cost results**
The total annual costs were 39.61 with Oxy-IR, 78.77 with Oxy-ER, 74.21 with Tol-IR and 63.91 with Tol-ER.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios (ICERs; i.e. the incremental cost per incontinent-free week) were calculated to combine the costs and benefits of the four treatment strategies that were also compared with no treatment (placebo).

The ICER was 5.26 for Oxy-IR versus no treatment, 84.82 for Oxy-ER versus Tol-ER, and 7.14 for Tol-ER versus Oxy-IR. Tol-IR was dominated by Tol-ER.

The scenario analysis showed that Tol-IR and Tol-ER were dominated in all scenarios by Oxy-IR, while the ICER with Oxy-IR versus no treatment ranged from 2.58 to 16.59. The ICER with Oxy-ER versus Tol-ER was 87.43 in scenario 1 and 1,375.5 in scenario 2, but it was dominated by Oxy-IR in scenario 3. The univariate sensitivity analysis showed that the base-case results were robust to variations in the clinical and economic data. Overall, persistence was the most influential factor.

**Authors’ conclusions**

Oxybutynin immediate-release (Oxy-IR), oxybutynin extended-release (Oxy-ER) and tolterodine extended-release (Tol-ER) might be cost-effective options for the treatment of overactive bladder or urge urinary incontinence. The choice of the most cost-effective strategy would depend on the payer’s willingness-to-pay for an additional unit of benefit (incontinent-free week).

**CRD COMMENTARY - Selection of comparators**

The authors justified their choice of the comparators. The strategies compared were appropriate for the study question since they were widely used in the UK. The authors reported the dosages and length of treatment. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data were obtained from a systematic review of the literature, the methods and conduct of which were explicitly reported. The authors provided a comprehensive description of the approach used to extract and then combine the primary estimates. The baseline characteristics of the patients included in the clinical trials were reported. Inclusion criteria were reported, and the inclusion of clinical trials enhances the robustness of the primary estimates. Further, the authors pointed out that the primary studies were well designed and executed. All studies were adequately powered and balanced at baseline. The issue of homogeneity among the primary studies was addressed by adjusting for differences in the patient populations. The issue of uncertainty around some clinical data (i.e. persistence) was addressed in the sensitivity analysis.

**Validity of estimate of measure of benefit**

The summary benefit measure was specific to the disease considered in the study. It would not be comparable with the benefits of other health care interventions. The impact of the treatments on quality of life was not evaluated, although the authors stated that symptoms of disease reduce the patients’ quality of life and impair normal functioning and daily activities.

**Validity of estimate of costs**

The analysis of the costs was consistent with the stated perspective and typical NHS sources of costs were used. A detailed breakdown of the cost items was reported. Extensive information on the unit costs and resource quantities was provided, which enhances the possibility of carrying out reflation exercises in other settings. All economic data were treated deterministically and sensitivity analyses were performed only on some costs. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors stated that a previous cost-effectiveness analysis carried out from the perspective of the NHS produced results similar to those observed in the current study. In terms of the external validity of the study results, the authors stated that the incorporation of measures of side effects and persistence was an attempt to translate efficacy data typical of a clinical trial setting to real practice; this is an interesting feature of the analysis. The issue of the generalisability of the results to other settings was not explicitly addressed, although several sensitivity analyses were performed. Extensive information on the calculation of treatment effect was provided. However, the authors noted that the use of a longer timeframe would have been useful. Moreover, it was pointed out that the possibility of switching across treatments was ignored, although the authors did provide a justification for this approach.

Implications of the study
The study results suggest that Oxy-IR, Oxy-ER and Tol-ER are efficient options for the treatment of urge incontinence.

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Benzhydryl Compounds /administration & dosage /economics /therapeutic use; Cost-Benefit Analysis; Cresols /administration & dosage /economics /therapeutic use; Delayed-Action Preparations; Drug Costs; Female; Humans; Male; Mandelic Acids /administration & dosage /economics /therapeutic use; Middle Aged; Models, Economic; Muscarinic Antagonists /administration & dosage /economics /therapeutic use; Phenylpropanolamine /administration & dosage /economics /therapeutic use; Randomized Controlled Trials as Topic; Time Factors; Tolterodine Tartrate; Treatment Outcome; Urinary Incontinence /drug therapy /economics

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