An economic evaluation of doxazosin, finasteride and combination therapy in the treatment of benign prostatic hyperplasia

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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 examined finasteride (FIN), a 5-alpha-reductase inhibitor, either alone or in combination with doxazosin (DOX), an alpha-blocker, for the treatment of benign prostate hyperplasia (BPH). The doses used were 5 mg FIN once daily and 4 mg DOX once daily.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population comprised men with moderate to severe symptoms of BPH and an enlarged prostate, who had not undergone surgical treatment with transluminal resection of the prostate (TURP). The base-case hypothetical patient was a 64-year old white male with a quasi-American Urologic Association (AUA) symptom score of 15, a prostate volume of 55 mL, and a serum prostate-specific antigen (PSA) of 2.8 ng/mL.

Setting
The setting was community care. The economic study was carried out in Ontario, Canada.

Dates to which data relate

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

Modelling
A model was used to combine the effectiveness data with data on resource use and patient preferences. Also, to extrapolate the clinical trial data to a 15-year timeframe. A semi-Markov model was used. The model included acute urinary retention (AUR), surgery and death as possible events.

Outcomes assessed in the review
The outcomes assessed were the stratified probability of AUR, TURP, surgery and its outcomes. The review also assessed the utility weights associated with relevant health states in the model.
Study designs and other criteria for inclusion in the review
The two clinical trials included in the review were randomised controlled trials. These both recruited patients with moderate to severe BPH. The authors did not report any inclusion or exclusion criteria.

Sources searched to identify primary studies
The method by which the primary studies were identified was not described. It appears that the selection might have been a convenience sample of two prominent studies published since a similar economic evaluation conducted by the Canadian Coordinating Office of Health Technology Assessment.

Criteria used to ensure the validity of primary studies
The method of study selection indicated that a formal review of the literature was not conducted.

Methods used to judge relevance and validity, and for extracting data
The method of study selection indicated that a formal review of the literature was not conducted.

Number of primary studies included
The review was based on two primary studies, the Proscar Long-Term Efficacy and Safety Study (PLESS) and the Medical Therapy of Prostatic Symptoms (MTOPS) study.

Methods of combining primary studies
The PLESS was identified as providing superior information for the study question, owing to it having inclusion criteria that specified patients with an enlarged prostate. Where both trials reported on any one outcome measure, the data from this preferred study was used. The MTOPS study was used to provide data on outcomes and treatments not included in the preferred trial.

Investigation of differences between primary studies
The authors reported that the primary distinction between the two trials was that patients were required to have an enlarged prostate upon digital rectal examination in the PLESS, but not the MTOPS study. They provided the average prostate volume at baseline to illustrate the difference in the study populations. They also acknowledged that the lower prostate volume in the MTOPS study made it less suitable for the study question.

Results of the review
The probability of AUR for all patients at year 4 was 1.3% with watchful waiting (no treatment), 0.7% with FIN, 1.0% with DOX and 0.4% with combination therapy. Data were also provided in the paper in a stratified manner (PSA > 1.3 ng/mL and PSA > 3.2 ng/mL).

The probability of surgery after AUR was 74.5% with watchful waiting, 40.0% with FIN, 74.5% with DOX and 40.0% with combination therapy.

The probability of elective TURP for all patients at 4 years was 2.5% with watchful waiting, 1.4% with FIN, 2.4% with DOX and 0.8% with combination therapy. Data were also provided in the paper in a stratified manner (PSA > 1.3 ng/mL and PSA > 3.2 ng/mL).

The probabilities for intermediate surgical outcomes (proportion of patients) were:
mild prostatism, 0.723 (90% confidence interval, CI: 0.54 - 0.9);
mild prostatism with incontinence, 0.021 (90% CI: 0.018 - 0.025);
mild prostatism with impotence, 0.136 (90% CI: 0.034 - 0.324);
no improvement in symptoms of prostatism, 0.095;
total urinary incontinence, 0.01 (90% CI: 0.007 - 0.014);
death, 0.015 (90% CI: 0.005 - 0.033).

The probabilities for longer term surgical outcomes (proportion of patients) were:
urethral stricture, 3.1 (90% CI: 0.5 - 9.7);
bladder neck contracture, 1.7 (90% CI: 1.3 - 2.1);
re-treatment probability per year, 2.1 (90% CI: 1.9 - 2.3).

The average utility at baseline was 0.8743.

The change in utility per change in AUA symptom score was 0.0138, while the change in utility following successful TURP was 0.0440.

Measure of benefits used in the economic analysis
The measure of health benefit used was the quality-adjusted life-years. The utility estimates were drawn from published studies (see 'Effectiveness Results' section above for values). The authors did not state the method of valuation or which values were used.

Direct costs
Resource use was reported separately from the costs. The direct costs included in the analysis were those of the health service, which comprised drug-related costs, urologist visits, diagnostic tests, monitoring, AUR costs and TURP costs. Resource use was derived from published studies and expert opinion. The prices used were based on published pricing lists, published estimates and charges. Discounting was relevant, as the costs were incurred during more than one year, and a rate of 5% per annum was used. The study reported the average costs for the price year 2003.

Statistical analysis of costs
Patient-level data were not available for statistical analysis. The variability surrounding the cost estimates derived from the literature was not reported.

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

Currency
Canadian dollars (Can$).

Sensitivity analysis
Several one-way sensitivity analyses were conducted to investigate variability in the data, extrapolation and generalisability of the results. The sensitivity analyses investigated the timeframe of the model, the discount rate, the probability of AUR and TURPS, the costs of AUR and TURP and the utility weights, and the effects of treatment on symptom improvement. The ranges used appear to have been selected on the basis of variations in the published literature.
Estimated benefits used in the economic analysis
For all patients, the estimates of QALYs gained over the 15-year timeframe of the model were 8.608 with watchful waiting, 8.787 with DOX, 8.709 with FIN and 8.930 with combination therapy. The health benefits were discounted at a rate of 5% per annum.

Cost results
For all patients, the total cost over the 15-year timeframe of the model was Can$2,254 with watchful waiting, Can$4,615 with DOX, Can$6,767 with FIN and Can$9,477 with combination therapy. The costs were discounted at a rate of 5% per annum.

Synthesis of costs and benefits
The costs and health benefits were synthesised to estimate the cost per QALY gained for FIN and combination therapy in comparison with DOX. FIN was dominated by DOX in the analysis. The cost per QALY gained with combination therapy compared with DOX was $34,085 for all patients. The results were relatively sensitive to reducing the model timeframe to 4 years, and to reducing the treatment effect on symptom improvement by 50%. Combination therapy appears to have been more cost-effective in patients with PSA greater than 3.2 ng/mL than in patients with PSA between 1.3 and 3.2 ng/mL.

Authors' conclusions
Combination therapy is a cost-effective pharmacologic treatment for patients with moderate to severe benign prostatic hyperplasia (BPH). Finasteride (FIN) might be suitable for patients who have failed doxazosin (DOX) and do not wish to progress to surgery, as it appears cost-effective relative to watchful waiting.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was justified as representing current practice in the authors' setting. You should decide whether DOX is a widely used treatment in your own setting. The authors acknowledge that an alternative alpha-blocker, tamsulosin, is increasingly used in their setting, and that this will impact on the incremental cost-effectiveness of FIN and combination therapy. They also acknowledged that there are a greater range of surgical options available. They justified their inclusion of only TURP in their model on the basis that it is the 'gold' standard and has the most available data.

Validity of estimate of measure of effectiveness
The authors did not report a systematic review of the literature. The authors were selective in their use of study evidence, as they wished to base their economic evaluation on two recent, prominent trials. The failure to systematically search for all available evidence meant that the potential for bias in the study results was not minimised. The authors used data from the available studies selectively. They used the PLESS where possible, owing to its inclusion criteria, and the MTOPS study for parameters not available in the PLESS. The analysis relied on the assumption that the relative treatment effect was independent of the baseline prostate volume in the two trials. The authors investigated the impact of basing their economic evaluation primarily on the MTOPS study in a sensitivity analysis. The trial data were extrapolated using a deterministic Markov model, thus uncertainty in the estimated treatment effects was not propagated through the model results.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a semi-Markov model and utility estimates from the literature. The study estimated a constant QALY change per change in AUA symptom score, which assumes that the AUA symptom score has interval properties, and this is unlikely to be true. The authors acknowledged that they did not include any disutility associated with surgery in their model. The baseline utility for patients with moderate to severe BPH was estimated to be 0.874, which appears to be quite high for an elderly hypothetical population. However, the authors did not provide enough detail of how this utility estimate was calculated to be able to assess its validity.
Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. The costs were reported separately from the quantities assumed for the model, which improves the generalisability of the model results. Resource use was estimated on the basis of published sources and expert opinion. Some sensitivity analyses were conducted around the costs, although a justification for the ranges used was not provided. The use of expert opinion rather than directly measured resource use increases the uncertainty in the model results. A statistical analysis of the prices was not performed, and some charges were used to proxy prices. This may limit the generalisability of the model results to settings outside of Canada. The costs were discounted appropriately and the price year was reported.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. They justified the application of data from North American sources to the Canadian setting. The issue of generalisability to settings outside of Canada was addressed in terms of the sensitivity analyses. The authors did not present their results selectively. The model was based on the selective use of the available evidence on DOX and FIN, so the results should be interpreted with caution. The authors concluded that FIN is cost-effective in patients who have failed DOX and who do not wish to progress to surgery. This conclusion goes beyond the scope of the model, as no attempt was made to model the use of FIN conditional on having failed treatment with DOX. The authors' conclusions about combination therapy reflected the scope of the analysis.

Implications of the study
The findings of the study suggested that combination therapy is a cost-effective pharmacologic treatment (under $40,000 per QALY) for patients with moderate to severe BPH. FIN might also be suitable for patients who have failed DOX and who wish to avoid surgery. This latter point may need further research to validate it. The authors did not make any specific suggestions for further research.

Source of funding
Supported by Merck Frost Canada.

Bibliographic details

PubMedID
15380054

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic alpha-Antagonists /economics /therapeutic use; Cost-Benefit Analysis; Doxazosin /economics /therapeutic use; Drug Therapy, Combination; Enzyme Inhibitors /economics /therapeutic use; Finasteride /economics /therapeutic use; Humans; Male; Middle Aged; Models, Economic; Prostatic Hyperplasia /drug therapy /economics

AccessionNumber
22005006105

Date bibliographic record published
31/12/2005