A health economic model to assess the long-term effects and cost-effectiveness of orlistat in obese type 2 diabetic patients

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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 orlistat (Xenical) in obese Type 2 diabetic patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised obese Type 2 diabetic patients without micro- or macrovascular complications. The could be suffering or not suffering from hypertension and/or hypercholesterolaemia.

Setting
The setting was not explicitly stated, but appears to have been that of the health service. The economic study was carried out in Belgium.

Dates to which data relate
The dates to which the effectiveness data related were not reported. The costs were reported for 1998, and were adapted to 2000 using a 3% inflation rate.

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

Modelling
A Markov state transition model was used to predict the complication rates and mortality over a 10-year period, with and without treatment with orlistat for 2 years. The authors assumed that the patients could not evolve at the same time to the micro- and macrovascular complications, which was a conservative assumption. It was assumed in the model that 5 years after discontinuing orlistat, the risk for complications returned to the values of the placebo. This assumption was made on the evidence that almost all weight is regained 5 years after a weight reduction programme is stopped.

Outcomes assessed in the review
The outcomes assessed in the review for both orlistat and no orlistat, were the yearly event rates of morbidity and mortality for obese Type 2 patients free of events at the beginning of the study, and without hypertension and hypercholesterolaemia. These yearly event rates for morbidity and mortality were assessed in terms of total death,
nonvascular death, macrovascular complications and microvascular complications. Macrovascular complications included nonfatal stroke, fatal stroke, total stroke, angina, nonfatal myocardial infarction (MI), fatal MI, sudden death, total coronary heart disease (CHD), and total macrovascular complications. Corrections were calculated for the base risks for MI, stroke, all-cause mortality and microvascular disease among obese patients with arterial hypertension. They were also calculated for nonfatal and fatal MI for obese patients with both arterial hypertension and hypercholesterolaemia. These outcomes were included in the model as input parameters.

The effect on mortality and micro- and macrovascular complications of treating patients with orlistat was assessed in two steps:

1. the effect of weight loss with orlistat on the risk factors, and
2. the effect of risk factors on morbidity and mortality.

**Study designs and other criteria for inclusion in the review**
The authors did not report any criteria for including studies in the review. The majority of the effectiveness data were derived from a randomised double-blind study, although the results were combined with data derived from other studies such as prospective observational studies.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
At least nine published studies of several types were included in the review. These included a randomised double-blind study and two prospective observational studies. These studies were published between 1992 and 2000.

**Methods of combining primary studies**
The majority of the effectiveness data were collected from the randomised double-blind study. These were with the results of the other included studies using a narrative method.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The base rates (without orlistat) in obese patients, free of events and without hypertension and hypercholesterolaemia, were as follows:

- total death rate, 0.0135;
- nonvascular death rate, 0.0068;
- nonfatal stroke rate, 0.0016;
fatal stroke rate, 0.0016;
total stroke rate, 0.0032;
angina rate, 0.0059;
nonfatal MI rate, 0.0068;
fatal MI rate, 0.0043;
sudden death rate, 0.0008;
total CHD rate, 0.0178;
total macrovascular complication rate, 0.0210; and
microvascular complication rate, 0.0067.

The rates for obese patients, free of events and without hypertension and hypercholesterolaemia, but treated with orlistat were as follows:
total death rate, 0.0099;
nonvascular death rate, 0.0053;
nonfatal stroke rate, 0.0009;
fatal stroke rate, 0.0013;
total stroke rate, 0.0022;
angina rate, 0.0064;
nonfatal MI rate, 0.0052;
fatal MI rate, 0.0027;
sudden death rate, 0.0005;
total CHD rate, 0.0149;
total macrovascular complication rate, 0.0171; and
microvascular complication rate, 0.0052.

The correction factors for obese diabetic patients with arterial hypertension were 1.03 for MI, 1.10 for stroke, 1.09 for all-cause mortality, and 0.81 for microvascular disease.

The correction factors for obese diabetic patients with both arterial hypertension and hypercholesterolaemia were 1.99 for nonfatal MI, and 1.98 for fatal MI.

For obese diabetic patients with hypercholesterolaemia, the same base risks for fatal and nonfatal MI as for patients without hypercholesterolaemia and given no orlistat treatment, were applied.

**Measure of benefits used in the economic analysis**
The measures of benefits used were the life-years gained (LYG) and the estimated mortality rate for the 10-year study
period.

**Direct costs**
The direct costs included in the cost analysis were the total health care costs per year for patients without complications (1,726 euros), with microvascular complications (2,578 euros), with macrovascular complications (3,844 euros), and with both micro- and macrovascular complications (5,443 euros). The resource quantities and the unit costs were not reported separately. These costs were included in the Markov model to extrapolate the costs for the 10-year period considered in the study. The costs were estimated from one published study. Discounting of the costs was carried out in the sensitivity analysis using a 3% discount rate. As the costs were incurred over a 10-year period, discounting would have been relevant for the base-case analysis. The costs reported were the average and incremental costs. The costs were reported for the year 1998 and were adapted to year 2000 using a 3% inflation rate.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
Euros.

**Sensitivity analysis**
Sensitivity analyses were carried out to analyse variability in data when:

- discounting of the costs was performed at a discounting rate of 3%;
- the effects of orlistat on the risk of events were increased and decreased in one standard deviation for obese diabetic patients without arterial hypertension and without hypercholesterolaemia, and for obese diabetic patients with arterial hypertension and with hypercholesterolaemia; and
- the catch-up period for recovering the weight lost was reduced to 2.5 years.

**Estimated benefits used in the economic analysis**
The authors reported the incremental benefits in terms of the number of LYG with orlistat, compared with placebo.

For obese diabetic patients without arterial hypertension and without hypercholesterolaemia at the beginning of the study, orlistat increased the number of LYG by 0.08 when compared with placebo.

For obese diabetic patients with arterial hypertension and without hypercholesterolaemia at the beginning of the study, there was an increase of 0.204 LYG with orlistat when compared with placebo.

For patients with hypercholesterolaemia but without arterial hypertension at the beginning of the study, the number of LYG was 0.227 with orlistat when compared with placebo.

Finally, among patients with arterial hypertension and hypercholesterolaemia, orlistat increased the number of LYG by 1.641 when compared with placebo.

The estimated mortality rate over the 10-year study period was 11.7% in the orlistat group, compared with 12.7% in the control group.
Cost results
When obese diabetic patients were not treated with orlistat, the cost for a patient without arterial hypertension and without hypercholesterolaemia at the beginning of the study was 15,573 euros; the cost for a patient with hypercholesterolaemia but without arterial hypertension was 15,741 euros; the cost for a patient with arterial hypertension and without hypercholesterolaemia was 15,450 euros; and the cost for a patient with hypercholesterolaemia and arterial hypertension was 15,444 euros.

When obese diabetic patients were treated with orlistat, the cost per patient was 17,180 euros for those who did not have hypercholesterolaemia or arterial hypertension at the beginning of the study; 17,255 euros for those with hypercholesterolaemia and without arterial hypertension at the beginning of the study; 17,128 euros for those with arterial hypertension and without hypercholesterolaemia at the beginning of the study; and 17,085 euros for those with both hypercholesterolaemia and arterial hypertension at the beginning of the study.

Among diabetic patients without hypercholesterolaemia and arterial hypertension at the beginning of the study, the incremental cost of being treated with orlistat when compared with no treatment was 1,608 euros. The difference was 1,514 euros for those patients with hypercholesterolaemia and without arterial hypertension at the beginning of the study. The difference was 1,678 euros for those with arterial hypertension but without hypercholesterolaemia, and 1,641 for those with both hypercholesterolaemia and arterial hypertension.

Synthesis of costs and benefits
The incremental cost-effectiveness ratio was calculated as the incremental cost of orlistat when compared with no treatment, divided by the corresponding incremental benefits.

For obese diabetic patients without hypercholesterolaemia and arterial hypertension at the beginning of the study, the cost per LYG when treated with orlistat in comparison with placebo was 19,986 euros. The cost-effectiveness ratio was 7,407 euros for those patients with hypercholesterolaemia and without arterial hypertension at the beginning of the study. The cost-effectiveness ratio was 7,388 euros for those with arterial hypertension but without hypercholesterolaemia, and 3,462 euros for those with both hypercholesterolaemia and arterial hypertension.

Sensitivity analyses showed that the cost-effectiveness ratio for patients without hypertension or hypercholesterolaemia at the beginning of the study increased considerably when the costs were discounted, and when the effects of orlistat on the events were decreased. For patients with hypertension and/or hypercholesterolaemia, the sensitivity analysis showed the robustness of the cost-effectiveness ratios.

Authors' conclusions
Orlistat was cost-effective in the treatment of obese diabetic patients, especially in the presence of hypercholesterolaemia and/or hypertension.

CRD COMMENTARY - Selection of comparators
The authors did not provide a justification for the comparator used (no treatment with orlistat). You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. They used data from the available studies selectively, and did not consider the impact of differences between the primary studies when estimating the effectiveness. The authors warned that they might have overestimated the effects of orlistat on
cholesterol for patients with hypercholesterolaemia, although they provided evidence that supported the estimation obtained.

Validity of estimate of measure of benefit
The estimation of benefits (LYG and mortality rates over the 10-year study period) was modelled in the Markov model, which seems to have been appropriate.

Validity of estimate of costs
The resource quantities and the costs were not reported separately, which introduced uncertainty into the reliability of the conclusions. The reporting of the costs was very concise, and therefore, it cannot be stated whether all the costs relevant to the perspective adopted (the health care consumer) were included in the analysis. Moreover, the reader has to consider that the adoption of a health care consumer perspective may be due to the fact that, in Belgium (where the study was carried out), the patients participate in the health care financing via co-payments and co-insurance. Therefore, this perspective is relevant in such a case, but it may not be relevant for a UK setting. Also, no sensitivity analysis of the prices was conducted. The price year was, however, reported.

The costs were incurred over a 10-year period but discounting was only considered in the sensitivity analysis, even though it was relevant due to the study period considered at analysis. The indirect costs were not included in the analysis, but were clearly relevant for this patient domain (for example, lost productivity, care by relatives) if a societal perspective were to be adopted. This would be more likely in the UK NHS context. The incremental analysis was correctly performed. However, the authors claimed that orlistat was cost-effective. This claim requires information on the opportunity cost, i.e., what benefit would be lost by diverting resources from a currently resourced technology in order to resource orlistat.

Other issues
The authors did not make appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed, as the authors stated that the results obtained may not be directly applicable to other countries due to differences in the treatment costs and in complications that may exist across different countries. The results were reported in full except for the costing. The authors' conclusions require some qualification in terms of cost-effectiveness.

Implications of the study
The authors state that further observational evidence on the longer-term benefits of orlistat would be important, in order to help decision-making and to validate the results of this study.

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Other publications of related interest


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