The effects of orlistat in patients with diabetes: improvement in glycaemic control and weight loss

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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; Roche Pharmaceuticals, Basle) and behavioural interventions for the treatment of obese patients with diabetes in a structured weight management clinic. The behavioural interventions consisted of a group education session on how to estimate fat intake, which should be less than 50 g/day, and advice to take regular exercise for up to 30 minutes, 5 times a week.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised overweight patients with diabetes, who had a body mass index (BMI) greater than 28 kg/m2.

Setting
The setting was a hospital-based clinic. The economic study was carried out in Manchester, UK.

Dates to which data relate
The effectiveness and resource use data referred to the period between May 2000 and May 2003. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the clinical analysis.

Study sample
The study was powered to have an 80% chance of detecting a 5% change in glycated haemoglobin (HbA1c) level for a 1-tailed test significance of 5%, allowing a 25% drop-out rate. All patients meeting the National Institute for Clinical Excellence criteria for orlistat, who were willing to monitor blood glucose levels at home and willing to attend monthly weight management clinics, were enrolled. It would appear that motivation to succeed (i.e. the ability to reduce weight by 2.5 kg in the 4 weeks prior to commencement of treatment on orlistat) was a further inclusion criterion, although this
was not clearly stated in the paper. One hundred patients were included in the study. Of these, 45 were males (mean age 54.5 years) and 55 were females (mean age 54.8 years). Ninety-one patients in total had Type 2 diabetes. Fifty-one patients were initially treated with insulin and 57 with oral hypoglycaemic agents. The number of refusals or excluded patients was not reported. There was no evidence that the study sample was representative of the study population.

**Study design**
This was a within-group comparison study with data collected in a single centre, with a follow-up period of 24 months. Of the original 100 patients, 18 stopped using orlistat during the first 6 months (6 experienced adverse events, 1 was lost to follow-up and 2 were nonresponders). A further 59 had stopped by 24 months.

**Analysis of effectiveness**
The analysis of data appears to have been based on treatment completers only. Changes in weight loss, BMI and HbA1c were reported. The use of insulin usage and oral hypoglycaemic agents were also reported as implying health improvements. Regression modelling was used to investigate the relationship between changes in weight loss and changes in insulin use after controlling for gender, age and BMI at baseline.

**Effectiveness results**
At 6 months:
- there were 82 completers;
- the mean weight loss of the completers was 7.1 kg or 6.2% (standard deviation, SD=4.0%), (p<0.001);
- the mean HbA1c fell by 0.62%, (p<0.001);
- the mean daily insulin dose of insulin users fell from 130 units to 90 units, (p<0.001); and
- the number of patients with a mean dose reduction of oral hypoglycaemic agents fell to 20 (44%; p>0.05).

The results of the regression analysis showed that the higher the HbA1c level at baseline, the greater its percentage improvement, (p=0.006).

At 24 months:
- there were 23 patients still receiving orlistat;
- the mean weight loss of completers fell from 104.7 kg (SD=32.9) at 6 months to 99.7kg (SD=32.4) at 24 months, (p=0.002); and
- the mean HbA1c level did not change significantly.

Of the 27 patients not receiving orlistat at 24 months and for whom information was available, there were no significant changes in weight or HbA1c level.

The results of the regression analysis showed that changes in insulin dosage and in HbA1c did not depend on weight loss or changes in BMI, although age was a significant predictor of insulin daily dose, (p<0.05).

**Clinical conclusions**
Orlistat seems to have a positive impact on weight loss and glycaemic control in patients with diabetes, with improvements sustained after a 24-month period.
Measure of benefits used in the economic analysis
No summary measure of health benefit was used in the economic analysis. Therefore, the study took the form of a cost-consequences analysis.

Direct costs
The costs reported would appear to relate solely to the use of antidiabetic medications (i.e. insulin and oral hypoglycaemics). The quantity of insulin used was reported, but not the quantities of the various oral hypoglycaemic agents or those of orlistat. The source of the unit costs for the antidiabetic agents was the British National Formulary. Information on the use of insulin was estimated by multiplying the number of daily insulin units by the UK average unit cost of human insulin using penfill cartridges. The costs were enumerated as the mean treatment cost per day at 6 months. Given the short time period, discounting of the costs was neither indicated nor undertaken. The price year was not reported.

Statistical analysis of costs
Statistical comparisons between the mean costs at baseline and at 6 months were reported.

Indirect Costs
The indirect costs were not reported.

Currency
UK pounds sterling (€).

Sensitivity analysis
No sensitivity analysis was undertaken.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The average cost of the diabetic treatments was 1.16 at baseline versus 0.83 at 6 months.

The cost of insulin for those on insulin therapy was 1.92 per day at baseline versus 1.33 after 6 months on orlistat.

Synthesis of costs and benefits
The costs and benefits were not combined because of the cost-consequences approach undertaken.

Authors' conclusions
The use of orlistat improved both weight and glycaemic control. It also reduced the intake of antidiabetic treatments and, consequently, their associated costs.

CRD COMMENTARY - Selection of comparators
The choice of the comparator appears to have reflected current practice. You should consider whether the administered doses at baseline represent current practice in your own setting. There were no details on the doses of orlistat administered.
Validity of estimate of measure of effectiveness
The study design, a within-group comparison study, was not the most reliable design with which to assess the effects of orlistat. The use of a randomised controlled trial would have made the results less prone to bias. The effect of the intervention may have been related not only to the use of orlistat, but also to "behavioural interventions relating to diet and exercise". Moreover, the sample appears to have included well-motivated patients only, which would restrict the generalisability of the findings to this type of patient. In addition, it is possible that the patients were monitored more frequently than would have been the case under usual care (being recalled every 3 months during the first 12 months of the study). More frequent monitoring with a protocol that specified insulin reduction under specified circumstances might also have reduced insulin use more than would have been the case under usual care. As the authors themselves acknowledged, "it is not possible to determine the extent to which observed effects were due to orlistat and which may be ascribed to the impact of lifestyle and diet modification following counselling ..." Therefore, there is some uncertainty regarding the internal and external validity of the clinical analysis.

Validity of estimate of measure of benefit
As the authors carried out a cost-consequences analysis, the reader is referred to the comments under the "Validity of estimate of measure of effectiveness" field (above).

Validity of estimate of costs
The perspective of the study was not stated, but it was limited to the use of antidiabetic medications. The percentage use of the various oral hypoglycaemics was reported, thus enabling the reader to judge whether the results are generalisable to their own setting. Although not reported, the unit costs of oral hypoglycaemics were derived from a readily available source (the British National Formulary). The assumed unit costs of insulin were reported. However, the costs of orlistat and the behavioural interventions do not appear to have been included in the economic analysis; their inclusion would have been necessary to estimate appropriately the costs of the intervention. In addition, the price year was not reported. Therefore, there is uncertainty surrounding the validity of the cost estimation.

Other issues
The authors compared their results with those from four other studies that showed similar reductions in weight following treatment with orlistat. They also reported, from another study, that the cost of insulin was far lower than the figure they themselves estimated. From the information provided it was not possible to assess which of these estimates was more likely to be correct. The issue of whether the results were generalisable to other settings was not addressed in the paper.

Implications of the study
The authors suggested that further research to evaluate the association between reduced glycaemic levels and age should be carried out. The study presented some relevant caveats that should be considered when interpreting the study results.

Source of funding
Supported by Roche Products Ltd.

Bibliographic details

PubMedID
16307710

DOI
10.1185/030079905X74943
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Anti-Obesity Agents /economics /therapeutic use; Blood Glucose /metabolism; Body Mass Index; Diabetes Mellitus, Type 2 /drug therapy; Female; Follow-Up Studies; Humans; Hypoglycemic Agents /economics /therapeutic use; Lactones /economics /therapeutic use; Male; Middle Aged; Obesity /drug therapy /physiopathology; Prospective Studies; Weight Loss

AccessionNumber
22006000042

Date bibliographic record published
31/08/2006

Date abstract record published
31/08/2006