Cost-effectiveness of sibutramine in the treatment of obesity
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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 the addition of sibutramine (SIB) to diet and lifestyle advice for the treatment of obesity, over a 1-year period. SIB was given at a dosage of 10 mg. Responders, defined as patients who lose 2 kg after 1 month and 5% of their initial weight after 3 months, continued treatment on a dosage of 10 mg for 12 months. Initial nonresponders (at 3 months) were given SIB at a dosage of 15 mg for a further 3-month period. Patients who failed again to reach a loss of 5% of their initial weight in these 3 months were categorised as nonresponders and treatment with SIB was discontinued.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of obese patients. These were defined as those individuals with a body mass index (BMI) greater than 30 kg/m2. The individuals were otherwise healthy.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2001. No dates for the resource use data were reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision tree was constructed to estimate the costs and benefits associated with 1 year of SIB versus diet and lifestyle advice. The model considered the impact of SIB on reduced risk of coronary heart disease (CHD), reduced incidence of diabetes, and quality of life gains due to weight loss itself. The time horizon of the model was 5 years. Following European guidelines, SIB treatment was continued only for “responders”, defined as patients who lose 2 kg after 1 month and 5% of their initial weight after 3 months. The hypothetical cohort of 1,000 patients considered in the study had the same demographics as one of the clinical trials providing data: male (20%) and female (80%) patients aged between 18 and 65 years (mean 42), with a BMI between 27 and 40 kg/m2 (mean 32.7). The treatment pathway and threshold for discontinuing treatment were clearly described and represented a key feature of the model.
Outcomes assessed in the review
The outcomes assessed were:

natural history weight gain and weight loss with placebo or SIB in both responders and nonresponders;

CHD risk reductions associated with SIB;

the percentage of all CHD events that were fatal;

survival;

the utility weight associated with a nonfatal CHD event;

the incidence of diabetes according to BMI and in the study groups;

the increased risk of mortality due to diabetes; and

the utility gains due to weight loss.

The probabilities associated with the threshold for discontinuing treatment were also reported in the tree.

Study designs and other criteria for inclusion in the review
Systematic reviews of the literature were undertaken to identify relevant studies. The evidence on SIB came mainly from two randomised trials, while other model inputs were derived from prospective studies. Life expectancy was obtained from life tables. No information on the other sources was provided.

Sources searched to identify primary studies
MEDLINE and EMBASE were searched for relevant studies.

Criteria used to ensure the validity of primary studies
No specific criteria were used to ensure the validity of the primary studies.

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

Number of primary studies included
Approximately 13 primary studies provided evidence.

Methods of combining primary studies
The primary studies appear to have been combined using a narrative method. In some cases the primary estimates were not combined and alternative sources of estimates were used in the sensitivity analysis.

Investigation of differences between primary studies
Not stated.

Results of the review
The natural history weight gain was 1 kg per annum. The weight loss over 1 year was 10 kg with SIB and 2 kg with
placebo. The average rate of weight regain for original responders who stopped SIB treatment at 12 months was 0.385 kg/month (95% confidence interval, CI: 0.359 - 0.411; p<0.001).

Significant CHD risk reductions due to SIB were observed in males and older females. For males, the absolute change in the percentage of 10-year CHD event risk between baseline and 12 months' treatment was -1.21 in the age class 25 - 34, -1.56 in the age class 35 - 44, -2.24 in the age class 45 - 54, and -3.60 for those older than 54 years. For females, the absolute change was -0.83 in the age class 45 - 54, and -2.20 for those older than 54 years. The reductions in young females were not statistically significant. For patients receiving placebo, there was no significant CHD risk reductions in any age class for males or females.

The percentage of all CHD events that were fatal was 33.33.

The utility weight associated with a nonfatal CHD event was 0.85.

The annual incidence of diabetes according to BMI was: 0.05% for BMI 23 - 23.9,
0.06% for BMI 24 - 24.9,
0.10% for BMI 25 - 26.9,
0.20% for BMI 27 - 28.9,
0.35% for BMI 29 - 30.9,
0.52% for BMI 31 - 32.9,
0.70% for BMI 33 - 34.9,
1.19% for BMI 35 - 36.9,
1.55% for BMI 37 - 38.9,
2% for BMI 39 - 40.9,
2.50% for BMI 41 - 42.9, and
3.15% for BMI 43 - 44.9.

The incidence of diabetes in the first year was 0.489% for patients receiving no treatment, 0.424 for patients receiving placebo, and 0.330 for SIB patients.

The increased risk of mortality due to diabetes was 33%.

The utility weight associated with diabetes was 0.95.

Utility gains due to weight loss were derived from two sources, and were 0.00142 per kg for placebo patients and 0.00185 per kg for SIB patients.

The values of utility gains from the alternative source were 0.00472 for placebo patients and 0.00297 for SIB patients.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
It was assumed that when nonresponders dropped out from treatment, their weight rose immediately to its natural
history level and the subsequent weight regain continued at the natural history rate. After the first year of SIB treatment, the difference in CHD risk between SIB and placebo narrowed in proportion to the estimated weight regain. The utility weight associated with a nonfatal CHD event applied not only to the year in which the event occurred, but also to all subsequent years.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). These were estimated by combining survival and quality of life data derived from the literature. The QALY gains were also reported in terms of their impact on weight loss, avoided CHD events, and diabetic cases avoided. A discount rate of 1.5% was applied to QALYs incurred in the future (3% in the US analysis).

**Direct costs**
Discounting was relevant as the long-term costs were estimated. An annual discount rate of 6% was used (3% in the US analysis). The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were drugs, monitoring (including the treatment of adverse events), and averted cases of CHD and diabetes. The cost/resource boundary of the NHS was adopted in the study. The costs were derived from the British National Formulary, Personal Social Services Research Unit, and published studies. The resource use data was derived mainly on the basis of authors’ assumptions. All of the costs were presented in 2000 values using the Health Service Cost Index.

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

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
UK pounds sterling (£) and US dollars ($).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were performed to address the issue of uncertainty in most of the model inputs. Variations in the components of QALYs (thus excluding benefits on CHD and diabetes, or assuming that benefits disappear after 1 year’ treatment), utility weights, mortality data, some cost assumptions, compliance, discounting, and rates of adverse events were investigated. Worst and best cases for SIB were also considered. Confidence intervals were used whenever possible, while arbitrary values were used when literature-based alternative data were not available.

**Estimated benefits used in the economic analysis**
The model showed that in a cohort of 1,000 patients, 1 year’ treatment with SIB resulted in 0.28 nonfatal CHD events, 0.14 CHD-related deaths and 0.94 incident cases of diabetes avoided. In the following 4 years, a further 0.36 nonfatal CHD events, 0.18 CHD-related deaths and 0.60 incident cases of diabetes would be avoided.

In a cohort of 1,000 individuals, the discounted QALYs gained with SIB over placebo in a 5-year period were 48.15 in terms of weight loss, 7.07 in terms of avoided CHD events, and 3.73 in terms of diabetic cases avoided. The estimated total gain in QALYs with SIB over placebo was 58.95.

In the US setting, the discounted QALYs gained with SIB over placebo in a 5-year period were 46.79 in terms of weight loss, 3.36 in terms of avoided CHD events, and 2.76 in terms of diabetic cases avoided. The estimated total gain in
QALYs with SIB over placebo was 52.91.

**Cost results**

Over the 5-year period, the total costs in the placebo branch were 251,297. In the SIB branch, drug and monitoring costs (including the treatment of side effects) were 556,611. However, the cost-savings due to averted CHD were 6,985 and those due to averted diabetes were 16,538. Therefore, the extra cost associated with SIB over placebo was 281,791.

In the US setting, the total costs in the placebo branch were $418,660. In the SIB branch, drug and monitoring costs (including the treatment of side effects) were $1,157,836. However, cost-savings due to averted CHD were $20,079 and those due to averted diabetes were $227,098. Thus, the extra cost associated with SIB over placebo was $491,999.

**Synthesis of costs and benefits**

Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative treatment options. The incremental cost per QALY of SIB in comparison with placebo was 4,780 in the UK setting and $9,299 in the US setting.

The sensitivity analysis showed that the base-case results were, in general, robust to variations in model inputs. There were some exceptions. For example, when low compliance rates were considered, the incremental cost per QALY with SIB increased substantially. Further, variations in the utility weights and frequency of monitoring had the greatest impact on the cost per QALY. Under the best-case scenario, the incremental cost per QALY with SIB was 5,809 in the UK and $5,242 in the USA. Under the worst-case scenario, the incremental cost per QALY with SIB was 34,260 in the UK and $61,758 in the USA.

**Authors’ conclusions**

One year of sibutramine (SIB) combined with diet and lifestyle advice was a cost-effective treatment for obesity in the UK and USA.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparator (diet and lifestyle advice alone) was based on the comparator used in the clinical trials that were the main source of evidence on SIB. Diet and lifestyle advice alone represents standard care in several settings. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from published studies and from authors’ assumptions. A systematic review of the literature was carried out to identify several model inputs. Other estimates appear to have been identified selectively. However, there was limited information on the methods and conduct of the review. In general, the authors reported the design and sample characteristics of the primary studies used to assess the most relevant model inputs. Similarly, the authors discussed the reasons for the choice of some values. Assumptions were also required when published data were not available, and the choice of such assumptions was explicitly justified. The most critical model inputs were varied in the sensitivity analysis.

**Validity of estimate of measure of benefit**

The use of QALYs as the summary benefit measure was appropriate because it captured the impact of the interventions on quality of life and survival. The two main co-morbidities associated with obesity were considered, although the authors stated that other co-morbidities should have been incorporated in the decision model. Discounting was applied, as recommended in UK and US guidelines. The use of an alternative discount rate for UK results was investigated. The assumptions made to assess utility weights were explicitly reported and were investigated in the sensitivity analysis. QALYs are comparable with the benefits of other health care interventions.
Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study and all the relevant categories of costs were included in the analysis. However, limited information on the unit costs and quantities of resources used was provided. Most of the costs were presented as macro-categories and a detailed breakdown of the costs was not reported. This limits the possibility of replicating the study. The source of the data was provided for most items. The price year was reported, which aids reflation exercises in other settings. The costs were treated deterministically, but were varied in the sensitivity analysis.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, although the extensive sensitivity analysis performed enhanced the external validity of the analysis. The authors noted some limitations of their study. For example, the model applied to an obese cohort of patients who were otherwise healthy. Thus, the impact of SIB in a patient population in which CHD and diabetes were already prevalent was not examined.

Implications of the study
The study results suggested that SIB should be used for obese patients who had attempted weight loss through diet and exercise but had failed. The authors suggested that further research should investigate the impact of monitoring costs associated with obese patients.

Source of funding
Supported by a grant from Abbott.

Bibliographic details

PubMedID
15005950

DOI
10.1177/0272989X03261565

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Appetite Depressants /economics /therapeutic use; Coronary Disease /complications /prevention & control; Cost-Benefit Analysis; Counseling; Cyclobutanes /economics /therapeutic use; Diabetes Complications;