TITLE: Pharmacological Interventions for Weight Loss: A Review of the Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

The number of overweight and obese individuals worldwide is increasing.1 Obesity is associated with significant morbidity and mortality2 and is also associated with a number of other chronic conditions including type 2 diabetes, coronary artery disease, hypertension, osteoarthritis, and sleep apnea.3 These obesity-rated conditions have significant economic costs and with the increasing incidence of obesity, these costs are burdening health care systems.2 In addition to dietary and surgical approaches to control obesity, the use of anti-obesity drugs is emerging as a viable therapeutic option to treat obesity.4 A recent report estimated the 2005 global statistics of anti-obesity drug costs at US$1.2 billion.1

Two anti-obesity drugs that will be discussed in this review are orlistat (Xenical®) and sibutramine (Meridia®). Orlistat is an inhibitor of gastric and intestinal lipases which can result in decreased intestinal fat absorption.5 Sibutramine blocks re-uptake of neurotransmitters within the brain and results in appetite suppression.5 Both drugs are approved for use in Canada and available by prescription only.6

With the increasing use of orlistat and sibutramine to treat obesity and the rise in obesity rates, there is a need to review the evidence regarding the use of these drugs. This report will review evidence for the clinical and cost-effectiveness of orlistat and sibutramine for the treatment of obesity.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of orlistat and sibutramine for weight loss?

2. What is the cost-effectiveness of orlistat and sibutramine for weight loss?
METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID MedLine, OVID Embase, The Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Results include articles published between 2003 and December 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, and economic studies.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment (HTA) reports, systematic reviews, and meta-analyses are presented first. These are followed by economic evaluations.

SUMMARY OF FINDINGS:

A large number of systematic reviews, meta-analyses, and economic evaluations identified therefore, only those published in 2005 or later were included for review. Included in this review are three HTAs, eight systematic reviews and meta-analysis, and seven economic evaluations.

All of the data presented represent placebo-corrected values unless otherwise stated.

Health technology assessments

The first HTA was conducted by the National Institute for Health Research HTA program in the UK. The objective was to review various obesity treatments including the pharmacological interventions orlistat and sibutramine. Studies included in the HTA were double-blind, placebo-controlled randomized controlled trials (RCTs) in overweight or obese adults (over 18 years of age) with a follow-up of at least one year. Fourteen RCTs involving orlistat or sibutramine were included. Orlistat or sibutramine combined with a low-fat/reduced-calorie diet resulted in a weight change of -3.01 kg (95% CI: -3.48 to -2.54 kg) for orlistat and -4.12 kg (95% CI: -4.97 to -3.26 kg) for sibutramine at the one year time point. Authors noted little change at later time points of 18 months and two years. Authors concluded that orlistat and sibutramine appeared to be beneficial for the treatment of obesity in adults.

A second HTA was prepared for the Agency for Healthcare Research and Quality (AHRQ) and evaluated approved pharmacological and surgical treatments of obesity. Although a number of drugs were considered in this HTA, only orlistat and sibutramine will be discussed. Both drugs were given in combination with recommendations for diet modification (i.e. low-fat and/or low-calorie diet). For inclusion in the HTA, studies had to be RCTs or controlled clinical trials involving 10 or more participants. Studies also had to contain sufficient information for authors to calculate the mean difference in weight at six months and/or at one year follow-up in their meta-analysis. A previously published meta-analysis of 29 trials involving individuals ranging in age from 34 to 54 years and treated with sibutramine was included in the HTA. Authors of the meta-analysis reported a mean difference in weight loss of -3.43 kg and -4.45 kg at six and 12 months, respectively. The authors of the HTA performed their own meta-analysis of 28 trials involving orlistat-treated patients (mean age 48 years) compared with placebo-treated patients, the mean weight-loss was 2.51 kg and 2.75 kg at six and 12 months, respectively. Noted adverse events for sibutramine included modest increases in heart rate and blood pressure and for orlistat, increase in diarrhea, flatulence, and bloating/abdominal pain. Authors concluded that sibutramine and orlistat were effective in promoting weight loss when given in combination with...
diet modification; however, the weight loss was modest at less than five kg at the one year time-
point. Authors did not conclude that one drug was more effective than others and suggested
that drug choice may be made based on tolerance to the expected side effects.

The third HTA identified was by the New Zealand Health Technology program assessed the
efficacy and safety of various weight loss medications including orlistat and sibutramine. All
identified studies evaluated drug treatment in combination with diet and/or lifestyle
modifications. The author of the HTA identified 10 systematic reviews and seven additional
RCTs regarding orlistat treatment for weight loss. The author noted that the patient populations
varied considerably between studies and some studies specifically assessed overweight or
obese patients with co-morbidities including type 2 diabetes or hypertension. For all patient
groups combined, the mean weight loss of patients treated with orlistat was 3.01 kg after one
year and 3.26 kg after two years. A weight loss of ≥5% of total body weight (which is considered
to be clinically significant) was reported in 58-78% of patients across all studies. Similarly, a
relatively large number of relevant studies involving sibutramine were identified including 10
systematic reviews and seven RCTs. Patient populations varied considerably between studies
and often populations with specific co-morbidities (type 2 diabetes and hypertension) were
evaluated. Study design (length of intervention and follow-up) and drug dosage also varied
considerably between studies and therefore, a combined weight loss was not calculated by the
authors; however, a study included by the author reported a placebo-corrected weight loss of
4.12 kg after one year of treatment with sibutramine in a mixed-population. The dose of
sibutramine used in the included studies varied between 5-30 mg per day. Authors noted that
the effect of sibutramine is dependent on dose and cited the sub-group analysis of dose-
response from one of the included studies. This study included a systematic review of 10 RCTs
involving patients treated with sibutramine (1-30 mg per day) and found that the number of
patients achieving a clinically-significant weight loss of ≥5% of total body weight varied from
25% with a dose of 1 mg per day to 77% with a dose of 30 mg per day. This study also reported
that 20% of placebo-treated patients experienced a clinically-significant weight loss. In terms of
side effects, trials noted gastrointestinal side effects for orlistat and increase in blood pressure
and heart rate in sibutramine-treated patients. The HTA included an analysis of economic
evaluations of both drugs. Two systematic reviews of the cost-effectiveness of orlistat reported
the incremental cost effectiveness ratio (ICER) to be £45,888 per quality adjusted life year
(QALY) in one study and £31,978 per QALY in the other study. These reviews suggested that
treating obese, otherwise healthy adults was not cost-effective and rather treatment should be
considered for obese patients with obesity-related co-morbidities such as hypertension and/or
hypercholesterolemia. One economic analysis was identified for sibutramine treatment and
estimated the cost per QALY (for weight loss alone without assumption of increased benefit
associated with improved risk profiles in patients with co-morbidities) using two different
economic models at £6,341 and £19,125. Authors concluded that sibutramine treatment had
greater clinical and cost-effectiveness than orlistat treatment; however, authors suggested that
because of the side effect profile, the use of sibutramine may be limited in patients with
hypertension or cardiovascular disease.

Systematic reviews and meta-analyses

Mannucci et al. (2008) conducted a meta-analysis of double-blind, randomized, placebo-
controlled trials involving overweight or obese adults (over the age of 18 years) and reported the
effect of orlistat and sibutramine on weight loss. Of note, the primary objective of this study was
to determine the effect of these drugs on serum lipid profiles independent of weight loss. Fifteen
studies involving orlistat (10,995 participants; 5,760 received active drug) and 10 studies
involving sibutramine (1,213 participants; 614 received active drug) were included. All studies
were of six to 12 months in duration. Both arms in all studies compared placebo or active drug to a hypocaloric diet. Their meta-analysis found the mean percentage weight loss of orlistat-treated participants at six or 12 months (depending on the study duration) to be 8.71±3.8 (range: 3.89-10.2) versus 5.25±3.5 (range: 1.3-8.0) for placebo. Sibutramine-treated participants experienced a mean percentage weight loss of 5.72±5.6 (range: 4.3-10.1) versus 0.96±3.0 (range: 1.0-2.7) with placebo. Authors concluded that both orlistat and sibutramine are effective in promoting weight loss.

A systematic review by Neovius et al. (2008) identified seven studies that directly compared mono-therapies of orlistat with that of sibutramine. The mean sample size of trials was 111 participants (range: 34-182) and the mean duration was seven months (range: 3-12 months). The average age of trial participants was not reported. The median weight loss for orlistat-treated participants was 8.0 kg (range: 5.5-9.5) and 11.7 kg (range: 10.1-13.1) for sibutramine-treated participants. The authors concluded that sibutramine was more effective than orlistat; however, when a sub-group analysis of two included studies that specifically assessed the effectiveness of orlistat and sibutramine in patients with type 2 diabetes or hypertension was performed, no significant difference was noted between the drugs. Authors noted that head-to-head studies are typically less likely to be sponsored by industry and therefore maybe be less prone to bias.

Padwal et al. (2008) systematically reviewed studies assessing the long-term effects of anti-obesity drugs including orlistat, sibutramine, and rimonabant, taken for a minimum of one year. Data regarding rimonabant will not be discussed in this review. Double-blind, randomized, placebo-controlled trials involving overweight or obese adults (over the age of 18 years) and with a follow-up duration of at least one year were considered for inclusion. Both trials that assessed weight loss and weight maintenance were included. Head-to-head trials were excluded. Sixteen trials involving orlistat (n=10,631 participants) with an average participant age of 47 years were included. Nine of the studies had targeted enrollment of participants with either type 2 diabetes or patients with at least one risk factor for cardiovascular disease (e.g. hypertension, dyslipidemia, or impaired glucose tolerance). Authors identified 10 trials involving sibutramine (n=2,623 participants) with an average participant age of 45 years. Five of the studies also had targeted enrollment of participants with type 2 diabetes or hypertension. Orlistat treatment resulted in a weight reduction of 2.9 kg (95% CI: 2.5-3.2 kg) and sibutramine treatment resulted in a weight reduction of 4.2 kg (95% CI: 3.6-4.7 kg). Authors concluded that both orlistat and sibutramine are effective in reducing weight; however, the internal validity of the studies was hindered by high attrition rates (averaged between 30% and 40%). A meta-analysis of these data performed by the same group was published previously while this systematic review was undergoing peer-review. As such, the meta-analysis contains the same data and was not appraised as part of our report.

A systematic review and meta-analysis of trials of weight-loss interventions was conducted by Franz et al. (2007). The authors evaluated the effect of diet, exercise, meal replacements, as well the anti-obesity drugs orlistat and sibutramine. Only the results from trials involving orlistat and sibutramine will be discussed herein. Thirteen studies used orlistat and seven studies used sibutramine. All trials involved overweight or obese adults (over the age of 18 years) and were a minimum of one year in duration. Authors did not report if trial participants had co-morbidities. Study duration ranged from 52 to 308 weeks. The treatment phase ranged between four and 54 weeks, although some included studies did not report the length of treatment phase. Where possible, weight loss was assessed at six, 12, 24, 36, and 48 months. For both drugs, the majority of the weight loss occurred within the first six months of the study. Participants treated with orlistat lost a mean of 8.3 kg (8% total body weight), 8.2 kg (8%), 7.7 kg (7%), 7.8 kg (7%),
and 5.8 kg (5.3%) at six, 12, 24, 36, and 48 months respectively. Participants treated with sibutramine lost a mean of 8.2 kg (8.4%), 8.2 kg (8.4%), and 10.8 kg (11%) at six, 12, and 24 months, respectively. The authors concluded that longer treatment with weight loss drugs was typically not associated with further weight loss, but rather weight maintenance.

A systematic review by Douketis et al. (2005) assessed long-term studies of dietary, lifestyle, surgical, and pharmacological strategies for weight loss including the use of orlistat and sibutramine. Inclusion criteria were randomized or non-randomized studies involving a minimum of 100 overweight or obese adults. For pharmacological studies, a follow-up duration of at least one-year was required for inclusion. Twelve studies assessing orlistat and five studies evaluating sibutramine for weight loss were included in this systematic review. The mean age of study participants varied from 40 to 58 years. Some of the included studies had targeted enrollment of participants with type 2 diabetes or hypertension; however, the precise number of studies was not reported. The mean weight loss after one year for all drugs (including metformin which was also evaluated by these authors) was 6.1±2.0 kg (range 3.9-10.3 kg) and 7.2±1.6 kg (range: 4.9-8.9 kg) after two years. The authors noted that only four of the included studies of pharmacological interventions had follow-up durations of at least two years.

A systematic review and meta-analysis by Horvath et al. (2008) was conducted to assess the long-term effects of pharmacological treatments for weight loss. Of note, the primary objective of this systematic review was to assess the effect of weight loss induced by orlistat and sibutramine on blood pressure and cardiovascular outcomes in hypertensive patients; weight loss was also reported. Eight RCTs (four involving each orlistat and sibutramine compared with placebo) were included in this systematic review. The age range of patients in orlistat studies was 46 to 55 years and study duration ranged from six to 48 months. For sibutramine, the age range was 46 to 53 years and the study duration ranged from six to 12 months. Participants on orlistat lost a mean of 3.74 kg (95% CI: 2.78-4.70 kg). A mean weight loss of 3.72 kg (95% CI: 2.59-4.85 kg) was observed for sibutramine-treated patients. Authors stated that the most commonly reported adverse events by patients treated with orlistat were gastrointestinal disturbances and one study reported a significantly higher proportion of participants with musculoskeletal pain. Reported adverse events by patients being treated with sibutramine included dry mouth, arthralgia (joint pain), and headache.

Li et al. (2005) conducted a systematic review and meta-analysis of trials assessing pharmacological treatments for obesity, including orlistat and sibutramine. For inclusion, studies had to be controlled clinical trials involving overweight or obese adults (over the age of 18 years) that were at least six months in duration. The authors performed a meta-analysis of 22 RCTs involving patients treated with orlistat. The mean age of enrolled participants was 48 years. Weight loss was assessed at one year and mean weight loss was 2.75 kg (95% CI: 2.20-3.31 kg). The authors reported on an existing meta-analysis of 29 RCTs of patients being treated with sibutramine. The mean age of enrolled participants ranged from 34 to 54 years. Weight loss was assessed at one year and mean weight loss was 4.45 kg (95% CI: 3.62-5.29 kg). Authors concluded that both drugs were effective in promoting modest weight loss when given in combination with diet recommendations, although no details regarding particular recommendations were given in the review.

A meta-analysis by Vettor et al. (2005) evaluated RCTs involving sibutramine treatment of obese patients with type 2 diabetes. To qualify for inclusion studies had to be double-blind, randomized, placebo-controlled trials with a treatment phase of at least three months. Participants were overweight or obese adults with diagnosed type 2 diabetes. Study duration ranged from three to 12 months. A total of 1,093 participants with type 2 diabetes were treated...
(552 received active drug and 541 received placebo). The mean weight loss experienced by sibutramine patients was 5.53±0.225 kg. The authors concluded that sibutramine may be useful in the weight management of obese patients with type 2 diabetes.

Economic evaluations

Results of the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study were published in 2004.\textsuperscript{17} The XENDOS study showed that lifestyle modifications and pharmacological therapy can decrease the risk of metabolic disorders in obese patients. Iannazzo \textit{et al.} (2008)\textsuperscript{18} assessed the data from the XENDOS study to evaluate the economic impact of lifestyle modifications with and without the combination of orlistat treatment. Authors developed a Bayesian probabilistic Markov model from a societal perspective and made the assumption that orlistat in combination with lifestyle changes would slow the rate of progression of diabetes and reduce mortality and non-fatal cardiovascular disease events. The sensitivity of the model was insufficient to allow for the detection of a link between weight reduction and cardiovascular risk. The time horizon of the model was 10 years (four years of treatment and six years of follow-up). Two scenarios were assessed and costs included the drug, primary and specialist visits, tests, hospitalization, and emergency room visits. In the first scenario, orlistat was given to every obese patient and the cost-utility was €43,300 per QALY. In the second scenario, orlistat was given only to at-risk patient populations (i.e. patients with impaired glucose tolerance), and the cost-utility was €10,160 per QALY. Authors concluded that the cost-utility was more favourable when given to targeted populations than to all obese patients. Authors also concluded that orlistat given to a targeted population had a cost-utility value that would be commonly recommended by some countries for funding.

A systematic review of economic evaluations of orlistat and sibutramine was conducted by Neovius and Narbro (2008).\textsuperscript{19} Nine studies regarding orlistat and four studies pertaining to sibutramine were included. All but one of the studies used placebo, no drug, or lifestyle modifications (including diet and exercise) as comparators. All but one of the studies performed sensitivity analyses; however, further information regarding the results of analyses and the perspective taken in each of the included studies was not reported in the systematic review. The median time horizon was 7.5 years. The median ICER from the cost-utility analyses was €16,000 per QALY. Authors noted that all but three of the included studies were funded by industry. If the median ICERs between non-industry-sponsored and industry-sponsored studies were compared, the ICER reported in non-industry-sponsored studies was much higher at €62,000 per QALY versus €15,000 per QALY for industry-sponsored studies.

van Baal \textit{et al.} (2008)\textsuperscript{20} evaluated the cost-effectiveness of orlistat treatment of obese patients in the Netherlands. The time horizon for the study was one year. The perspective of the analysis was from that of a health-care provider. Sensitivity analysis found that costs were sensitive to assumptions about long-term weight loss maintenance. Cost-effectiveness estimates were made for: a low-calorie diet alone, orlistat alone, and the combination. The authors used the RIVM Chronic Disease Model and attributed gains in length and quality of life to the prevention of chronic diseases. Costs associated with general practitioner appointments, dietitian appointments, food diaries, and drugs were used to evaluate the costs over a one year period. An assumption was made that 23% of the weight loss achieved after one year can be maintained in the long term. The ICER for a low calorie diet compared to no intervention was €17,900 and €58,800 for the combination approach compared to diet alone. The authors concluded that a low-calorie diet was most cost-effective.
A study by Ara and Brennan (2007) assessed the cost-effectiveness of sibutramine compared to placebo and to diet and lifestyle advice received in primary care in non-diabetic obese patients in European countries. The model used quantified the benefits associated with weight loss including increased quality of life, reduced risk of coronary heart disease, and decreased risk of diabetes. The perspective of the analysis was from that of a health-care provider. Results of the sensitivity analysis showed that the model is sensitive to changes in the rate of utility per kilogram lost. The ICER per QALY ranged from €10,734 in Switzerland to €13,707 in Germany. The authors concluded that sibutramine maybe be considered cost-effective for the treatment of obesity.

An economic evaluation of weight loss interventions including diet, exercise, behavioural modifications, and treatment with orlistat in overweight and obese women in the US was conducted by Roux et al. (2006). Authors used a Monte Carlo approach to simulate the natural history of 10,000 overweight or obese, but otherwise healthy women aged 35 years. The model assisted in the projection of change in life years and QALY associated with drug treatment. A societal perspective was taken for this analysis. Sensitivity analysis demonstrated that results were most influenced by obesity-related effects on quality of life and assumptions regarding long-term weight loss maintenance. Treatment with orlistat was for six months followed by a decreased maintenance dose for six additional months. Authors found the most cost-effective strategy was a combination of diet, exercise, and behavioural modifications with an ICER of US$12,640 per QALY. The diet and pharmacotherapy strategy was less cost-effective and as such, the authors did not provide the actual ICER.

Hertzman (2005) evaluated the cost-effectiveness of using orlistat to treat obesity in a one year weight management program in Sweden. A decision tree was developed and the ICER for orlistat in combination with diet modifications was €13,125 compared with diet alone. The perspective of the analysis was from the Swedish healthcare system. Of note, the calculations were based on whether a participant responded (i.e. experienced a ≥5% weight loss) within the first three months on orlistat. Sensitivity analysis demonstrated that results were most influenced by assumptions regarding long-term weight loss maintenance. The author concluded that orlistat was cost-effective for the promotion of weight loss in overweight and obese individuals.

Lacey et al. (2005) estimated the cost-effectiveness of orlistat combined with calorie-reduced diet versus a calorie-reduced diet alone in overweight and obese adults in Ireland. A health-care perspective was taken for the analysis. The model involved treatment of responders (i.e. those who experienced a ≥5% weight loss in the first three months of treatment) after the three month time point. The ICER of the combination treatment versus diet alone was €16,954 per QALY. Sensitivity analysis demonstrated that results were most influenced by drug dosage and assumptions regarding long-term weight loss maintenance. Authors concluded that orlistat was a cost-effective option in patients who responded to the drug within the first three months of treatment.

Limitations

The evidence for clinical effectiveness orlistat and sibutramine included in this report comes predominately from systematic reviews and meta-analyses of RCTs which is considered to be high quality evidence; however, information regarding the quality of the RCTs was often lacking. Other methodological details including patient characteristics (age and gender) were often not reported in the systematic reviews or meta-analyses. In the majority of the studies, drug therapy was combined with diet modifications. Informative descriptions of diet modifications (including
caloric and fat counts) were not made in most studies. Information regarding the number of participants with co-morbidities was often not reported in studies. In general, the availability of methodological details was low. It was also not clear from the majority of studies at what time the calculation of weight change in treatment and placebo groups was performed, i.e. at the end of the treatment phase or during follow-up. Some of the studies did not report weight loss (in either kg or percentage) for the drugs separately and instead, reported mean weight loss using either orlistat or sibutramine. In addition, adverse events were not reported in all studies and information regarding attrition was also lacking. It may have been helpful to know what percentage of attrition was due to non-tolerance of an expected side effect of drug treatment.

Although it was often mentioned in the included studies that many of the assessed RCTs were industry-sponsored, the precise number included in the systematic reviews/meta-analyses was rarely given. Moreover, several of the reports included in this review were authored by individuals who disclosed a conflict of interest or reported previous payment or employment with pharmaceutical companies producing one of the drugs.

A number of economic evaluations were identified by our literature; however, none were Canadian evaluations. Economic studies were performed in a variety of countries and health care systems therefore, the types of costs included in the studies varied. Moreover, not all of the economic evaluations provided significant detail regarding the types of costs included and the length of time horizon. Some of the evaluations did not provide separate calculations for each of the drugs and instead reported an overall ICER for drug treatment. For these reasons, it is difficult to predict if the findings can be generalized to Canada and our health care system.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Overall, all of the included studies that assessed the clinical effectiveness of either orlistat or sibutramine demonstrated that both drugs were capable of promoting weight loss. The majority of studies assessed either orlistat or sibutramine, but two studies evaluated both drugs and one of these was a direct comparison study. These two studies concluded that sibutramine was more effective than orlistat. One possible reason for the lack of direct comparison studies is that these studies may be less likely to be industry sponsored. With respect to adverse events, reporting was inconsistent throughout studies, but typically orlistat was associated with gastrointestinal disturbances and several reports suggested that sibutramine might increase blood pressure and heart rate. Indeed adverse reactions have been reported to Health Canada in patients with a history of cardiovascular disease, those with unstable or uncontrolled hypertension, and other contraindicated conditions. Our literature search identified a number of economic evaluations of orlistat and sibutramine treatment of obesity. Eight economic evaluations (one HTA and seven economic evaluations) were included in this report. Two studies reported that treatment with either orlistat or sibutramine was not cost-effective when compared with diet or lifestyle modifications alone. The six remaining studies all reported that orlistat and sibutramine were cost-effective; however, the HTA was the only study that suggested that sibutramine was more cost-effective than orlistat (the other studies either evaluated only one drug or deemed the two drugs to be equivalent in cost-effectiveness). The limitations in the reporting of the clinical studies, the absence of Canadian cost-effectiveness information, the presence of co-morbidities, as well as the unique adverse event profiles of each drug should perhaps be considered when deciding whether to use orlistat or sibutramine for the treatment of overweight or obese individuals.
REFERENCES:


