Clinical effectiveness and cost-effectiveness of using drugs in treating obese patients

What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review

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Executive summary

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Executive summary

Background

Obesity [defined as a body mass index (BMI) ≥ 30 kg/m^2] represents a considerable public health problem and the prevalence of obesity in England is reported to have increased between 1993 and 2004 from 13.6% to 24.0% among men and from 16.9% to 24.4% among women. It has been projected that 40% of Britons may be classed as obese by 2025. Overweight and obesity are associated with a significant range of comorbidities and are linked with increases in mortality.

The primary aim of the management of obesity is to achieve weight reduction in the interests of health. For obese patients who cannot achieve or maintain a healthy weight by non-pharmacological means, drug therapy is recommended in combination with non-pharmacological interventions such as dietary modifications and exercise.

Objectives

The objective of this research was to evaluate the clinical effectiveness and cost-effectiveness of pharmacological interventions compared with each other and with standard care in obese patients in primary care. Specific objectives included to analyse an existing database of clinical information from primary care; conduct a full systematic review of the published evidence on the clinical effectiveness of orlistat (Xenical®, Roche; Alli®, GlaxoSmithKline), sibutramine (Reductil®, Abbott) and rimonabant (Acomplia®, Sanofi-Aventis); undertake a full synthesis of the available evidence including the use of network meta-analysis; undertake a systematic review of the published evidence of the cost-effectiveness of the agents; use decision-analytic modelling and probabilistic sensitivity analysis to assess the relative cost-effectiveness of the three agents in terms of the incremental cost per quality-adjusted life-year (QALY) gained; and use expected value of information techniques to determine the potential benefits of future head-to-head trials of the agents.

Since the research question was formulated, two of the three pharmacological treatments have been withdrawn for safety reasons. Although the data for all three have been retained in the clinical and economic analyses, the value of information analyses exploring the potential benefits of future head-to-head trials for the agents have not been conducted.

Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of orlistat, sibutramine and rimonabant within their licensed indications for the treatment of obese patients. Electronic bibliographic databases including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–present), Web of Science and Conference Proceedings Citation Index (1990–present), BIOSIS Previews (1969–present) and Current Controlled Trials were searched in January 2009 and the reference lists of relevant articles were checked. Studies were included if they compared orlistat, sibutramine or rimonabant with lifestyle and/or exercise advice (standard care), placebo or metformin.

All studies were assessed for quality using an extended tool initially developed by Jadad *et al.* [Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing

the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12]. Where outcome data were missing measures of precision (such as standard errors), these were derived/imputed using previously established methods. Pair-wise meta-analysis was carried out for each comparison for the outcomes of achieved 5% weight loss, achieved 10% weight loss, weight and BMI at each of three time points (3, 6 and 12 months). Mixed-treatment comparison (MTC) methods were used to compare all treatments investigated within a single model (with placebo used as the reference category throughout). The MTC analysis was conducted using a Bayesian Markov chain Monte Carlo method. A logistic regression model was used for the binary outcomes and a linear regression model for the continuous outcomes.

To appropriately populate the economic decision model described in *Chapter 5,* a UK epidemiological model of the natural history of how changes in BMI affect the risk of major clinical events (development of diabetes, myocardial infarction, stroke and death) is required together with a model of how BMI levels change as a population ages. Longitudinal data from the General Practice Research Database (GPRD) were explored to determine time-to-event outcomes for all-cause mortality, myocardial infarction, stroke and onset of type 2 diabetes mellitus (T2DM). This model of the natural history of how changes in BMI affect the risk of major clinical events was conducted in order to appropriately populate the economic decision model. Subgrouping into cohorts with or without T2DM, Weibull proportional hazards regression models were derived to obtain the estimated hazard of each event of interest. These data were also used to determine the natural trajectory of BMI over time, for cohorts with or without T2DM, using multilevel models adjusted for sex and the interaction between age and sex, with age centred at 45 years.

A cohort simulation model was developed to explore the potential cost-effectiveness of pharmaceutical treatments for obesity. The pharmacological interventions (plus diet and exercise advice) were compared with placebo (plus diet and exercise advice). Effectiveness evidence (changes in BMI) was informed by the results of the MTC analyses. Initial transitions to obesity-related comorbidities and the natural trajectory of BMI over time were informed by the GPRD analyses. Health-related quality-of-life values were modelled using European Quality of Life-5 Dimensions data derived from respondents in the Health Survey for England and all costs were UK specific.

Results

Clinical results

Overall, 94 studies involving 24,808 individuals were included in the clinical meta-analysis. A total of 83 trials included data on weight change, 41 trial data on BMI change and 45 and 36 trial data on 5% and 10% body weight loss, respectively. Generally, the data quality of the trials included was low with poor reporting of standard errors and standard deviations.

Overall, the results show that the active drug interventions are all effective at reducing weight and BMI compared with placebo. In the case of sibutramine, the higher dose (15 mg) resulted in a greater reduction than the lower dose (10 mg). Although data were limited, the combination of orlistat and sibutramine also ranked highly. Interestingly, those interventions that have now been withdrawn from use (sibutramine and rimonabant) seem to be the most effective; however, their effectiveness is outweighed by the increase in adverse events.

General Practice Research Database results

Results from the seven BMI risk models showed consistent increases in risk as a result of an increasing BMI. This pattern was evident across all models except for the diabetic cohort with outcome myocardial infarction, for which a non-statistically significant ($p = 0.838$) reduction in

risk was observed. Adjustments for key confounders, such as age, sex and smoking status, were found to be statistically significant at the 5% level, in all seven risk models. More flexible survival models were investigated; however, the added complexity was deemed unnecessary.

A large variation in BMI trajectories was observed. Applying linear trajectory models showed an average increase in BMI of 0.040 per year for the diabetic cohort, for both men and women. The equivalent non-diabetic cohort model showed an increase in BMI of 0.175 per year for women; however, a statistically significant (at the 5% level) interaction between age and sex was observed, resulting in a slightly reduced increase in BMI of 0.145 per year for men. Baseline estimates (age 45 years) of BMI were similar across cohorts.

Economic results

The literature review identified 16 economic evaluations describing the costs and benefits associated with the three interventions. Compared with lifestyle advice, the mean incremental cost-effectiveness ratio for orlistat (sibutramine, rimonabant) ranged between £970 (£6941, £9303) and £59,174 (£10,042, £35,876). Although there was a wide variation in the modelling approaches and evidence used in the studies, the variable reported to have the largest effect on the results in the majority of the models was the period of weight regain modelled. Many of the models were also sensitive to changes in the values used to estimate the quality-of-life benefits attributed to weight changes, and the discount rates used. Only one study directly compared the pharmacological interventions, and the authors reported that rimonabant was cost-effective compared with either orlistat or sibutramine.

With an average cost per QALY of £557 compared with placebo, the results of the deterministic analyses suggest that sibutramine 15 mg dominates (the average costs are lower and the average QALYs are higher) the other three active interventions. The model is robust to variations in the key parameter values tested with the exception of the baseline BMI value. Although the probabilistic results show a larger range of uncertainty in the incremental QALY gain associated with both sibutramine treatments than in the QALY gain associated with orlistat, the net benefit analyses show that sibutramine 15 mg is the most cost-effective alternative for thresholds > £2000 per QALY. However, both sibutramine and rimonabant have been withdrawn because of safety concerns relating to potential treatment-induced fatal adverse events. Assuming that the adverse event occurs while on treatment, if the proportion of patients who experienced a fatal adverse event was greater than 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant) the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

Discussion

This is the first MTC of anti-obesity treatments to have been carried out. It utilises cutting-edge statistical methodology to compare treatments for which no head-to-head trials have been carried out, and hence we also present the first economic evaluation based on this evidence base.

Since the initiation of this project the Sibutramine Cardiovascular Outcomes trial has been published. The weight-loss data from this trial were not included in the MTC analysis as these were not reported for the time points of interest. However, as these data are broadly in line with our results, their exclusion is unlikely to have changed the conclusions drawn for the effectiveness outcomes considered.

There are several limitations of the analyses presented in this work. The clinical data were poorly or inaccurately reported in many studies, which could have produced inaccuracies in the

analyses. Our conservative assumptions, which were made to overcome the limitations of these data, may have underestimated the treatment effects in the MTC analyses. Although we regard the inclusion of the UK-specific data from the GPRD to be a particular strength of this work, the analyses are not without limitations because of (1) considerable inconsistencies in the clinical coding within the GPRD data set and (2) computational issues hindering more complex analyses of the substantial data sets. Finally, we were unable to accurately reflect the potential adverse event rates for sibutramine and rimonabant in the economic model, or present results separately for different subgroups, because of a paucity of effectiveness evidence in these areas.

Both sibutramine and rimonabant were effective medications for obesity management. Since their withdrawal clinicians have been limited to prescription of orlistat for weight reduction and clinicians are awaiting results of a number of new agents currently in the early stages of evaluation.

Conclusions

Currently, orlistat is the only licensed medication for the management of obesity. In clinical practice orlistat should be considered to aid weight reduction along with lifestyle interventions in those individuals who have not been successful in reducing their weight with lifestyle alone.

Our MTC of anti-obesity treatments shows that all of the active treatments are effective at reducing weight and BMI. The economic results show that, compared with placebo, the treatments are all cost-effective when using a threshold of £20,000 per QALY, and, within the limitations of the data available, sibutramine 15 mg dominates the other three interventions. However, if the proportion of patients who experienced a fatal adverse event was greater than 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant), the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

This work has highlighted many areas of methodological research that could be explored, including assessing inconsistencies within a network to determine differences between the results of pair-wise and MTC analyses; the use of meta-regression methods to look for effect modifiers; exploring the effect of local publication bias; and the use of joint models to analyse the repeated measures of BMI and the time-to-event processes simultaneously. From a clinical perspective, a long-term clinical trial for orlistat reporting hard clinical end points (cardiovascular events, onset of T2DM, incidence of cancer) would be particularly informative both from a clinical angle and to inform future economic evaluations. Clinical data from subgroups with high prevalence rates of obesity are also needed. Finally, robust long-term observational data in obese cohorts would be useful to inform the risk models that underpin the economic modelling.

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Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/85/02. The contractual start date was in January 2009. The draft report began editorial review in February 2011 and was accepted for publication in June 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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