

Antiobesity drug therapy: a call for more rigorous end-point evaluation



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'There is a clear need for a more systematic and comprehensive evaluation process for both current and future antiobesity agents.'

Over 1.1 billion people worldwide are overweight or obese and at risk for the numerous potential complications of excess body fat [1]. Prevalence estimates for adult obesity, which continue to rise in both developed and developing nations, are over 20% in many countries and have reached 32% in the USA [2,101]. Consequently, in the coming decades, marked increases in premature mortality, healthcare utilization and the incidence of chronic conditions, such as cancer and cardiovascular disease, are expected to result.

Individual lifestyle modification, idyllically viewed as the solution to the obesity epidemic, clearly has had limited effectiveness [3]. Obesity is a complex disorder that requires a sophisticated, multifaceted treatment approach at both the individual and societal levels. Pharmacotherapy is indicated in patients with medically complicated obesity and body mass index (BMI) levels of 27 kg/m² or greater, or in patients with BMI levels of 30 kg/m² or greater [3]. Drug therapy for obesity has traditionally languished on the fringes of mainstream medical science. To some extent, cynicism towards antiobesity drugs has been unjustifiably fueled by negative stereotypes of obesity as a condition borne from a 'lack of willpower' [4]. In addition, highly publicized cases of serious adverse events associated with past antiobesity drugs have cast a cloud over the entire therapeutic class. Obesity drug development is a legitimate and essential enterprise. Already, the efforts to identify new drug targets have resulted in major advances in our understanding of the intricate pathways involved in body weight regulation [5]. However, caution is indeed warranted and a systematic and comprehensive approach to the evaluation of new and existing antiobesity drugs is an absolute necessity.

Historical pitfalls of obesity pharmacotherapy

Although thermogenic agents, such as thyroid hormone, have been used to induce weight loss since the 1800s [6], the first agents officially approved for the treatment of obesity were the amphetamines and related congeners (Table 1). The anorectic agent desoxyephedrine was the first of this class approved by the US FDA in 1947 [7]. Amphetamines and related compounds have primarily only been studied in short-term clinical trials and result in average placebo-subtracted weight reductions of less than 4 kg in follow-up periods of less than 1 year [8]. They are not commonly prescribed for obesity because of their addictive potential and unfavorable adverse-effect profile (Table 1). In addition, aminorex, a sympathomimetic compound structurally related to amphetamines, released in Europe in 1965, was removed from the market 7 years later after published reports associated the drug with a 1000-fold increase in the odds of developing pulmonary hypertension [9].

'Obesity drug development is a legitimate and essential enterprise.'

Studies involving the combination agent Fen-Phen[®] (fenfluramine and phentermine) generated a great deal of interest in antiobesity drug therapy in the 1990s [10,11]. Fen-Phen consisted of fenfluramine, a serotonergic agent, and phentermine, an amphetamine derivative (Table 1). Combination therapy minimized adverse effects while maintaining efficacy. In one 34-week study involving 121 obese patients, Fen-Phen significantly reduced weight by 11% more than placebo [11]. However, in 1996, a prominent report was published associating fenfluramine and its D-isomer, dexfenfluramine, with an increased risk of pulmonary hypertension [12]. By 1996, over 50 million patients worldwide had been prescribed fenfluramine [6]. Subsequent data emerged, noting an increased risk of cardiac valvulopathy with fenfluramine therapy [13]. Dexfenfluramine and fenfluramine were removed from the market in 1997 [6,13].

Although technically not regarded by many as true antiobesity agents, ephedrine and phenylpropanolamine are sympathomimetic agents that have been used as weight-loss supplements and have subsequently been associated with serious adverse events. Ephedrine, a common ingredient of many over-the-counter decongestants and herbal preparations, such as Ma Huang, minimally reduced weight and was associated with adverse effects, such as tremor and palpitations [6]. Ephedrine-containing dietary supplements were banned by the FDA in 2004 [102]. Phenylpropanolamine, also commonly sold as a decongestant, was removed from the market in 2000 after it was found to be associated with an increased risk of intercerebral hemorrhage in women [14].

'In 2005, the global antiobesity drug market was valued at US\$1.2 billion...'

Current antiobesity drugs approved for long-term use

In 2005, the global antiobesity drug market was valued at US\$1.2 billion, with almost 70% of this revenue generated from sales of orlistat (Xenical®) and sibutramine (Meridia®, Reductil®) [103]. Orlistat, a pancreatic and gastric lipase inhibitor, reduces dietary triglyceride absorption by approximately 30% [15]. Sibutramine, a serotonin- and noradrenaline-reuptake inhibitor, was initially developed as an antidepressant. This agent primarily increases satiety, with possible secondary effects to increase thermogenesis [15]. Sibutramine does not have the addictive potential of amphetamines nor has it been linked to pulmonary hypertension or valvular heart disease. In contrast to fenfluramine and dexfenfluramine, sibutramine only inhibits serotonin uptake and does not promote serotonin release.

Rimonabant (Acomplia®), the newest antiobesity drug on the market, was approved for use in the EU in 2006 and is under consideration for approval in the USA. Rimonabant blocks endocannabinoid-1 receptors, resulting in appetite reduction and several peripheral actions to reduce body weight (Table 1) [15].

Placebo-subtracted weight losses resulting from orlistat, sibutramine or rimonabant average 5 kg or less in clinical trials of 1–4 years duration (Table 1) [16,17]. Modest improvements in cardiovascular risk factors also may result. Orlistat has also been shown to reduce the

incidence of diabetes in a 4-year trial [18]. Currently, it is not clear if this represents a true preventive effect as opposed to a 'delay' or 'masking' effect [19]. High attrition rates (between 30–60%) have limited the internal validity of many trials involving all three agents [20]. Major adverse effects for each drug are summarized in Table 1.

'Evidence of a beneficial effect on end points, such as cardiac disease, cardiovascular mortality or total mortality, is not required for the approval or ongoing use of antiobesity drugs.'

Current lack of morbidity & mortality end-point data

Evidence of a beneficial effect on end points, such as cardiac disease, cardiovascular mortality or total mortality, is not required for the approval or ongoing use of antiobesity drugs. Many feel that such a requirement would be unrealistic, given that thousands of patients would need to be studied for several years in order to have adequate power to detect a clinically important reduction in events. While limiting enrollment to high-risk populations would significantly reduce sample-size requirements, to date, antiobesity drug trials have almost exclusively avoided enrolling such patients and have instead focused on repeatedly re-examining such surrogate end points as change in weight, blood pressure, lipid profiles and glycemic control.

In 2002, sibutramine, which can raise blood pressure and heart rate, was temporarily removed from the Italian market amid concerns of adverse cardiac events and two cases of sudden death [21]. After review, the European Agency for the Evaluation of Medical Products concluded that the drug was not causally implicated and that its risk:benefit ratio remained favorable [6]. However, as a condition of ongoing approval, the regulatory agency required that further studies be performed demonstrating that the drug was safe. In response, the manufacturer commissioned the Sibutramine Cardiovascular Outcome Trial (SCOUT), a multicenter, double-blind, placebo-controlled randomized trial of 9000 obese and overweight patients evaluating the effect of sibutramine on myocardial infarction (MI), stroke and cardiovascular mortality [22].

Table 1. Past and current approved antiobesity drugs.

Drug(s) (trade name)	Mechanism of action	Major adverse effects	Comments
Centrally acting anorectic agents			
Amphetamine and related congeners: DEA schedule II* : amphetamine or dexamphetamine (Biphphetamine®), methamphetamine or desoxyephedrine (Desoxy® [®] , Hydrim®)	Sympathomimetic amines that potentiate catecholaminergic activity primarily by promoting release.	Sympathomimetic effects including hypertension, tachycardia, nervousness, palpitation, aggression and tremor.	Short-term (<1 year), small, placebo-controlled trials generally show weight losses of 4 kg or less. Not approved for long-term use. Phentermine is most commonly prescribed.
DEA schedule III : benzphetamine (Didrex®), phendimetrazine (Bontril® [®] , Plegine® [®] , Prelu-2® [®] , X-Trozzine®)	Mazindol blocks norepinephrine reuptake.	Schedule II and III agents are not used due to addictive potential.	
DEA schedule IV : diethylpropion (Tenuate®), mazindol (Sanorex® [®] , Mazanor® [®]), phentermine (AdipeX-P® [®] , Fastin™ [™] , Ionamin® [®] , Oby trim®)	Promote serotonin release and inhibit reuptake.	Sympathomimetic, pulmonary hypertension and cardiac valvulopathy.	Removed from the market in 1997.
Fenfluramine (Pondimin®) and dexfenfluramine (Redux®). Combination marketed as Fen-Phen®	Sympathomimetic amine that increases norepinephrine levels and blocks serotonin uptake.	Sympathomimetic and pulmonary hypertension	Approved in several European countries in 1965. Removed from the market in 1972.
Aminorex (Menocil®)	α- and β-agonist with norepinephrine-releasing properties. Also increases thermogenesis.	Sympathomimetic	Licensed in Denmark in the 1970s. Elsewhere, primarily used OTC. Banned by the US FDA in 2004.
Ephedrine	α- and β-agonist with norepinephrine-releasing properties.	Sympathomimetic, hemorrhagic stroke	Primarily used OTC as weight loss supplement. Withdrawn from the market in 2000.
Long-term approved agents			
Sibutramine (Meridia® [®] , Reductil®)	Monoamine-reuptake inhibitor (primarily serotonin and norepinephrine). Primary action is to increase satiety with secondary effects on thermogenesis.	Weight loss of 4.3 kg (95% CI: 3.6–4.9) in studies of 1-year. May increase blood pressure and pulse rate.	Weight loss of 2.7 kg (95% CI: 2.3–3.1) over 1 year and a 37% reduction in diabetes incidence in high-risk patients. Gastrointestinal side effects limit tolerance. Multivitamin prescribed concurrently to prevent fat-soluble vitamin deficiency. Half-strength dosage recently approved for OTC use in the USA.
Orlistat (Xenical®)	Inhibits gastric and pancreatic lipase by binding covalently to the serine moiety on the active site. Limits breakdown and subsequent absorption of triglycerides by 30%.	Endocannabinoid-1 receptor antagonist. Acts centrally to reduce food intake and peripherally to decrease lipogenesis, increase thermogenesis and augment adiponectin activity.	Weight loss of 4.6 kg (95% CI: 4.3–5.0) over 1 year.

*Schedule I drugs have the highest potential for abuse and Schedule V have the lowest [105]. CI: Confidence intervals; DEA: Drug Enforcement Administration; OTC: Over the counter.

At least one other major outcomes study in obesity pharmacotherapy is underway. The Comprehensive Rimonabant Evaluation Study of Cardiovascular END points and Outcomes (CRESCENDO) study is a double-blind, placebo-controlled, randomized trial examining the impact of rimonabant on MI, stroke and cardiovascular death in 17,000 centrally obese patients at high cardiovascular risk [104].

Morbidity & mortality end points should be a requirement for ongoing use

In my opinion, the ongoing approval (after initial release) of current and new antiobesity drugs should be contingent upon the performance of methodologically rigorous morbidity and/or mortality outcomes trials. This would include evaluation of the effects of the drug upon the incidence of MI, stroke, sleep apnea, cardiovascular mortality and/or total mortality. Such trials should be planned in advance and executed within the first half-decade of drug approval. Given the lack of morbidity/mortality evidence to-date, a placebo control group would be the appropriate reference standard at this time.

There are several reasons why such end-point data are needed:

Obesity is a chronic illness associated with a substantial increase in cardiovascular and overall mortality. Weight regain occurs if therapy is discontinued. In many cases, treatment will need to be continued indefinitely and, because of this potential for long-term therapy, proper end-point evaluation is a must.

When the need for long-term therapy is considered in the context of the hundreds of millions of patients eligible for antiobesity drug therapy, the potential use of these agents is unrivalled by any other therapeutic class of drugs. Furthermore, projections of future exposure must also include inappropriate usage of antiobesity drugs by normal weight individuals. In one study, 13% of individuals taking antiobesity drugs did not meet current criteria for treatment [23]. 50% of patients taking aminorex were only slightly (10%) overweight and would also not meet current criteria for drug treatment [9]. The enormous potential usage of antiobesity drugs dictates the need to be certain that, at the very least, these drugs do not have a detrimental effect on morbidity and mortality end points.

The net reduction in body weight and associated risk factors attributable to drug therapy is modest [16,17]. A patient who was significantly obese prior to taking an antiobesity drug invariably

remains significantly obese during therapy. Accordingly, surrogate end points alone are an inadequate measure of the ultimate benefit of the drug, particularly given prior examples in the cardiovascular field where improvements in surrogate end points did not translate into reductions in more clinically relevant ones [24,25].

‘Performing methodologically rigorous trials evaluating morbidity/mortality end points will more clearly legitimize antiobesity drug therapy.’

Performing morbidity/mortality studies will also encourage the enrollment of high-risk individuals into clinical trials. These are the patients that stand to gain the most from treatment and are not the patients that should be being systematically excluded from clinical trials.

Obesity drugs are costly and this is particularly troublesome for a patient population that is disproportionately socioeconomically disadvantaged. In the UK, a 1-month prescription for orlistat, sibutramine and rimonabant each cost GB£40–55 or US\$80–110 [105]. Furthermore, economic evaluations of antiobesity drugs are based upon models that assume these agents favorably impact upon morbidity and mortality end points [26]. There are no data to verify many of these assumptions. It is critical that these assumptions be verified so that more accurate benefit/risk assessments of these agents can be performed.

‘Morbidity and mortality trials ... show that the field of antiobesity therapeutics is evolving in the right direction.’

History has shown that antiobesity drugs can cause serious adverse effects. In addition, many question the basic premise of using drugs to treat obesity. Both of these factors contribute to stigmatization of antiobesity drug treatments. Performing methodologically rigorous trials evaluating morbidity/mortality end points will more clearly legitimize antiobesity drug therapy.

Morbidity/mortality trials are expensive but not prohibitively so and such studies are entirely feasible. Orlistat has been available for nearly a decade and has been studied in clinical trials involving over 10,000 patients. Many identically designed trials have been repeatedly performed, with minor modifications made to the patient population under study (e.g., different ethnic groups) [16]. It is much more useful to generate

morbidity/mortality end point data rather than repeatedly demonstrating nearly identical benefits on surrogate end points.

‘...there needs to be a change in philosophy such that studies such as SCOUT are planned and executed in a proactive manner, rather than in reaction to concerns raised about the potential harm of a drug.’

In exchange for performing morbidity and mortality outcome trials, incentives can be provided to pharmaceutical companies. For example, extension of the exclusive-rights period to sell a drug may be considered [27]. This would ensure that companies have the opportunity to recoup the costs of performing such trials. In addition, a lack of a beneficial effect on morbidity/mortality end points does not automatically imply that a drug should be removed from the market. At the very least, a trial with neutral results can provide reassurance that the drug is not harmful. Other end points, such as improvements in quality of life and reductions in the severity of arthritis pain, are also important, provided these reductions are clinically

significant. However, morbidity/mortality data do provide a much more accurate assessment of the net overall benefit of the drug and the cost:benefit ratio of prescribing a given agent.

Future perspective

The next decade will mark a critical period in the history of obesity pharmacotherapy. The high (and increasing) prevalence of obesity will fuel interest and investment in new and effective treatments. Improved understanding of the pathways responsible for weight regulation has already identified many new drug targets, and numerous new agents are currently under development [28]. As the majority of these are in early-to-mid-phase testing, it will take at least 5–10 years before the most advanced are available for clinical use.

Morbidity and mortality trials, such as SCOUT and CRESCENDO, show that the field of antiobesity therapeutics is evolving in the right direction. However, there needs to be a change in philosophy such that studies such as SCOUT are planned and executed in a proactive manner, rather than in reaction to concerns raised about the potential harm of a drug. All stakeholders, including industry, funding agencies, regulators,

Executive summary

- Obesity is a highly prevalent chronic condition leading to considerable morbidity and mortality.
- There is an urgent need for new and effective treatments. Exploring novel drug treatments is important and necessary.

Historical pitfalls of obesity pharmacotherapy

- There are several past examples where postmarketing studies have identified serious adverse effects associated with antiobesity drug treatments.

Current antiobesity drugs approved for long-term use

- Orlistat, rimonabant and sibutramine are the three agents currently prescribed for long-term treatment of obesity.
- All three agents reduce weight by less than 5 kg, may modestly improve some cardiovascular risk factors, are expensive and have specific adverse effects.

Current lack of morbidity & mortality end-point data

- There are no data evaluating the effect of antiobesity drug therapy on cardiovascular morbidity, cardiovascular mortality or overall mortality.
- The approval of antiobesity drug therapy is based on surrogate end points, such as weight loss and improvements in cardiovascular risk factors.
- Two major trials examining morbidity/mortality end points are underway for sibutramine (Sibutramine Cardiovascular OUTcome trial [SCOUT]) and rimonabant (Comprehensive Rimonabant Evaluation Study of Cardiovascular End points and Outcomes [CRESCENDO]). The SCOUT trial was commissioned in response to concerns regarding the cardiovascular toxicity of sibutramine.

Morbidity & mortality end points should be a requirement for ongoing use

- Morbidity/mortality trials should be planned in advance and executed for all antiobesity drugs.
- This is particularly important in obesity since it is a highly prevalent chronic condition requiring long-term therapy, prior agents have been found to be toxic, current drugs are costly, there is potential for off-label use and the overall risk:benefit ratio is largely unknown.

Future perspective on antiobesity therapy

- The potential market for antiobesity drugs will likely increase and many new agents are currently under investigation.
- All stakeholders have a vested interest in pursuing a proactive approach to the comprehensive evaluation of antiobesity drugs that includes examination of morbidity/mortality end points.

clinicians and patients, have a vested interest in ensuring that this occurs. For manufacturers of antiobesity drugs, the importance of such data as a means to 'legitimize' the use of antiobesity drugs cannot be underemphasized. Ultimately, we must learn from past lessons and strive to offer the best possible treatments to those that suffer from this highly significant and globally prevalent disorder.

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