What Cost Weight Loss?

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Obesity has important adverse health consequences associated with multiple metabolic, structural, degenerative, neoplastic, and psychological effects that reduce quality of life and increase mortality. Given the epidemic of obesity in the United States and worldwide, treatment of obesity has emerged as 1 of the greatest present unmet medical needs and a target for pharmacological interventions. Factors underlying the population’s rapid increase in excess weight, as well as reasons for difficulty achieving and sustaining weight loss, remain incompletely understood. Medications have been used to assist in weight loss for almost 80 years, but adverse effects frequently restrict their utility. Norepinephrine reuptake inhibitors are available for short-term administration to promote weight loss, but weight regain is common when use is discontinued. The weight loss drugs fenfluramine and dexfenfluramine, intended for long-term use, were removed from the US market in 1997 because of the occurrence of left-sided valvular heart disease; phenylpropanolamine was withdrawn in 2000 for its association with hemorrhagic stroke; and rimonabant was available briefly in Europe but was withdrawn because of its association with depression and suicidal ideation before its approval in the United States. Currently, there is only 1 medication (orlistat) approved for the long-term treatment of obesity by the US Food and Drug Administration (FDA) after the recent voluntary withdrawal of sibutramine from the US market. In contrast, surgical treatments for obesity have become important alternatives to pharmacotherapy, especially since the advent of less invasive laparoscopic techniques. Surgically induced weight loss is often substantial and is associated with improvements in obesity-related diseases such as diabetes mellitus, hypertension, dyslipidemia, and obstructive sleep apnea, as well as with reductions in cancer risk and mortality. With the development of less invasive techniques, apparent reduced procedure-related morbidity, and the absence of alternatives, bariatric surgical procedures are being performed with increasing frequency.

With great hope for the approval of novel weight loss agents by the medical community, in 2010 the Endocrinologic and Metabolic Drugs Advisory Committee to the FDA evaluated multiple new agents for weight management, including phentermine/topiramate (Qnexa) on July 15, 2010, lorcaserin (Belviq) on September 16, 2010, and naltrexone/bupropion (Contrave) on December 7, 2010, as well as the postmarketing cardiovascular safety of sibutramine (Meridia) as examined in the Sibutramine Cardiovascular Outcomes Trial (SCOUT) on September 15, 2010. All 3 new agents achieved clinically meaningful weight loss according to the 2007 FDA guidance criteria. The guidance stipulates a drug would be considered effective if either of 2 criteria were satisfied, including (1) a mean efficacy criterion, in which the difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant, or (2) the categorical efficacy criterion, in which the proportion of subjects who lose ≥5% of baseline body weight in the active-product group is at least 35% and is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant. Although they met weight loss criteria targets (Table), each agent was associated with variable risk-benefit profiles, and after careful review, the FDA or the advisory committees considered the balance of risk to benefit to be generally unfavorable. For each agent, the number of patients needed to successfully demonstrate significant and sustained weight loss in the development programs was considerably less than the number required for safety exposure to rule out risks that were specific topics of concern.

Weight Loss Pharmaceutical Agents in 2010 Phentermine/Topiramate Phentermine monotherapy was approved in 1959 for the short-term treatment of obesity. When initially approved in 1959, there was no restriction on the duration of its use. In approximately 1973, the indication for all anorectics was limited to short-term use. Although the phen-fen (phentermine-fenfluramine) combination, of which phentermine was a component, was linked to increased risk for cardiac valvulopathy, this appears attributable to the fenfluramine component. Phentermine induces central norepinephrine release and promotes weight loss by reducing food intake. Topiramate monotherapy was approved in 1996 for the treatment of seizures and in 2004 for migraine prophylaxis. Topiramate exhibits a combination of properties that include effects on sodium channels, enhancement of γ-aminobutyric acid (GABA)–activated chloride channels,
Table. Mean Weight Loss on Active Treatment or Placebo in Randomized Controlled Trials of Recent Weight Loss Drugs Reviewed by the FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active Treatment Weight Loss</th>
<th>Placebo Weight Loss</th>
<th>Mean Difference From Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat 120 mg TID</td>
<td>4.1</td>
<td>1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Rimonabant 20 mg QD</td>
<td>-6.5</td>
<td>-1.7</td>
<td>-4.8</td>
</tr>
<tr>
<td>RIO-North America</td>
<td>-6.9</td>
<td>-2.1</td>
<td>-4.8</td>
</tr>
<tr>
<td>RIO-Europe</td>
<td>-7.4</td>
<td>-1.9</td>
<td>-5.5</td>
</tr>
<tr>
<td>RIO-Lipids</td>
<td>-5.5</td>
<td>-1.6</td>
<td>-3.9</td>
</tr>
<tr>
<td>Qnexa (phentermine/topiramate) 15/92 mg QD</td>
<td>-10.9</td>
<td>-1.6</td>
<td>-9.3</td>
</tr>
<tr>
<td>OA-302 (no diabetes)</td>
<td>-9.8</td>
<td>-1.2</td>
<td>-8.6</td>
</tr>
<tr>
<td>OA-303 (16% with diabetes)</td>
<td>-9.8</td>
<td>-1.7</td>
<td>-8.1</td>
</tr>
<tr>
<td>Lorcaserin 10 mg BID</td>
<td>-5.9</td>
<td>-1.7</td>
<td>-4.2</td>
</tr>
<tr>
<td>APD356-009 BLOOM</td>
<td>-5.8</td>
<td>-2.2</td>
<td>-3.6</td>
</tr>
<tr>
<td>APD356-011 BLOSSOM</td>
<td>-5.9</td>
<td>-2.8</td>
<td>-3.1</td>
</tr>
<tr>
<td>Pooled, no diabetes</td>
<td>-5.8</td>
<td>-2.5</td>
<td>-3.3</td>
</tr>
<tr>
<td>Contrave (naltrexone 32 mg/buproprion 360 mg) QD</td>
<td>-6.1</td>
<td>-1.3</td>
<td>-4.8</td>
</tr>
<tr>
<td>NB-301 (no diabetes)</td>
<td>-6.1</td>
<td>-1.3</td>
<td>-4.8</td>
</tr>
<tr>
<td>NB-302 (no diabetes)</td>
<td>-9.3</td>
<td>-5.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>NB-303 (week 28 primary end point)</td>
<td>-6.5</td>
<td>-1.9</td>
<td>-4.6</td>
</tr>
<tr>
<td>NB-304 (diabetes)</td>
<td>-5.0</td>
<td>-1.8</td>
<td>-3.2</td>
</tr>
<tr>
<td>Sibutramine 10–15 mg/d</td>
<td>-4.97</td>
<td>-0.69</td>
<td>-4.28</td>
</tr>
</tbody>
</table>

FDA indicates Food and Drug Administration; TID, 3 times per day; QD, daily; RIO, Rimonabant in Obesity; BID, 2 times per day; BLOOM, Behavioral Modification and Lorcaserin for Overweight and Obesity Management; and BLOSSOM, Behavioral Modification and Lorcaserin Second Study for Obesity Management.

Adapted from Table 2, page 16, of FDA briefing document on NDA 200063 from December 7, 2010. Adapted from Table 2, page 16, of FDA briefing document on advisory committee meeting September 15, 2010. In the SCOUT study (Sibutramine Cardiovascular Outcomes Trial), changes in weight were assessed from the time of enrollment. The design of the trial was to place all subjects on active drug during the first 6-week lead-in, when all subjects lost 5% of baseline body weight after 1 year of treatment compared with 20% of those treated with placebo; however, adverse events led to high withdrawal rates. Potential safety issues of concern included an imbalance in depression and cognitive-related complaints; potential cardiovascular risk from the sympathomimetic amine activity of the phentermine, with a small increase in heart rate; reduced serum bicarbonate (due to the carbonic anhydrase inhibition of topiramate), which could exacerbate metabolic acidosis in susceptible individuals; and the potential for teratogenicity that has been demonstrated with topiramate in mice, rats, and rabbits. In consideration of the overall benefit-risk of PHEN/TPM, the Endocrine and Metabolic Advisory Committee voted 6 in favor of approval and 10 against. The FDA has declined approval of Qnexa for weight management at this time.

Lorcaserin

Lorcaserin (Lorqess; Arena Pharmaceuticals, San Diego, CA), a novel serotonergic agent, has greater binding affinity and activation of the 5-hydroxytryptamine (5HT) 2c than the 2a or 2b receptor subtypes, and given the tissue distribution of the receptor subtypes, it would be expected to have a reduced cardiac valve risk profile compared with earlier serotonergic agents, such as fenfluramine. Lorcaserin registration trials included over 7200 individuals. The placebo-corrected weight loss observed in the lorcaserin-treated groups was approximately 2% and 3.4% at the 10-mg daily and twice-daily doses, respectively. Forty percent and 47% of patients lost ≥5% of baseline body weight when treated with the lorcaserin 10 mg daily and twice-daily doses, respectively, compared with 23% of placebo-treated patients. Furthermore, lorcaserin was associated with improvements in systolic and diastolic blood pressure, lipoprotein lipid levels, fasting glucose and insulin concentrations, and concentrations of C-reactive protein, all thought to portend potential cardiovascular benefits. The development program did prospectively adjudicate cardiac valve abnormalities using appropriate core laboratory methods, and this analysis did not demonstrate increased risk for valvular heart disease; however, neuropsychiatric and cognitive-related adverse events occurred with approximately double the frequency in patients treated with lorcaserin compared with placebo. In addition, mammary tumors were seen in female rats treated with lorcaserin at doses 7-fold that proposed for clinical use, although no imbalance in reported cancer incidence was seen in the clinical program. In consideration of the overall benefit-risk of lorcaserin, the Endocrine and Metabolic Advisory Committee voted 5 in favor of approval and 9 against. The FDA has declined approval of Lorqess for weight management at this time.

Sibutramine

Sibutramine (Meridia; Abbott Laboratories, Abbott Park, IL) provides an example of a marketed weight loss drug that had cardiovascular safety concerns at the time of initial approval that were subsequently addressed by a postapproval safety study. Sibutramine was first approved by the FDA in 1997 for obesity management. The drug has sympathomimetic properties, acting centrally to block the neuronal uptake of inhibition of excitatory neurotransmission through actions on kainate and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, and inhibition of carbonic anhydrase isoenzymes, but specific mechanisms promoting weight loss remain unclear. In combination, phentermine and topiramate (PHEN/TPM; Qnexa, Vivus, Inc, Mountain View, CA) promote greater weight loss than either agent alone, as assessed in phase 3 trials that included approximately 3800 patients. PHEN/TPM 15/92 mg/d resulted in approximately 9% placebo-corrected weight loss, and 62% of PHEN/TPM-treated subjects lost ≥5% of baseline body weight after 1 year.
norepinephrine and serotonin, as well as stimulating peripheral β3-adrenergic receptors to induce satiety.10,11 Findings reviewed at the time of initial approval demonstrated that sibutramine led to a placebo-adjusted mean weight loss of approximately 4%, with twice as many patients (responders) losing at least 5% of baseline body weight as those randomized to placebo, consistent with the new FDA guideline for obesity drugs; however, drug effects also included a notable increase in systolic and diastolic blood pressure and heart rate. On the basis of these adverse hemodynamic effects, initial product labeling warned against use of the drug in patients with a history of coronary artery disease, stroke, congestive heart failure, arrhythmia, or uncontrolled hypertension. Despite these warnings, a number of adverse cardiovascular events were reported in Europe in 2002, which led the European regulatory authorities to require the sponsor to perform a formal safety study to definitively address the cardiovascular risk profile of this compound.

When the initial development program of a new drug reveals potential adverse effects on cardiovascular biomarkers, there may be considerable challenges in acquiring a sufficient number of adverse events to rule out a safety concern, especially for a drug not intended for use in populations such as those at high risk for cardiovascular events. This challenge was highlighted in the SCOUT trial, reviewed as part of the safety assessment for continued approval in the United States by the Endocrinologic and Metabolic Drugs Advisory Committee at the September 15, 2010, meeting along with integrated safety information from previous trials (excluding SCOUT).12 The original drug development program included 46 studies of 9303 overweight or obese subjects (5812 taking sibutramine and 3491 taking placebo) and was primarily focused on demonstration of efficacy and limited in its ability to evaluate safety in regard to cardiovascular or mortality outcomes. For example, cardiovascular events were acquired via adverse event reporting and were not prospectively adjudicated as to the ischemic origin of the event. Furthermore, 26 of the studies were short-term (≤24 weeks), and most patients enrolled were at low risk for cardiovascular events. Not surprisingly, cardiovascular adverse events were rare, reported in 0.5% of subjects taking sibutramine and 0.6% taking placebo, with only 4 deaths noted in each group (sibutramine and placebo). Thus, these early efficacy studies gave no hint of a cardiovascular safety signal in spite of concerns related to the known increase in blood pressure and heart rate with the drug. This left regulators and providers with residual uncertainty and inability to definitively conclude the drug was safe on the basis of the available data, and the product labeling warning informed against use in highest-risk people.

The SCOUT trial addressed many of these concerns.13 Subjects were enrolled who had an increased risk of cardiovascular events (compared with the efficacy studies summarized above) and who had an elevated body mass index and a history of cardiovascular disease, cerebral vascular disease, peripheral artery disease, or type 2 diabetes mellitus with an additional cardiovascular risk factor. The rationale was to increase the potential number of events that caused irreversible cardiovascular harm, with the expectation that because the underlying mechanism of these events was common to all risk groups, the relative risks could be generalized. As seen in many recent cardiovascular outcome trials, despite enrolling a population at enhanced risk, the anticipated annual rate of cardiovascular events (projected to be 7%) was not achieved, and thus, the study was modified to extend and restrict the recruitment to subjects at the highest risk (history of cardiovascular disease and type 2 diabetes mellitus) to increase the rates of events, with the hope that events would be lower in the sibutramine-treated participants. There were 3 prospectively defined risk groups, which included subjects with diabetes mellitus alone, those with cardiovascular disease alone, and those with both conditions. The study design included a 6-week single-blind lead-in phase in which 10,744 subjects received 10 mg of sibutramine daily plus lifestyle modification. A total of 9804 subjects were subsequently randomized (940 did not complete the run-in because of adverse events, protocol violations, or withdrawal of consent). The mean duration of exposure to sibutramine or placebo was 3.4 years, but only 58% of subjects completed the trial on study medication. The primary end point was adjudicated major adverse cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, and resuscitated cardiac arrest, assessed with an intention-to-treat analysis. The results demonstrated a hazard ratio for the primary end point of 1.16 (95% confidence interval [CI] 1.03–1.31, \( P=0.015 \)). The excess cardiovascular risk was driven by significant increases in nonfatal myocardial infarction and nonfatal stroke but not by cardiovascular death. However, the fact that the drug was neutral with regard to cardiovascular death is in contrast to the expectation of patients and providers and expressed in the FDA obesity guidance, that successful weight loss would be associated with a decrease in mortality. In the prespecified patient subgroups, the hazard ratio for the primary end point was 1.01 (95% CI, 0.74–1.38) in subjects with diabetes mellitus only, 1.28 (95% CI, 0.92–1.78) in subjects with cardiovascular disease alone, and 1.18 (95% CI, 1.02–1.37) in subjects with combined cardiovascular disease and diabetes mellitus. Although there was an apparently greater hazard ratio for major cardiovascular events in patients with underlying cardiovascular disease relative to diabetes mellitus alone, the probability value for interaction was 0.56, which indicates that the magnitude of increased risk was not different across the 3 patient strata. Furthermore, the upper bound of the 95% CI for the primary end point was 1.38 for the diabetes mellitus-alone group and 1.37 for the cardiovascular disease and diabetes mellitus group, which means that the amount of risk excluded by the data was identical for the lowest- and highest-risk groups.

On the basis of the results of SCOUT, the FDA Endocrine and Metabolism Advisory Committee was asked to evaluate the safety of sibutramine, with voting options ranging from making no changes to the product labeling to removing the drug from the market. A major question before the committee was the appropriateness of applying the results of a safety study that had enrolled patients for whom the product has a specific warning against its use. The sponsor (responsible for the design and conduct of the study) argued that the diabetes
mellitus-alone subgroup from SCOUT most resembled subjects for whom the drug was intended, and because the point estimate of harm was 1.01 in that subgroup, the risks could be mitigated by simply excluding patients with cardiovascular disease from use in a revised product label. The challenge with this argument was the statistical homogeneity of the hazard ratios across the 3 subject subgroups and the similar 95% upper boundaries in the diabetes mellitus group compared with the overall result, combined with the absence of a mortality benefit in any group. Although the absolute risk for a cardiovascular event was lower in the diabetes mellitus-only subgroup (6.5%) than for the cardiovascular and diabetes mellitus subgroup (11.9% given placebo), given the exposure of a weight loss drug in the US population, the overall relative risk excess (16% in the total study population) remained substantial.

Although health is better in those subjects who never become obese or in those who can control their obesity by losing weight via a combination of dietary modification and exercise, only a minority of people achieve substantial weight loss through lifestyle. When one chooses a medication, it is important to remember that the mechanism by which weight loss drugs are presumed to lead to cardiovascular health benefits is through loss of weight per se, because the drugs themselves would not be expected to be cardioprotective. The possibility that survival benefits from weight loss may take longer to manifest further complicates drug development and approval processes. In the case of the sympathomimetic drugs, the issue was whether the loss in weight would offset the potential increase in cardiac risk caused by the drug. In the case of sibutramine, responders to the drug (those who met the categorical criterion of 5% weight loss) could be identified in the first several months of treatment, because those subjects lost significant amounts of weight, whereas nonresponders did not. However, in the SCOUT trial, sibutramine continued to be administered for up to 6 years regardless of the individual subject’s degree of weight loss. Subjects not losing weight would therefore be exposed to the risk of the drug without any anticipated benefit. Thus, it remains unknown whether it would be better to lose weight with sibutramine than to remain obese when nonpharmaceutical approaches are unsuccessful. Although the on-treatment analysis of SCOUT yielded similar results as the primary analysis for risk of cardiovascular events, it remains unclear whether the early responders taking sibutramine did better than those who did not lose weight in the placebo group.

Because there were no data to support the idea that monitoring either vital signs or degree of early weight loss would be predictive of subjects who should not continue the drug, there did not appear to be a particular low-risk subgroup of patients or a hemodynamic or weight loss response profile that could guide clinical decisions for use of the drug that would substantially alter the overall unfavorable risk-benefit ratio of sibutramine. After weighing the overall evidence presented by the FDA and the sponsor, the committee was split regarding whether the drug should be removed from the market versus simply applying greater restrictions through labeling. On October 8, 2010, the FDA asked for the voluntary withdrawal of sibutramine from the US market, a request with which Abbott, the maker of sibutramine, complied.

**Naltrexone/Bupropion**

The naltrexone slow-release (SR)/bupropion SR combination (Contrave; Orexigen, La Jolla, CA) functions as a μ-opioid receptor antagonist combined with a norepinephrine and dopamine receptor inhibitor. The active ingredients have been used in humans for more than 20 years. Bupropion has neuronal effects that lead to reduced energy intake and increased energy expenditure, whereas naltrexone is expected to potentiate this effect.14,15 The drug combination was evaluated by the Endocrine and Metabolic Advisory Committee on December 7, 2010, and similar concerns to those exhibited by sibutramine were raised. Findings were presented from four 56-week phase 3 trials, including 1 trial in subjects with diabetes mellitus. In all 4 trials, the mean placebo-subtracted weight loss was less than 5%, thus missing 1 FDA criterion for approval, but 2 studies did meet the categorical criterion of the proportion of patients who achieved >5% weight loss being greater than 35% of the subjects and twice that seen in the placebo group. As with sibutramine, weight loss in these phase 3 trials was associated with improvements in the lipid profile (reduced triglyceride and increased high-density lipoprotein cholesterol levels) and improvements in glucose metabolism in subjects with diabetes mellitus. In addition, the naltrexone SR/bupropion SR trials documented better patient-reported outcomes (using questionnaires nonvalidated by FDA standards). However, the hemodynamic properties of the drug combination mirrored sibutramine, including an attenuation of the expected weight loss–induced reduction in blood pressure and an absolute increase in pulse by 1 to 2 bpm. Separate analyses evaluated responders (≥5% decrease in body weight) versus nonresponders in the placebo and treated groups. Although all subjects randomized to active drug had a sustained increase in heart rate, placebo responders had a net decrease. Similarly, placebo responders had the greatest decrease in systolic and diastolic blood pressure and pulse-rate product relative to placebo nonresponders or drug responders (and nonresponders). Thus, only the placebo responders in the naltrexone SR/bupropion SR phase 3 trials demonstrated an association between effective weight loss and a concordant improvement in all the biomarkers of blood pressure, heart rate, lipids, and glycemic control among people with diabetes mellitus.

Safety concerns included increased rates of hypertension, seizure, and syncope compared with placebo. There was 1 death in a subject taking naltrexone/bupropion, which was attributed to myocardial infarction, and 2 additional subjects experienced a nonfatal myocardial infarction; 1 participant had a cerebrovascular accident while taking placebo. Clearly, the safety database was inadequate to form any judgment as to the overall risks and thus the cardiovascular and mortality risk-to-benefit ratio of naltrexone SR/bupropion SR. It remains uncertain whether the reductions in lipids, improvements in glycemia, and sense of well-being mitigate hemodynamic changes and other risks for patients unable to achieve effective weight loss with nonpharmaceutical approaches. Further consideration needs to be given to the fact...
that only approximately half of the randomized subjects completed the 56-week trial period. With regard to reasons for discontinuation in active-treatment compared with placebo participants, there were more adverse events among treated subjects, similar numbers who withdrew consent or were lost to follow-up, and more withdrawals among placebo subjects because of insufficient weight loss. Even if naltrexone/bupropion combination therapy were considered safe and effective, the public health benefit could be questionable if a large number of subjects cannot or will not complete a year of therapy; however, for those who do (which could be a substantial number of people, given the prevalence of obesity), the benefit may be greater than that estimated by the intention-to-treat analysis. An important consideration for the naltrexone SR/bupropion SR review was a discussion between the sponsor and the FDA regarding commitment to perform a postmarketing outcome trial to determine the actual risk of cardiovascular and seizure events (based on acquisition of a sufficient number of events). Implied was the ability of such a trial to provide more conclusive information on the FDA guidance to achieve the goal of clinical benefit from a weight loss intervention (reduced morbidity and mortality and improved biomarkers) while demonstrating an adequate level of safety and compliance to achieve an improvement in overall individual health and overall public health. In consideration of the overall benefit-risk of the naltrexone SR/bupropion SR combination, the Endocrine and Metabolic Advisory Committee voted 13 in favor of approval and 7 against. In that context, 8 also voted to require an adequately designed controlled clinical trial to assess the drug’s effect on cardiovascular risk before approval, 11 voted to make that a postapproval requirement, and 1 abstained. On June 2, 2011, the FDA requested a large safety study of Contrave before its approval, and the FDA plans an advisory committee for 2012 to discuss the need for cardiovascular safety of all obesity drugs.

Weight Loss: What Is Acceptable Benefit and Risk?

This overall experience continues to emphasize the key concerns and uncertainties deliberated by the FDA and the advisory committee. Together, these studies and development programs demonstrate that weight loss induced by different pharmacological mechanisms does not equate to the same magnitude of clinical benefit or risk. It is unclear whether patients would take a drug for a sufficient time to realize sustained risks unless they also demonstrated benefit in terms of weight loss, so it is difficult to quantify the risk of chronic use or meaningful improvement in public health associated with weight loss agents. Must a drug be of benefit to the entire population, or can one evaluate risk and benefit for trying therapy in a general population but then continue its use in weight loss responders alone?

The end point of weight loss could be viewed as cosmetic unless the benefits extend to well-defined clinical outcomes such as reduced mortality, reduced risk of cardiovascular disease, decreased blood pressure, improved lipid profile, or reduction of obesity-related morbidities, such as diabetes mellitus, sleep apnea, and osteoarthritis, and importantly, improved quality of life. The FDA guidance links a “reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers, such as blood pressure, lipids and HbA1c.”

What can be learned from the recent FDA review of 3 new weight loss drug products and sibutramine in particular? Can common standards be developed that provide a more unified and informative approach to defining drug safety for this class of drugs?16 There are substantial parallels to the newer regulatory guidance for diabetes mellitus medications, which require an independent cardiovascular end-points committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and 3 trials, as well as sufficient numbers of events to assess cardiovascular safety before marketing, with trials designed so that meta-analysis can be performed on phase 2 and 3 trials. Importantly when trial participants in the integrated trial analysis who receive the weight loss agent are compared to subjects on placebo, the upper bound of the estimated risk ratio should be less than 1.8; noting the 95% confidence interval risk boundary as a key component of the overall risk assessment.

In contrast, the 2007 FDA guidance on products for weight management recommends a safety database of at least 3000 subjects randomized to active doses of drug and 1500 to placebo, all for 1 full year of treatment. The guidance further states, “the above sample size will provide 80% power to rule out with 95% confidence an approximately 50% increase in the incidence of an adverse event that occurs at a rate of 3% in the placebo group (ie, 4.5% versus 3%).” This, of course, assumes a baseline cardiovascular risk of 3% on placebo, which is considerably higher than noted in the initial development of sibutramine and the other weight loss drugs.

A full cardiovascular outcome trial is expensive to conduct and can take years to complete, which creates concern that requiring an outcome trial before product approval and subsequent marketing (at which time industry gains the ability to generate income from sales to support the cardiovascular outcome trial) might significantly forestall clinical availability and inhibit development of new agents. However, delay in obtaining these important safety data could put many patients at undue risk. Physicians and patients would be left trying to decide which drugs to prescribe or take with limited knowledge regarding the balance between benefit and cardiovascular or other risk.

A targeted approach would first focus on the mechanism of action of the drug. If preclinical and early clinical evidence indicates a concern that the drug may increase cardiovascular risk (as would be the case for sibutramine, phentermine/topiramate, and the naltrexone/bupropion combinations), then exposure to the drug product would need to be sufficient to rule out specific cardiovascular safety concerns. However, in the case of lorcaserin, cardiovascular risk was not a major concern, and therefore, the cardiovascular safety requirements for approval could be less. Second, the FDA guidance for diabetes mellitus drugs now requires that the upper bound of the 95% CI be below certain thresholds for drug approval. A similar approach could be applied to obesity drugs, with a negotiation between the sponsor and the FDA as to the exact boundaries. This approach would respect the feasibility of
acquiring the safety data in the target population. Finally, the risk-to-benefit ratio would be further supported if sponsors would measure additional clinical benefits beyond weight loss per se.

Obesity remains a major health challenge, with associated risks for illness, disability, and reduced quality of life. Weight loss is in fact an acceptable primary end point for drug development, but only if associated with a reduction in the medical complications of obesity, including but not limited to reduced risk of cardiovascular and cancer events, sleep apnea, osteoarthritis, and depression and improved quality of life. Thus, weight loss should result in additional clinical and societal benefits. When there are limited medical approaches to a health problem, a smaller magnitude advance may be acceptable. On the basis of these recent weight loss drug examples, there are several lessons that can be applied to new and existing drugs for weight loss.

In light of the experience of reviewing weight loss drugs in 2010, the approach to developing an adequate safety database should target the potential risks of the drug as defined by its mechanism of action, preclinical data, and early exposure in humans. For example, sibutramine, phentermine, and bupropion have sympathomimetic properties that would predispose to an increased risk of cardiovascular events, a pharmacological profile not seen with lorcaserin. In contrast, a potential increased risk of cancer was implied in the lorcaserin preclinical development program. These pharmacological properties should be taken into account in the design of clinical studies for drug approval intended to define the safety profile of a particular drug, by ensuring that adequate numbers of relevant adjudicated events are included in the overall safety database. In general, the FDA does not know the final results of all the animal carcinogenicity studies until the New Drug Application is submitted and the agreed-upon phase 3 studies are completed. This timing makes it difficult for the FDA to prospectively advise the sponsor on specific safety monitoring to evaluate preclinical signals of concern in the phase 3 studies.

When the primary end point of a development program is a specific amount of weight loss in a specific proportion of the treated population (relative to placebo), the design of the efficacy trials will likely not be sufficient to rule out any significant cardiovascular safety concern. Thus, additional well-designed safety studies will be necessary for the overall assessment of the risks and benefits of a new drug. These large safety studies would be justified by the anticipated very large numbers of obese people for whom the new drug might be considered, many of whom would have an increased risk for cardiovascular disease.

Typically, the goal of a safety program is to acquire enough safety events of interest to exclude a certain level of risk.\textsuperscript{17} This can best be determined when the new drug is compared with a placebo control and not some other form of active therapy. At present, with limited pharmacological options for weight management other than bariatric surgery, this requirement would not be difficult; however, when additional effective agents do make it to market, this will be increasingly difficult to accomplish.

The design of a safety study should evaluate both the intent-to-treat and on-treatment populations. The intent-to-treat population best reflects the risk of the drug in subjects with varying degrees of exposure related to drug compliance and discontinuation. The on-treatment analysis reflects the duration of exposure and presumably maximal risk associated with the drug. Clinical trials in obesity tend to have increased drop-out rates for a variety of reasons. An intention-to-treat analysis with imputation of missing data would not be ideal for a safety study, because many patients who would be included in the final analysis would not be fully exposed to the drug.

Patients included in a drug safety study may need to reflect a higher-risk group than the typical patient intended to use the drug. This is particularly true for cardiovascular and other potentially identified safety concerns, such as depression. However, drug development restricted to the highest-risk cardiovascular patient population may alter the risk-benefit ratio. In a low cardiovascular risk population, there would be a similar potential for benefit of weight loss on noncardiovascular morbidities that might offset a small increase in the risk ratio for cardiac events when the absolute event rates are low. Thus, pound for pound, the noncardiovascular benefits of weight loss should be the same in those with or without increased risk of cardiovascular events. This would allow physicians to selectively target individuals who would anticipate the greatest clinical benefit over the shortest exposure interval necessary to determine a weight loss response while minimizing the absolute excess risk of cardiovascular events.

The FDA obesity guidance currently links the efficacy criteria for degree of weight loss with expected improvement in biomarkers and other indicators of clinical benefit, including reduced mortality. Although not all obese people have a similar burden of cardiovascular risk factors, obesity drug development programs should be designed to demonstrate clinical benefits in addition to weight loss per se. Regulatory agencies should provide specific recommendations as to the degree of improvement in risk factors such as blood pressure and lipid profiles that could be interpreted as supporting the overall clinical benefit of a particular obesity drug. With a broader definition of efficacy (potentially requiring larger trials), the opportunity to rule out safety concerns would be enhanced, which hopefully would present a better “benefit-to-risk” ratio than has been observed in the current drugs approved or recently reviewed.

What the new agents, sibutramine, and the SCOUT trial in particular have taught us is that the cost of weight loss may be particularly high for specific drugs. Thus, the safety standards for drug approval need to target specific mechanisms of risk unique to a particular drug or drug class. The development program should acquire a sufficient number of relevant safety events to make an informed benefit-to-risk assessment by the FDA, associated advisory committees, and ultimately, patient providers. Physicians do not need to prescribe newly available agents to patients with substantially higher risk profiles than those in the clinical development programs. Given the substantial personal and societal health and economic burden of obesity and the limited treatment options, there is room for medications that may be appropriate for only a subset of the
population. Finally, the ability to monitor for safety signals and mandate further clinical trials after approval of drugs is necessary to balance the need to allow new medications on the market to meet patient needs while not compromising safety.

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Disclosures

None.

References


Key Words: adverse drug event ■ cardiovascular events ■ drugs ■ obesity ■ safety