Review
EPIDEMIOLOGY/GENETICS

Obesity

Why Do We Need Drugs to Treat the Patient with Obesity?

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Objective: Obesity is a public health problem, which increases the risk of chronic diseases and mortality. Weight loss can reduce mortality and improve most of the detrimental health consequences of obesity.
Design and Methods: This paper was developed from two presentations to the US Food and Drug Administration (FDA), which has responsibility for reviewing and approving drugs to treat obesity.
Results: A weight loss of 5% or more is sufficient to significantly reduce health risks in individuals with impaired glucose tolerance, hypertension, or nonalcoholic fatty liver disease. Slightly more weight loss (16% on average, achieved by surgery) reduces mortality. The goal of medicating for obesity is to help more patients achieve more weight loss. A barrier to drug approval has been the concern that weight loss medications might be used by individuals with little or no health risks, thus mandating a low side effect profile for approval of any drug. This limits the options for patients who have obesity-related health problems that could improve with weight loss. Recently the FDA signaled interest in identifying health benefits in higher risk patients that might justify medications with higher risk; however, the potential impact on a large segment of the population has led the FDA to consider requiring a cardiovascular outcome trial for all obesity medications, either prior to or after approval.
Conclusion: This review argues that drugs are needed for obesity because they enhance behaviorally induced weight loss and that new medications for obesity are needed in the approval process.

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Obesity is a Public Health Problem

Obesity has a long history (1), but beginning in the 1980s the prevalence in the USA, defined by a body mass index (BMI) >30 kg/m^2, began to rise more rapidly (2,3), and it has now reached what some would describe as ''epidemic'' proportions (2-4). In the USA, data from the 2009-2010 US National Health and Nutrition Examination Survey (NHANES) showed that 35.5% (95% CI, 31.9-39.2%) of men were obese (BMI >30 kg/m^2) and 35.8% (95% CI, 34.0-37.7%) of adult women were obese [5], which is more than double the rate in 1980.

The increasing prevalence of obesity carries with it increased risks for diabetes, the metabolic syndrome, nonalcoholic fatty liver disease, heart disease, and cancer among other comorbidities (6-8). Clearly the ''brakes'' that prevented the rapid increase in obesity before 1980 no longer work effectively, and new preventive strategies are needed if we are to halt the medical consequences of increasing prevalence of higher BMIs. However, no matter how effective preventive strategies are there will always be people who need treatment for the potential hazards of excess weight. Furthermore, one cannot ignore a problem already affecting over 1/3 of the US adult population.

Underlying the current epidemic of obesity are both an increase in the abundance of good tasting foods (9,10), much of it available at low, and sometimes subsidized, prices (11) and a society in which physical exertion and recreational physical activity are often at low levels (12). Furthermore, once weight gain has occurred, the body resists weight loss through neuroendocrine and autonomic nervous system signals that reduce energy requirements and increase appetite (8,13,14).

The available treatments for obesity fall into several categories, including diets of many kinds (8), physical activity programs including efforts to increase the mobility of the population (15), lifestyle changes that made their appearance as a treatment for obesity only 40 odd years ago (16) but are now a key component of most treatment programs for obesity (8,17,18). Drugs and surgery make up the other two categories of treatment options for the patient with obesity (8). As weight loss is achieved by creating negative energy balance, even surgery and medications require behavioral changes around diet and physical activity for effectiveness. This review will focus on why drugs are needed to treat obesity and criteria for selecting safe and effective ones.

Obesity Increases the Risk of Mortality and Morbidity

It is clear that obesity enhances the risk for many diseases and has often been labeled a disease in its own right (8,13,14). The idea that obesity is a disease has a long history (1,19). The quote below from one of the first English language monographs devoted to obesity, written in 1760, makes this point clearly:

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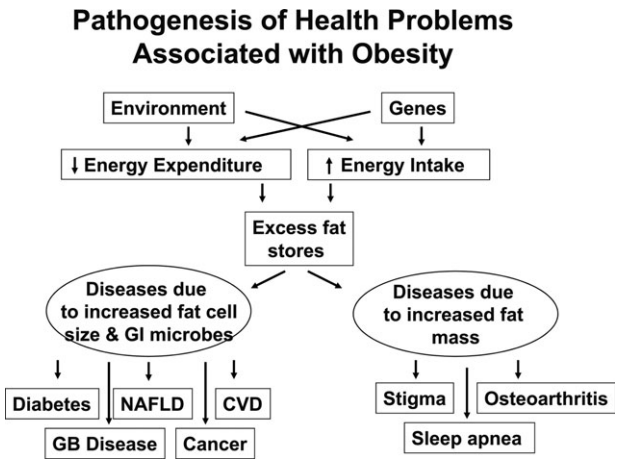

FIGURE 1 Obesity produces risks through increased fat mass and through the metabolic consequences of products released from adipose tissue (19).

''Corpulency when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers'' (19)

The health problems that obesity produces can be divided into two groups: those resulting from the increased fat mass associated with a heavier body and the metabolic consequences of enlarged fat cells and fat stores that secrete many products, some with detrimental effects (Figure 1) (20). In an analysis of pooled mortality studies, Whitlock et al (21) showed that among over 900,000 people, the mortality from obesity increased 30% for every 5 BMI units. The large size of this population that permits the identification of those diseases was impacted most by obesity. Death from diabetes increased more than 116% per 5 BMI units, hepatic disease 80%, and renal disease 60% per 5 BMI units. The current rapid increase in the number of diabetic patients can, in large part, be attributed to the steady increase in obesity (21,22).

In addition to producing diseases, obesity is stigmatized (23). Obese patients are viewed by many as unsuccessful, unpleasant, unintelligent, overindulgent, weak-willed, and lazy. Health care professionals often hold to the assumption that obesity can be prevented by self-control, that patient's noncompliance explains the failure of weight loss, and that obesity is caused by emotional problems (24-26).

Weight Loss Improves Health Outcomes

A mountain of data show that weight loss improves health outcomes (8) and reduces health care costs (27). The most striking examples are in patients who have undergone bariatric surgical operations as treatment for their obesity. Comparing large samples of individuals who had gastric by-pass surgery with matched controls, Adams et al (28) showed that those with a gastric by-pass had a lower mortality and decreased deaths from cardiovascular disease and cancer. The Swedish Obese Subjects (SOS) study reached similar conclusions using a control group of obese patients who were matched on over 20 factors at the same time as an obese patient was assigned to one of three surgical procedures (vertical banded gastroplasty, gastric banding, gastric-bypass). After an average follow-up of 11 years, and with average weight loss of 16%, mortality was reduced by 29% in the operated patients (29).

Morbidity, particularly type 2 diabetes (30,31), was also significantly reduced by surgical intervention. After 10 years of follow-up in the SOS study, the incidence of new cases of diabetes was 24% in the unoperated controls compared to only 7% in the operated group. This benefit of weight loss on diabetes has also been shown in both the Diabetes Prevention Program and Look AHEAD Trial, where weight loss is associated with improvement in cardiometabolic risk factors in people with diabetes or at risk for developing diabetes (32-36).

The incidence of new cases of hypertension, high triglycerides, and high uric acid was also reduced (37,38) in the SOS study of bariatric patients, compared to controls. Other diseases, especially cardiovascular disease (including cardiovascular mortality) (39), have been shown to be reduced by weight loss in the SOS study. Both impaired mobility (40) and sleep apnea benefit from weight loss (41).

Drugs Currently Approved to Treat Obesity

Drugs approved by the US Food and Drug Administration (FDA) for the treatment of obesity are shown in Table 1. The drugs that are available for use fall into several categories (42), including an intestinal lipase inhibitor (43), monoamine agonists that affect either the noradrenergic system with approval for short-term use (8), or the serotonin-system (lorcaserin) (44), which is approved for long-term use. All of these drugs have been approved as monotherapy. One combination of medications (topiramate + phentermine) has also been recently approved (45), and another (bupropion and naltrexone) is under consideration by the FDA (46). The mean weight loss shown in Table 2 represents that achieved with medication(s) given as an adjunct to lifestyle therapy. Monotherapy rarely achieves more than 6-8% weight loss from baseline, whereas combination therapy produces greater weight losses.

It is a common practice to express weight loss by subtracting the weight loss induced in the lifestyle/placebo control group from the weight loss seen with the drug to give the ''placebo-subtracted'' weight loss. As lifestyle/placebo effects can vary by several folds between studies, this may obscure the effect of the medication. Figure 2 (43) plots weight loss from a meta-analsysis of data for two groups of pooled studies. Shown in the left two bars are the weight losses with lifestyle versus controls (21 studies). The right hand pair of bars shows the lifestyle/placebo weight loss versus weight loss with orlistat/lifestyle (12 studies). The ''placebo-subtracted'' data for each pairing of studies, shown at the bottom of the figure, are the same (3.0%), for each of the meta-analyses; but the actual weight loss with orlistat/lifestyle is 3% more than the lifestyle/placeo group. Drugs and lifestyle intervention each contribute to the amount of weight loss achieved.

How much Weight Loss is Needed to Reduce Health Risks

Two analyses done nearly 20 years ago suggested that a weight loss of >5% would be associated with reduced health risks (47,48). An analysis of changes in body weight by Sjostrom et al (38) showed a linear relationship between the change in body weight and most risk factors except total cholesterol that did not decline until body weight had declined by more than 30%; HDL-cholesterol increased linearly.

TABLE 1 Medications approved for obesity

Generic name and year of approval	Trade name(s)	Dosage	DEA schedule
Pancreatic lipase inhibitor approved by FDA for long-term use			
Orlistat,1999	Xenical	120 mg three times daily before meals	Not scheduled
Orlistat, 2007	Alli (Over-the-Counter)	60 mg three times daily before meals	Not scheduled
Serotinin-2C receptor agonist approved by FDA for long-term use			
Loraserin, 2012	Belviq	10 mg twice daily	not scheduled
Combination of phentermine-topiramate approved by FDA for long-term use			
Phentermine-topiramate, 2012	Qsymia	3.75 mg/23 mg 7.5 mg/46 mg 11.25 mg/69 mg 15 mg/92 mg	IV, because of phentermine component
Noradrenergic drugs approved for short-term use			
Diethylpropion, 1959	Tenuate Tenuate dospan	25 mg three times a day 75 mg every morning	IV
Phentermine, 1959	Adipex and many others	15 to 30 mg/d	IV
Benzphetamine, 1960	Didrex	25-50 mg three times/d	III
Phendimetrazine, 1959	Bontril Prelu-2	17.5-70 mg three times daily 105 mg daily	III

*Drug Enforcement Agency evaluation pending.

Of course the greater the weight loss, the greater the effect on risk factors, but for most, 5% produced a clinically significant response. An analysis of weight loss by Douketis et al (49) found, as did Leblanc et al (43), that diet/lifestyle produced < 5 kg weight loss after 2-4 years and that pharmacologic therapy provides 5-10 kg after 1-2 years. Improvements in cardiovascular risk factors were seen mainly in those with pre-existing risk factors.

The effect of weight loss on glycemic measures is most striking in those patients who already have abnormalities. The Diabetes Prevention Program provides one approach to estimating the effect of various amounts of weight loss on risk of diabetes. After 2.8 years of treatment with an intensive lifestyle program the risk of diabetes in persons with impaired glucose tolerance was reduced by 58% compared to the placebo group (32). When the weight loss curve for this trial was modeled mathematically, it showed that a weight loss of 3% produced a 50% reduction in risk of developing type 2 diabetes and a 10% weight loss reduced the risk of diabetes by nearly 90% (50) (Upper panel of Figure 3).

Weight loss in the range of 5-10% has also been associated with improved mobility, reduction in signs and symptoms of sleep apnea and improvement in symptoms of urinary stress incontinence in women (49,41,51). This degree of weight loss is also associated with improved Weight-Related Quality of Life Scores (52,53).

The Sibutramine Cardiovascular Outcome (SCOUT) Trial, although controversial, provides several lessons about the use of drugs to treat obesity (54,55). In this trial all participants had either diabetes or prior cardiovascular events and all were treated with sibutramine for 6 weeks and then randomly assigned to either placebo or sibutramine for the remainder of the trial. When weight loss during the first 6 weeks was used to predict study end-point over the next 5 years, there was a significant reduction in deaths, which was related in both randomized groups to the initial weight loss over 6 weeks (see lower panel of Figure 3). The effect of 5% weight loss is shown by lines added to this figure. Sibutramine was voluntarily withdrawn from the market because' in the study, cardiovascular events were increased in those with prior events. There were 70% of those exposed to sibutramine, however, who did not achieve a weight loss of 5% or more illustrating that those who are not achieving weight loss should be re-evaluated for the medications they are using.

What Predicts Weight Loss

The best predictor of weight loss after 1 year is the initial rate of weight loss. In trials with orlistat a weight loss of >2 kg in the first month or >4 kg at 3 months predicted significantly greater weight loss compared to at 1 year weight loss those with less weight loss (56,57). Individuals losing more than 5% of their body weight after 3 months of treatment with sibutramine, a drug that has been removed from the market by the US Food and Drug Administration, had a significantly larger weight loss and improved cardiovascular risk profile at 1 year (58). For the two drugs most recently approved (phentermine/topiramate and lorcaserin) the labels have stopping rules and require that a threshold of weight loss be achieved in order to continue the drug.

How Long should We Treat Patients with Medications?

Trials with the first generation of anti-obesity drugs in the 1950s and 1960s used protocols lasting 6-12 weeks, sometimes with a

TABLE 2 Medications that have been evaluated for weight loss and their placebo treatments

Drug	Number of studies	Average duration of treatment	Mean weight loss, drug given with behavioral therapy (kg)
Drugs approved by the FDA for Obesity			
Phentermine	6	13 weeks	−6.4
Diethylpropion	9	18 weeks	−6.5
Mazindol	22	11 weeks	−5.7
Orlistat	15	≥1 year	−5.3
Phen/topiramate	2	≥1 year	−10.2
Lorcaserin	2	1 year	−5.8
Drugs withdrawn by FDA			
Phen/fenfluramine	1	34 weeks	−14.2
Sibutramine	10	≥1 year	−6.4
Drug approved elsewhere but not by FDA and subsequently withdrawn			
Rimonabant	4	≥1 year	−6.3
Drugs approved by the FDA for an indication other than obesity			
Fluoxetine	6	24 weeks	−4.8
Bupropion	2	24 weeks	−8.0
Topiramate	6	24 weeks	−8.0
Pramlintide	3	16 weeks	−4.4
Exenatide	12	24 weeks	−2.9
Liraglutide	8	24 weeks	−2.8
Metformin	3	1 year	−2.8
Drug under review by the FDA			
Buprop/naltrex	2	≥1 year	−8.7
Drugs under investigation for treatment of obesity			
Cetilistat	1	12 weeks	−4.1
Tesofensine	1	6 months	−11.3
Pram/phentermine	1	24 weeks	−11.3
Pram/leptin	1	24 weeks	−11.5

Adapted from Refs. 43,63,64,65.

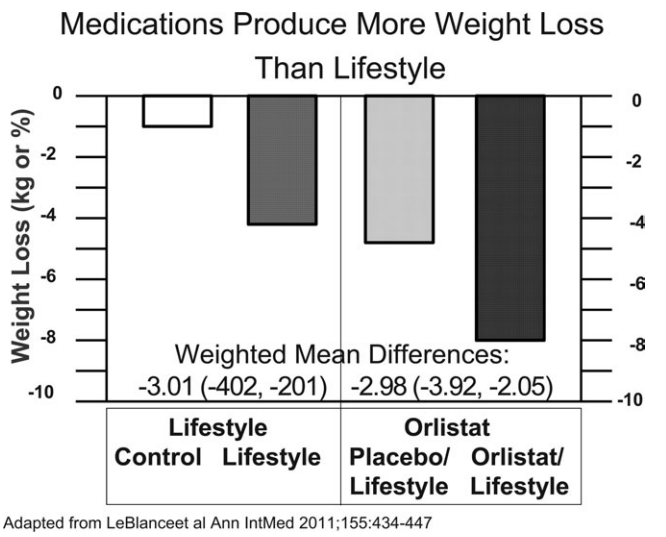

FIGURE 2 Comparison of weight loss between control and treatment groups. Left-hand bars show weight loss in control and lifestyle comparisons. Right-hand bars show the comparison of lifestyle and orlistat plus lifestyle. At the bottom are the weight mean differences (placebo-subtracted data) for the two sets of bars. #<Data from LeBlanc et al Ann Int Med 2011(37).

cross-over design. However, if one recognizes the chronic, relapsing nature of obesity (13) a chronic care model and ''continuous'' therapy seems rational. Is long-term treatment with medications still the standard of good clinical practice with overweight/obese patients? Analysis of the pattern of weight loss in individuals who initially lost more than 10% of their body weight in the Look AHEAD trial shows that nearly 40% maintained most of this loss over the next 3 years (59). The strategies for maintenance were different from those for the active weight loss period and targeted monitoring for regain with re-instituting strategies for weight control if regain occurs. It may well be that a reasonable strategy is that after initial drug treatment, for those who lose 10% or more initially, a period without treatment is in order, with weight monitoring and with resumption of medications should they gain weight again. The idea of focusing more effort on those who have more trouble losing weight with less effort on those who are successful was recently proposed by Jakicic et al. (60) and deserves more study.

Evaluating New Anti-Obesity Drugs – the Current Approach:

There are currently two weight loss criteria included in the draft FDA Guidance (61). First, a new drug must achieve more than 5% mean weight loss after subtracting the placebo effect when both drug and placebo groups are treated with lifestyle intervention. Second, the percent of patients achieving 5% weight loss on drug must be greater than 35% and at least twice that of the placebo group. By requiring 5% more mean weight loss than placebo the FDA punishes Good Clinical Practice, which would encourage the best possible behavioral treatment program to be employed with a drug. A small placebo effect resulting from a ''minimal'' lifestyle program producing 1-2% mean weight loss, however, enhances the apparent benefit of the drug. A similar criticism applies to the second criterion. This criterion too punishes Good Clinical Practice for the same reason; a weaker lifestyle intervention magnifies the medication effect and does not encourage development of the best lifestyle program to use with the drug.

New Directions from the FDA in Regulating Obesity Drugs

In 2012, representatives from the FDA and various interest groups met under the leadership of the George Washington University School of Public Health and Health Services. This effort led to the publication of a consensus report regarding considerations for obesity drug development, ''Obesity Drug Outcome Measures.'' FDA concerns are on population-level effects of approving obesity medications and they are clearly articulated in this document. If these medications are focused primarily on weight loss, rather than on the treatment of obesity, a medical condition, then the criteria for safety will be very stringent. If the focus is on improvement in feeling, function, or survival, then there may be some tolerance for adverse

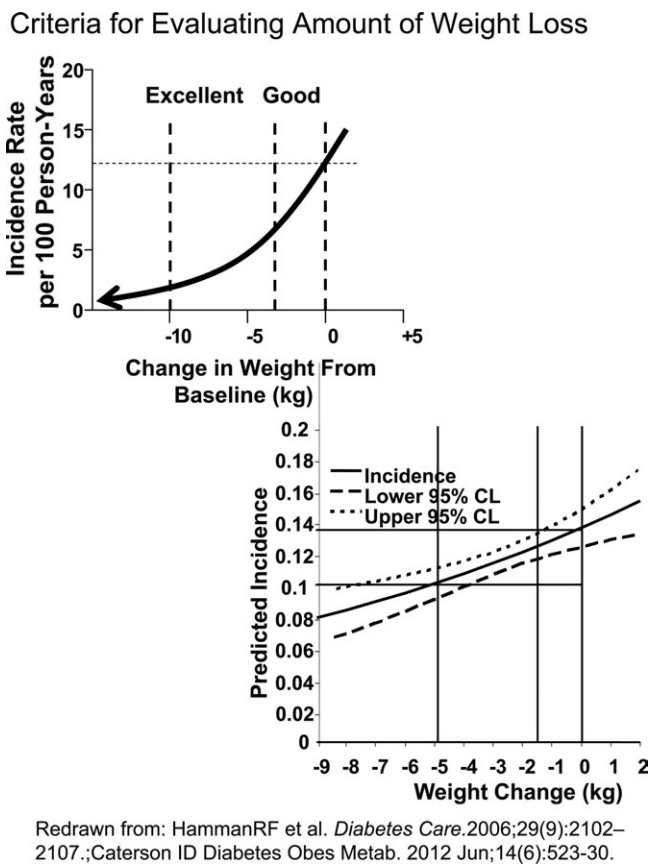

FIGURE 3 Two methods of selecting weight loss targets based on the risk of developing diabetes mellitus or the risk of developing a composite cardiovascular outcome. The upper left-hand figure shows the weight loss modeled from the Diabetes Prevention Program (43). As weight loss increased the conversion rate to diabetes was logarithmically reduced. The dashed vertical lines to the left of the "0" point show the weight loss (3 kg) for a 50% reduction in the risk of diabetes and the weight loss for 90% reduction (about 10 kg). The lower right-hand figure shows the weight loss and 95% confidence interval for the 5 years incidence of the primary end-point in the SCOUT trial based on weight loss during the first 6 weeks (44). All participants in the SCOUT trial were treated with sibutramine for 6 weeks before randomization. Their predicted incidence of achieving the composite end-point was logarithmically reduced as the magnitude of the initial weight loss increased. The vertical solid lines to the left of "0" are drawn to show the weight loss that would reduce the 95% confidence limits below the incidence with no weight loss. The left vertical line shows a weight loss of 5 kg reduced the incidence of events by about 40% (0.14-1.0).

events. In other words, if the risk:benefit equation is such that a low risk population for treatment requires low-risk medications. If individuals are being treated for weight related issues with medical problems, then a higher risk medications might be appropriate.

The FDA also signaled acceptance of combination therapy for obesity in the approval of phentermine/topiramate combination in 2012. The data in Table 2 express actual weight loss from baseline rather than placebo-subtracted weight loss (43,62,63,64). In this way, the known variability of placebo effects is avoided (65). Most of the drugs in the upper half of the table were used as single agents (monotherapy), and have weight losses that are more than 5% below baseline, the amount of weight loss shown to reduce risk in at-risk populations. The combinations of drug in the lower part of the table usually produced more weight loss, sometimes more than twice as much as with monotherapy. This clinical data suggest that effective treatment for obesity, like effective treatment for many other chronic diseases, may lie in combining drugs with different mechanisms of action that can enhance the size of the therapeutic effect.

TABLE 3 Unintended consequence seen with some therapies for obesity

Year	Drug	Consequences
1892	Thyroid hormone	Hyperthyroidism
1932	Dinitrophenol	Cataracts/neuropathy
1937	Amphetamine	Addiction
1968	Rainbow pills	Deaths/arrhythmias
1972	Aminorex	Pulmonary hypertension
1997	Phentermin/fenfluramine	Valvulopathy
1998	Phenypropanolamine	Strokes
2003	Herbal Ma huang	Heart attack/stroke
2011	Sibutramine	Cardiovascular death

Adapted from Ref. 8.

One particular problem with regulatory approval is that clinical trials for obesity have high proportion of drop-outs. ''Missing data'' produces lack of confidence in results. But for medications being studied for obesity treatment, as compared to medications for blood pressure control for example, the endpoint is readily apparent to the patient. Participants in weight loss studies observe their weight at home and may be reluctant to return for weighing at a clinic if they are not losing to their satisfaction, thus producing drop-out rates of 40% or more over 1 year. For this reason, in addition to an intention-to-treat analysis, an analysis of those who complete these studies is also often used because this shows what the weight loss would be for individuals completing the trial. Drop-outs are particularly important during the early part of the trial when there is rapid weight loss. Drop-outs that occur after weight loss has reached its nadir, generally at 6 months, have much less effect on the overall estimate of weight loss. The importance of analyzing drop-outs is what they tell us about the use of the drug and potential undesirable side-effects.

Another problem with regulatory approval for drugs used to treat obesity has been their unexpected and often unintended consequences (Table 3), which has given the class an aura of risk (8). Recently, an FDA Advisory Panel recommended a cardiovascular outcome trials or *all* the obesity medications, whether or not they have signals indicating a potential to produce cardiovascular disease. The rationale for this was that since all future diabetes medications must have cardiovascular outcome trials, then future obesity medications should have this requirement also, even though this criterion does not apply to other classes of drugs. There are both practical and ethical concerns with a cardiovascular outcomes study. This is illustrated with the SCOUT (54,55). First, to obtain a result in a reasonable period of time, this trial enrolled individuals with pre-existing cardiovascular disease or diabetes mellitus when the labeling of the drug indicated that cardiovascular disease was a contraindication to treatment with sibutramine. Second, treatment with the drug was continued for up to 6 years, even when patients did not

achieve clinically meaningful weight loss. Seventy percent of the patients assigned to the treatment with sibutramine failed to lose more than 5% of their body weight. In a setting of good clinical practice, the drug would have been discontinued. In my view, if a cardiovascular outcomes trial is indicated from the data obtained during registration trial, I would be opposed to approve the drug rather than expose a large population of high risk patients to a drug that might have detrimental effects.

What Might the Future for Obesity Pharmacotherapy Look Like?

A number of trends in obesity management seem to be emerging and these provide a foundation for predicting what is likely to happen with obesity pharmacotherapy in medical practice. First, there seems to be a consensus emerging on the need to better risk prediction in weight-related comorbidities. Identifying patients who might benefit from behavioral, pharmacologic, surgical, and other interventions are likely to be based on more than just BMI and may incorporate other genetic, biological, and social factors. Second, for overweight and obese patients who have been identified as likely to receive health benefits from weight loss, third party payers are likely to reimburse for treatments. This is heralded by announcements that intensive behavioral therapy for obesity will be reimbursed by Medicare providers. As we develop appropriate medical practice-based treatment strategies, medications will also be reimbursed. Obesity and its medical complications will be managed as a chronic disease; combinations of medications are likely to be commonly used. And last, as our knowledge expands of the biology that underlies the behaviors that support reduction of food intake and increase in physical activity, we will identify additional drugs with diverse biologic targets to aid in helping patients achieve medical benefits from weight loss.

Do *all* patients need medications to be successful in weight loss so as to achieve health benefits? Of course not. But, physicians need tools – drugs and devices – to help patients who need the benefits of weight loss and who cannot succeed without help.

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