Comparative Efficiency and Safety of Pharmacological Approaches to the Management of Obesity

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Obesity and overweight are reaching global epidemic proportions affecting more than 1.1 billion individuals worldwide. Excess weight is associated with an increased mortality, chronic morbidity (including type 2 diabetes, arterial hypertension, cardiovascular diseases, and certain cancers), decreased quality of life, and considerable health care costs (1).

Antiobesity drugs work through different mechanisms either in the central nervous system (CNS) or in the peripheral tissues. These mechanisms include: *1*) suppression of food intake in the CNS, *2*) decreased gut absorption of nutrients, and *3*) increased energy expenditure or oxidation of nutrients. The efficacy of antiobesity drugs should be evaluated by their ability to reduce fat stores (preferentially visceral adipose tissue), maintain weight loss, diminish obesity-related health risks, and thus decrease morbidity and mortality, and improve quality of life. An ideal antiobesity drug should be administered orally, devoid of major side effects, and distributed at affordable price. Treatment with antiobesity drugs can be considered in obese patients who failed to achieve a sufficient weight loss to a program of lifestyle change, diet, and physical activity. However, the drug treatment of obesity should be an integral part of the comprehensive obesity treatment program that includes diet, exercise, and cognitive behavioral intervention (2,3). Treatment of obesity should be individually tailored taking into account the degree and character of obesity, age, sex, and the presence of comorbidities (4). Drugs used for the treatment of obesity in the past were associated with serious side effects (psycho-stimulatory, depression, addiction, cardio-excitatory effects, pulmonary hypertension, and valve disease). Antiobesity agents that possess cardio-excitatory and psycho-stimulatory effects (e.g., phentermine, ephedrine, and caffeine mixture) have still been available for the short-term use in some countries (<3 months).

SIBUTRAMINE AND ORLISTAT— Currently, only two drugs, sibutramine and orlistat, are prescribed for long-term administration. The most important trial evaluating the long-term efficacy of sibutramine was the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) in duration of 2 years (5), while the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study assessing orlistat efficacy in preventing type 2 diabetes in obese subjects was carried out over a 4-year period (6). Meta-analysis of randomized trials revealed that sibutramine led to 4.2 kg and orlistat to 2.9 kg weight reduction in comparison with placebo (7). Four of the seven studies comparing sibutramine and orlistat monotherapy showed that sibutramine was significantly more efficacious for weight loss, and the remaining three studies showed equivalent effects (8). Modest weight loss (5–10%) in response to antiobesity drug treatment was associated with an improvement in lipid and glycemic profile. Sibutramine improved concentrations of HDL cholesterol and triglycerides, whereas orlistat reduced the incidence of diabetes and improved concentrations of total cholesterol and LDL cholesterol (7). Norris et al. (9) conducted a meta-analysis on the efficacy of orlistat and sibutramine in obese adults with type 2 diabetes and found only modest reductions of glycated hemoglobin (0.4% with orlistat, 0.7% with sibutramine). The improvement in lipid profile in response to sibutramine and orlistat is greater than can be expected from weight loss per se. A systemic review and a meta-analysis on attrition rate in trials with weight loss medications reported either similar total dropout rate for orlistat and sibutramine (10) or somewhat lower dropout rate on sibutramine (8).

The sibutramine treatment favorably affects inflammatory cytokines, serum hormonal levels (resistin, adiponectin), and the transport of leptin through the blood-brain barrier. Antiobesity effects and adverse events are related to the mechanisms of action of both drugs. Sibutramine selectively inhibits reuptake of serotonin, norepinephrine, and partly dopamine in the hypothalamus. This action results in an enhanced satiety and slightly increased thermogenesis (11). Orlistat reduces dietary fat absorption by inhibition of gastrointestinal and pancreatic lipase. The peripheral sympathomimetic activity of sibutramine leads to an increase in both systolic (sBP) and diastolic blood pressure (dBP) and pulse rate. However combined analysis of two placebo-controlled trials concluded that sibutramine treatment is unlikely to elicit a critical increase in blood pressure even in hypertensive patients with well-controlled hypertension. This is explained by the clonidine-like effect of sibutramine, which is mediated through activation of central α-2 adrenoreceptors (12). A recent meta-analysis of long-term changes in blood pressure following orlistat (12 trials including 5,540 patients) and sibutramine (6 trials including 1,495 patients) treatment in placebo-controlled trials of 12-months duration revealed a

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modest decrease in both sBP (−1.9 mmHg) and dBP (−1.5 mmHg) in response to orlistat treatment, whereas sibutramine treatment led to a modest increase in sBP (+0.5 mmHg) and dBP (+1.7 mmHg) (13). It should be pointed out that the reduction of blood pressure in patients with type 2 diabetes after orlistat treatment was less pronounced and the increase in blood pressure after sibutramine was higher. A recent experience from the Sibutramine Cardiovascular Outcomes (SCOUT) trial clearly indicated that sibutramine administration should be strictly avoided in patients with a history of cardiovascular disease, including those with uncontrolled hypertension (14,15).

Ten years of experiences with sibutramine and orlistat in the treatment of obesity and related conditions in both adults and adolescents were recently reviewed (16–18). In addition to obesity, the efficacy and safety of both drugs in the treatment of nonalcoholic fatty liver disease, polycystic ovary syndrome, and binge eating disorder were reported. Improvement in health-related quality of life was shown in sibutramine-treated patients who achieved moderate weight loss (19). Sibutramine treatment–induced weight loss is associated with improvement in eating attitudes as documented by increased dietary restraint and decreased dietary disinhibition and hunger scores (20). The weight loss with orlistat is not related to eating behavior attitudes but is associated with personality traits such as "order" and "deliberation" and thus, in contrast to sibutramine, is more demanding and requires greater adherence (21).

Orlistat inhibits gastrointestinal and pancreatic lipase and thus the weight loss and favorable metabolic effects are mainly achieved by 30% reduction in dietary fat absorption. Because of the insignificant intestinal absorption and subsequent low bioavailability of orlistat, both its antiobesity effects and side effects (steatorrhoea, oily spotting, fecal incontinence) are mediated via the gastrointestinal tract. The administration of orlistat is contraindicated in patients with malabsorption syndrome and cholestasis. Until now, no definite association between liver injury and orlistat administration has been established. Orlistat blocks the absorption of fat-soluble vitamins and β-carotene, and thus their substitution is recommended during the long-term administration of orlistat.

IS TESOFENSINE THE SUCCESSOR OF SIBUTRAMINE?

—Tesofensine is a recently discovered norepinephrine-, dopamine-, and serotonin-reuptake inhibitor, which might have the potential to evoke a weight loss twice that of currently approved drugs (22). A considerable effect of tesofensine on appetite sensations and a moderate effect on energy expenditure at night can contribute to its strong weight-reducing effect (23). The observed weight loss was mainly because of the loss of fat mass and was accompanied by a significant decrease in anthropometric measures of abdominal obesity as the waist circumference and the sagittal abdominal diameter. Beneficial effects of tesofensine administration were demonstrated on the levels of total cholesterol, triglycerides, insulin, adiponectin, and hemoglobin A_{1c}. The most frequently observed adverse events (nausea, dry mouth, constipation, and insomnia) are similar for tesofensine and sibutramine. Increases in pulse rate, but no significant increases in sBP and dBP, were observed after 24-weeks' treatment with tesofensine in a dose of 0.25 or 0.50 mg. However, these findings on the efficacy and safety of tesofensine with regard to its potential adverse effects (cardiovascular and CNS) need confirmation in phase III trials conducted in larger cohorts of obese patients.

IS CETILISTAT THE SUCCESSOR OF ORLISTAT?

—The efficacy and safety of cetilistat, a novel inhibitor of gastrointestinal lipases, was determined in both obese nondiabetic (24) and diabetic (25) patients. Similar weight reductions were observed in patients treated with cetilistat and orlistat (25). Weight reductions (from −3.3 kg to –4.3 kg) achieved by the treatment with different doses of cetilistat (60 mg t.i.d., 120 mg t.i.d., 240 mg t.i.d.) over a 12-week period were statistically significant compared with placebo (24,25). The treatment with cetilistat resulted in significant reductions in total and LDL cholesterol levels in obese patients (24) and in an improved glycemic control in obese patients with diabetes (25). Cetilistat treatment was well tolerated and exhibited fewer side effects compared with orlistat. Significantly reduced frequency of gastrointestinal adverse events after cetilistat could be attributable to structural differences between the two molecules and their interaction with fat micelles in the intestine (25).

LEPTIN: TREATMENT OF RELATIVE LEPTIN DEFICIENCY?

—Obesity, metabolic, neuroendocrine, and behavioral consequences of the rare congenital leptin deficiency in humans are efficiently reversed by the treatment with recombinant leptin (26). On the other hand, subjects with common obesity are hyperleptinemic compared with normal weight individuals and resistant to the central hypothalamic effects of endogenous leptin and less sensitive to exogenous leptin (27). However, some obese subjects who have recently lost weight exhibit a relative leptin deficiency and reduced concentrations of thyroid hormones that could be reversed by an administration of exogenous leptin (28). Further studies are needed to support the role of leptin administration for weight maintenance in subjects who develop relative leptin deficiency in response to calorie deficit.

MELANOCORTIN-4 RECEPTOR AGONISTS

—In contrast to the rare congenital leptin deficiency, melanocortin-4 receptor (MC4R) mutations are the most common causes of monogenic obesities. MC4R deficiency is responsible for 0.5–2.5% of severe obesities. Two novel MC4R agonists were recently identified that were able in vitro to activate mutated human MC4R (29). However, clinical trials are required to confirm the efficiency and safety of these compounds in humans.

LORCASERIN: A SAFE SUCCESSOR OF DEXFENFLURAMINE?

—Dexfenfluramine addressed serotoninergic hypothalamic appetite control mechanisms and led to body weight loss, increased adherence to a weight management program, and favorably affected cardiometabolic health risks in both obese nondiabetic (30) and diabetic (31) patients. However the mechanism of dexfenfluramine action—stimulation of serotonin release, inhibition of its reuptake, and direct stimulation of postsynaptic serotonin receptors—was also associated with serious side effects such as valve disease and pulmonary arterial hypertension (32,33). In response to these observations, fenfluramine and dexfenfluramine were voluntarily withdrawn from the market in 1997 (33).

In order to avoid adverse peripheral side effects, a new selective serotonin agonist, lorcaserin, has recently been developed. Lorcaserin selectively activates 5-HT2C receptors, which are located primarily in the hypothalamus, thalamus, and limbic structures and are virtually absent in peripheral tissues. This way, unfavorable cardiovascular side-events are avoided (34). The administration of lorcaserin to obese subjects in both short-term (2 weeks) and long-term (1-year and 2-year) trials resulted in decreased body weight and waist circumference as well as in improved cardiometabolic risk profile and quality of life (35–37). At 1-year follow-up, significantly more patients lost 5% of their body weight in the lorcaserin group than in the placebo group (47.5 vs. 20.3%, $P < 0.001$), corresponding to an average weight loss of 5.8 ± 0.2 kg with lorcaserin and 2.2 ± 0.1 kg with placebo (37). No drug-related effects on heart valves, pulmonary artery pressure, or depression and suicidal ideation were recorded. Transient headache, nausea, and dizziness were the most frequently reported side-effects (35,37).

DRUGS BLOCKING CANNABINOID AND DOPAMINERGIC RECEPTORS

The blockade of cannabinoid CB1 receptors (with rimonabant or taranabant) and dopaminergic D1/D5 receptors (with ecopipam) exerted favorable effects on body weight and cardiometabolic health risks (38–41). However, because of the increased risks of psychiatric adverse events, i.e., depressed mood disorders, anxiety, and suicidal ideation, rimonabant was withdrawn from the obesity treatment (42), and pharmaceutical companies discontinued clinical trials with taranabant and ecopipam as antiobesity agents (40,41). Rimonabant positively influenced dyslipidemia and insulin resistance not only by decreasing the food intake in the brain but also by blocking peripheral CB1 receptors. CB1 blockade favorably affects lipogenesis in fat stores and liver, glucose uptake in skeletal muscle, and adiponectin secretion in adipose tissue.

Knowledge of peripheral targets of CB1 antagonists led to the development of a new CB1 antagonist, TM38837, which specifically acts in the peripheral tissues because of the lowered propensity to pass the blood-brain barrier (43). The phase I clinical trial with TM38837 was successfully completed in 2009 (J.M. van Gerver, unpublished results).

COMBINATION DRUGS

Approaches with two drug combinations of decreased doses were recommended to increase both the safety and efficacy of antiobesity treatment. However combinations of sibutramine and orlistat exhibited no advantages over the monotherapy with sibutramine alone (44,45). Combining fenfluramine and phentermine was aimed to achieve fewer adverse events and better appetite control (46). This drug combination, quite efficient in terms of weight loss and thus widely prescribed (over 18 million prescriptions in the U.S. in 1996!), was later shown to be associated with an increased risk of valvular heart disease (32). Phentermine interferes with the clearance of serotonin, and this way a combination of fenfluramine and phentermine may potentiate the untoward effects of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome (32).

Recently, several new drug combinations were investigated. The antidepressant bupropion, which acts as norepinephrine and dopamine reuptake inhibitor and melanocortin pathways stimulator, was combined with the opioid antagonist naltrexone, which antagonized proopiomelanocortin neurons inhibition by endogenous opioids. A sustained-release (SR) combination of naltrexone and bupropion was well tolerated and produced synergistic weight loss, which significantly exceeded that induced by placebo or by either drug alone (47,48). Naltrexone SR/bupropion SR (NB) combination therapy as an adjunct to behavior modification applied for 56 weeks induced significantly greater weight loss compared with behavior modification alone (9.3 ± 0.4% vs. 5.1 ± 0.6%, $P < 0.001$) (49). NB treatment was associated with improvements in body fat distribution, lipid profile, glucose homeostasis, and quality of life (49). The most frequent adverse event in response to NB treatment was nausea. NB combination treatment was not associated with increased depression and suicide attempts. Moreover, those using NB combination treatment exhibited fewer adverse psychiatric events than those using its components given separately (48,50). Transient increases in both sBP and dBP during the initial phase of NB treatment should however be carefully evaluated in future studies (48,50).

The addition of amylin (pramlantide) to leptin (metreleptin) restores leptin responsiveness in subjects with common obesity and after 12-months' treatment results in significant weight loss (−11.5 kg), reduction in triglycerides (−8%), total cholesterol (−8%), fasting blood glucose (−4 mg/dL), insulinemia (−22%), and insulin resistance/homeostasis model assessment (−25%) (51). However, these combinations of antiobesity agents as well as other recently developed combinations—bupropion and zonisamide, phentermine and topiramate, pramlantide and sibutramine (52), pramlantide and phentermine (52)—require further long-term studies and a careful evaluation with regard to their efficacy and potential adverse events (53). Combination therapies using phentermine should consider that an administration of phentermine is recommended for a short-term period only.

GUT HORMONES

Several hormones of the gastrointestinal tract such as glucagon-like peptide 1 (GLP-1), cholecystikinin, amylin, pancreatic polypeptide, peptide YY ($PYY_{3–36}$), oxyntomodulin (OXM), and ghrelin have been found to play important roles in energy balance regulation, and some have recently been investigated as pharmaceutical targets for obesity (54). The administration of physiological doses of gut-derived appetite-regulating agents is expected to be an efficient, specific, and thus a low side-effect approach in the treatment of obesity.

The GLP-1 is secreted from L-cells of the intestine in response to a meal. GLP-1 suppresses elevated glucagon secretion by pancreatic β-cells, enhances insulin secretion, decreases apoptosis in pancreatic β-cells, increases satiety in the brain, and delays gastric emptying. Postprandial GLP-1 secretion is reduced in diabetic patients compared with nondiabetic patients. GLP-1 receptor agonists such as liraglutide and exenatide represent a new treatment option for patients with diabetes, and especially those who are obese. A recent review of randomized controlled trials evaluated six trials with exenatide and six trials with liraglutide that were administered either alone or combined with oral antidiabetic drugs (55). Both drugs improved glycemic control, induced comparable weight losses, and reduced blood pressure (55). The most frequent side effects were transient mild nausea and minor hypoglycemia, which were less common with liraglutide

than with exenatide (56). Antibodies developed with a lesser frequency in liraglutide-treated subjects than in those treated by exenatide, likely because of its greater structural similarity with human GLP-1 (97 vs. 52%). However, it is encouraging that the development of antibodies does not affect the drug efficacy. Combining GLP-1 analogs with metformin in obese patients with diabetes seems a reasonable approach, as both drugs possess the weight-lowering properties (57,58). The disadvantage of GLP-1 agonists is a need for parenteral administration—once daily with liraglutide and twice daily with exenatide. A recent study demonstrated that a long-term version of exenatide administered once weekly produced sustained glycemic control and weight loss over 52 weeks (59). Other recently developed GLP-1 agonists with prolonged half-lives such as taspoglutide and albiglutide may also allow weekly dosing.

Several trials evaluating the use of GLP-1 agonists as antiobesity drugs have been in progress. Only a few of the results have been published. A small-scale study conducted in overweight nondiabetic women with polycystic ovary syndrome demonstrated that a combination of exenatide with metformin favorably influenced body weight, insulin sensitivity, and menstrual cyclicity. These beneficial effects were more pronounced with combination treatment than with administration either of exenatide or metformin alone (60).

Other gut hormones (e.g., amylin, OXM, $PYY_{3–36}$) as potential antiobesity drugs are currently being investigated (61). Amylin is cosecreted with insulin by pancreatic β-cells in response to meal intake. Amylin inhibits food intake in the area postrema via specific amylin receptors, regulates gastric emptying, and suppresses inappropriate postprandial glucagon secretion. Sustained weight loss of 7.2 kg in response to a 12-month treatment with synthetic amylin analog pramlintide (360 μg twice daily) was demonstrated in obese and relatively healthy subjects (62). The most common side effect with pramlintide treatment was mild nausea. Both OXM and $PYY_{3–36}$ are cosecreted with GLP-1 from intestinal L-cells. OXM inhibits food intake in the hypothalamus by binding to three different receptors (GLP-1 receptor, glucagon receptor, and independent OXM receptor). Only preliminary data on energy intake, energy expenditure, and weight loss in humans after OXM and $PYY_{3–36}$ have been available (61). The less frequent nausea after administration of OXM than after GLP-1 agonists encourages further clinical studies. To improve clinical usefulness of treatment, the breakdown-resistant analogs of OXM and intranasally administered analogs of $PYY_{3–36}$ have been developed. A recently published study suggested that the anorectic effect of $PYY_{3–36}$ and OXM can be additive (63). Coadministration of $PYY_{3–36}$ and OXM intravenously reduced energy intake by 42.7% in comparison with saline control. This energy intake reduction after combined hormone administration was more pronounced than during infusions of either hormone alone.

DURATION OF TREATMENT WITH ANTIOBESITY DRUGS

Long-term administration of antiobesity drugs should be indicated according to the weight loss achieved in response to an initial 3-months' therapy (64,65). A meta-analysis of sibutramine studies revealed that a weight loss of 4 kg at 3 months predicted weight loss >5% at 12 months (65). The drug administration should be discontinued in patients who do not respond to 3-months' drug treatment. It has been demonstrated that intermittent treatment with some antiobesity drugs (phentermine, sibutramine) may be as effective as their continuous administration and may diminish both the side effects and costs (66,67). On the other hand, the long-term replacement of antiobesity drugs with placebo is followed by weight regain as demonstrated in the studies with sibutramine, lorcaserin, and rimonabant conducted over a 2-year period (5,37,39). It therefore should be considered that future drug treatment of obesity should be indicated for lifelong administration as in treating other complex diseases.

CONCLUSIONS

Currently available antiobesity drugs result in only modest weight loss accompanied by reductions of cardiometabolic health risks. Adverse events related to existing antiobesity drugs however, call for careful assessment of the risk/benefit profile in each new agent designed to treat obesity. Further studies evaluating the effect of antiobesity drugs on morbidity and mortality end points in appropriate target populations are needed. It is expected that the new compounds, which have recently been tested in clinical trials, will possess more advantages over the currently available agents both with regard to their efficacy and safety (68). However, it will be necessary for medical authorities to persuade not only physicians and patients but also the drug-regulating agencies (and their committees) that the drug treatment of obesity (de facto obesities) must evaluate antiobesity drugs just as they do those for other complex diseases (such as hypertension) and take into account their specific pathogenesis and character, age of a patient, and presence of comorbidities (69).

ADDENDUM

On October 8, 2010, the following statement was released by the Abbott Laboratories: "Abbott believes sibutramine has a positive risk/benefit profile in the approved patient population, but will comply with the FDA's [Food and Drug Administration's] request and will voluntarily withdraw Meridia® (sibutramine) from the U.S. market."

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