Currently Available Drugs for the Treatment of Obesity: Sibutramine and Orlistat

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Abstract: The currently available drugs for long-term treatment of obesity are sibutramine and orlistat. They have been shown to be able to induce significant weight loss, with important co-morbidity reduction, allowing the maintenance of reduced body weight for at least 1-2 years. Cardiostimulating and gastrointestinal adverse effects are however not negligible.

Key Words: Pharmacotherapy, sibutramine, orlistat, body weight, fat, energy balance, physical activity, diet.

INTRODUCTION

The prevalence of obesity has been increasing worldwide during the past years and is reaching epidemic proportions in industrialized countries [1]. This problem represents an enormous burden on health care systems and, most importantly, the quality of life of the affected individuals is substantially lowered. Even though extensive research and public awareness efforts have been made over the previous decades, the proportion of people affected is still rising.

There is growing evidence that obesity, especially central obesity, has an important impact on predisposing risk factors for coronary heart disease, including dyslipidemia, glucose intolerance, insulin resistance, and elevated blood pressure. Reversal of these metabolic abnormalities associated with obesity is one of the most important targets in the actual clinical management of obesity [2,3].

Although diet and lifestyle changes remain the cornerstones of therapy for obesity [4], weight losses are often small and long-term maintenance of clinically significant weight loss, defined as a loss of 5-10% of initial body weight, remains unsatisfactory [4], in particular because of the long-term non-compliance with these changes. Despite this established fact, a better comprehension of the weight loss barriers will certainly optimize the chances of success and improve the effectiveness of obesity management.

Over the last decade, obesity research focused on the exploration of new biochemical pathways that could lead to the development of new pharmacological interventions. In this regard, the use of pharmacological agents for long-term treatment of obesity has been considered to play an adjunct role as part of an overall weight reduction program that includes diet, physical exercise and behavioral support [5]. However, it is suggested that a pharmacological approach be considered only for patients with body mass index (BMI) > 30 kg/m^2, or BMI > 27 kg/m^2, when additional co-morbid factors are present [1]. Altogether, this paper will summarize the mechanisms of action, adverse effects and efficacy of the two current available obesity drugs as well as presenting the perspectives of the authors on the future of pharmacotherapy in obesity.

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1. CURRENTLY AVAILABLE DRUGS FOR THE TREATMENT OF OBESITY: SIBUTRAMINE AND ORLISTAT

There is probably no medical condition for which a safe and effective form of pharmacotherapy is more highly desired than for obesity. Neither is there a condition for which effective treatment would spare so much suffering for so many individuals. There is abundant evidence from epidemiological studies to suggest that morbidity from diabetes, cardiovascular disease, cerebrovascular disease, osteoarthritis, sleep apnea and certain cancers could all be reduced in proportion to a reduction in body fat content. Past forms of pharmacotherapy for obesity have often been misguided and currently available drugs are less effective than expected. However, the growing understanding of peripheral signals and central nervous system (CNS) pathways involved in the regulation of adiposity makes it very likely that effective new drugs will become available to treat obesity in the near future [6]. Be that as it may, only two drugs, sibutramine (Meridia®, Abbott Laboratories) and orlistat (Xenical®, Hoffman-La Roche), are currently approved by the Food and Drug Administration (FDA) in the United States of America, the Therapeutic Products Directorate (TPD) in Canada, and the European Medicines Agency (EMEA) for long-term use in obesity.

1.1. Sibutramine

Mechanism of Action and Efficacy

Introduced in 1997, sibutramine, a centrally acting agent, is a racemic mixture of the + and – enantiomers of cyclobutanemethanamine with the formula 1-(4-chlorophenyl)-*N,N*-dimethyl-(2-methylpropyl)-hydrochloride monohydrate [structural formula of sibutramine is shown in Fig. (**1**)]. Sibutramine and its active metabolites are inhibitors of the reuptake

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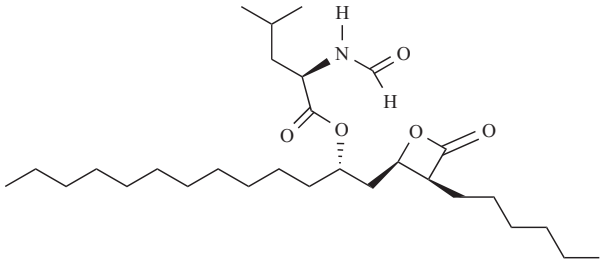

Fig. (1). Structural formula of sibutramine.

of monoamines, primarily serotonin and noradrenalin and, to a lesser extent, dopamine. Although ineffective as an antidepressant, for which purpose it was originally developed, sibutramine was found to reduce body weight and appetite and increase satiety [7-9]. More than 10 prospective, randomized controlled trials of sibutramine have supported its efficacy [10]. An analysis of three trials of at least 1-yr duration showed that patients on sibutramine lost 4.3 kg or 4.6% more weight than those taking placebo; 34% more patients achieved at least 5% weight loss, and 15% more patients achieved at least 10% weight loss in the sibutramine group compared with placebo [11].

Adverse Effects

The most common adverse effects are dry mouth, constipation, and insomnia. On the average cardiostimulatory effects, systolic blood pressure increases by about 4 mm Hg, and diastolic blood pressure by 2-4 mm Hg, while heart rate increases by about 4 beats/min [10]. Despite these changes, the safety and efficacy of sibutramine have been demonstrated in subjects with controlled hypertension. However, it is recommended that blood pressure and pulse rate be monitored regularly. The use of sibutramine is contraindicated in individuals with concomitant use of monoamine oxidase inhibitors or other serotonin reuptake inhibitors. To date, there has been no association between the use of sibutramine and valvular heart disease, as was observed with the use of fenfluramine and dexfenfluramine [12]. Also, sibutramine given at 2-5 times the therapeutic dose was found to lack abuse potential in comparison with 20 mg of D-amphetamine [13].

However, it is somewhat paradoxical that an anti-obesity agent, sibutramine in this case, has the potential of promoting weight loss with the concomitant effect of depriving the users of some metabolic effects which are of high importance for them. Indeed, the perspective for the physiologist is to achieve a global improvement of body's functionality. It is therefore a challenge for these scientists in obesity management to preserve all of the cardiac properties the better they can in the presence of weight reduction.

Positive Effects of Physical Activity in Conjunction with Sibutramine on Cardiovascular Profile

A progressive clinical tri-therapy combining sibutramine and a supervised diet-exercise intervention was found to favor a satisfactory benefit-risk profile since it enhanced weight loss without inducing increases in heart rate and blood pressure [14]. In this regard, Fig. (**2**) shows that the addition of exercise to a diet/sibutramine treatment six weeks after its implementation maintained a high level of body weight loss while reversing the cardiostimulating effect of the medication.

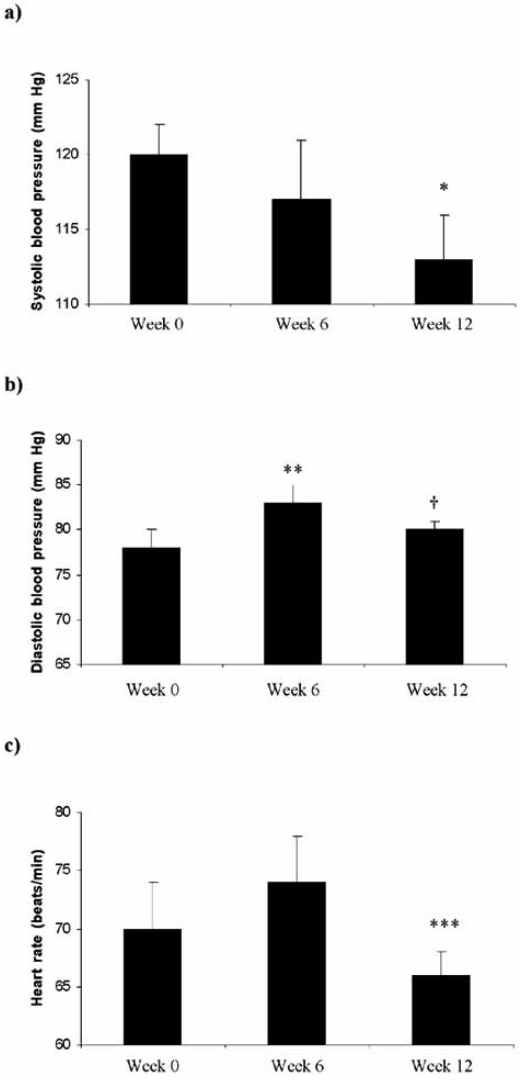

Fig. (2). The impact of a 12-week clinical tri-therapy treatment (week 0 to week 6: diet + sibutramine, week 6 to week 12: diet + sibutramine + exercise) on (**a**) systolic blood pressure, (**b**) diastolic blood pressure and (**c**) heart rate. *Significantly different from before treatment: $p<0.02$, **week 6 significantly different from week 0: $p<0.01$, † week 12 *vs*. week 6: $p=0.06$, ***week 12 significantly different from week 6: $p=0.02$. Data adapted from Bérubé-Parent *et al.* [14].

In this respect, physical exercise offers a support to pharmacotherapy without some non desired side effects. Indeed, the sympathetic nervous system (SNS) and adrenal medulla are important regulators of many physiological processes, not only concerned with the control of blood pressure, but also of metabolism. It is important to realize that activation of the SNS and adrenal medulla usually occurs selectively, rather than in an all or none manner, and that in some circumstances there can be activation of some tis-

sues/organs and suppression of the SNS supply to others. There are evidence that the SNS affects energy expenditure, with studies in both animals and humans pointing to activation of β-adrenoreceptors as being of major importance. Thus, any alteration in the activity or effectiveness of the SNS or adrenal medulla could affect resting energy expenditure and influence the development of obesity [15].

Cardiac economy is of major concern by physiologists. As discussed above, sibutramine, the most prescribed pharmacological anti-obesity agent, has the potential to induce negative cardiostimulatory side effects. Since obese individuals are at greater risk of developing cardiac problems, the potential of sibutramine to produce increases in heart rate and blood pressure is a particular matter of concern for health professionals. On the other hand, physical exercise offers the alternative of cardiac economy since its stimulating effects appear to be specific to the components of energy metabolism. This argument is supported by the fact that exercise training has been shown to increase skeletal muscle β-adrenoreceptors [16] and decrease cardiac β-adrenoreceptors [17] in animals. This observation is clinically relevant since up to now exercise is the only known strategy that offers such a potent support to weight loss/weight maintenance strategy without the non-specific stimulating side effects of thermogenic drugs on cardiac function.

As shown in Fig. (**3**), sibutramine has the potential to induce negative cardiostimulatory side effects. Indeed, at the end point of studies (weight loss ≈ 5 kg), Hanotin *et al.* [18]

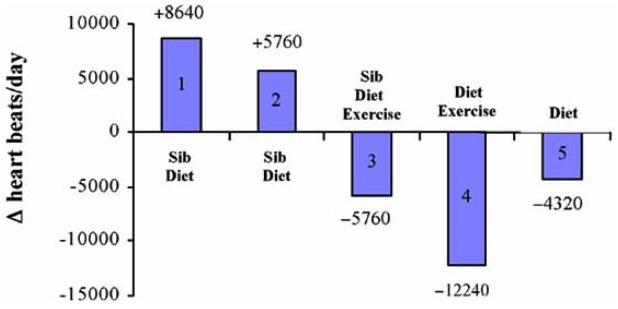

Fig. (3). Impact of 15 mg sibutramine (Sib) and diet (1), 10 mg sibutramine and diet (2), 10 mg sibutramine combined with diet and exercise (3), diet and exercise alone (4), and diet alone (5) on variation of seated heart rate expressed on a 24 h basis. Data for each condition are from the following references: (1) Hanotin *et al.* [18] and Bray *et al.* [19], (2,3) Bérubé-Parent *et al.* [14], and (4,5) Doucet *et al.* [20].

and Bray *et al.* [19] noted significant increases in heart rate of about 4 and 6 beats/min for subjects who received 10 or 15 mg/day sibutramine compared with placebo. In addition, systolic and diastolic blood pressures were increased by up to 2.8 and 4.2 mm Hg, respectively, with 10 mg sibutramine once daily [19]. Since many candidates for treatment with sibutramine are characterized with high blood pressure and/or are at risk of developing coronary heart disease, it is certainly advisable to minimize the increase in blood pressure and heart rate caused by sibutramine treatment. It is also important to mention that in most studies, sibutramine was used in conjunction with a dietary prescription for weight loss. However, after initial diet prescription, further dietary counseling was usually not given during the course of these studies. As depicted in Fig. (**3**), the variation in heart rate (beats/day) is increased for 15 mg sibutramine combined with diet (+8640 beats/day; Hanotin *et al.* [18] and Bray *et al.* [19]). Data from Bérubé-Parent *et al.* also showed an elevation in heart rate with 10 mg sibutramine combined with diet (+5760 beats/day; Bérubé-Parent *et al.* [14]). In contrast, the same authors have observed a decrease in heart rate when supervised physical exercise was added to sibutramine 10 mg plus diet (−5760 beats/day; Bérubé-Parent *et al.* [14]). Interestingly, Doucet *et al.* showed that physical activity and a low-fat diet induced a substantial reducing effect on heart rate in subjects displaying comparable morphological characteristics (−12240 beats/day; Doucet *et al.* [20]). In the same study, diet alone favored a lower effect on heart rate variation than with physical exercise combined (−4320 beats/day; Doucet *et al.* [20]). Taken together, these observations suggest that physical activity is an important treatment modality to consider in conjunction with the use of sibutramine in order to preserve the cardiac properties of patients.

1.2. Orlistat

Mechanism of Action and Efficacy

Orlistat (tetrahydrolipstatin), a non-centrally acting agent, was approved by the FDA in 1999 for the management of obesity [structural formula of orlistat is shown in Fig. (**4**)]. Orlistat, an inhibitor of pancreatic and gastrointestinal lipases, prevents the absorption of approximately 30% of dietary fat. Pooled results of 11 prospective randomized controlled trials demonstrated that subjects treated with orlistat displayed a 2.7 kg or 2.9% greater reduction in weight than placebo-treated patients after 1 year of follow-up [11]. Orlistat reduces low-density lipoprotein (LDL) cholesterol and total cholesterol levels independently of reductions in body weight, decreases the progression to a diabetic state, and leads to better glycemic control in patients with diabetes [10,21].

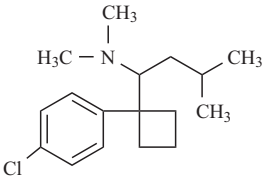

Fig. (4). Structural formula of orlistat.

Weight loss resulting from orlistat is associated with a significant reduction of systolic and diastolic blood pressure (−4.9 *vs*. −2.4 mm Hg and −3.7 *vs*. −1.8 mm Hg, respectively, *vs.* placebo, $p<0.05$) [22]. A meta-analysis of five studies demonstrated that patients reporting isolated systolic hypertension (systolic blood pressure > 140 mm Hg) show higher reductions compared with controls (−10.9 *vs*. −5.1 mm Hg, $p<0.05$) [23].

Adverse Effects

Side effects due to the mode of action include oily spotting, liquid stools, fecal urgency or incontinence, flatulence,

and abdominal cramping. As orlistat may impair the absorption of fat-soluble vitamins, a multivitamin supplement should be taken 2 h before or after the medication. It is important to mention here that the side effects associated with the use of orlistat are attenuated if the patient follows a low lipid diet in concomitance with the drug treatment. In this respect, the prevention of non desired effects of this medication by a low-fat diet may be likely to accentuate weight loss. Accordingly, low-fat diet could be to orlistat as what physical exercise may be to sibutramine regarding the prevention of side effects.

Because their mechanisms of action differ, it is reasonable to ask whether combined therapy with orlistat plus sibutramine might produce a greater degree of weight loss than is achievable with either agent alone. One study of 34 obese women addressed this issue [24]. Subjects were treated with sibutramine for 1 year and achieved a mean weight loss of 11.6% of initial weight. They were then randomly assigned in a double-blind fashion for an additional 16-week period of treatment with either sibutramine plus placebo or sibutramine plus orlistat. The study demonstrated that addition of orlistat produced no additional weight loss during the 16 wk of combined therapy. This finding suggests that weight loss with currently available agents may be limited to about 10% of initial weight. Only 20-30% of unselected individuals will come close to this degree of weight loss and body weight begins to rise again after 12-18 months of treatment.

In summary, large-scale and long-term trials lasting up to 2 years have demonstrated that the two currently pharmacological agents available for the long-term treatment of obesity (sibutramine and orlistat) are able to induce significant weight loss over and above that produced in control groups. Important reductions of co-morbidities are also usually observed. These drugs allow the maintenance of the reduced body weight for at least 1-2 years. The weight loss that can be attributed to these drugs is in general modest, *i.e.* up to 10% weight loss. However, the reduction of ±25% in most of the well-known co-morbid conditions is usually more pronounced than the magnitude of the weight loss itself. On the other hand, adverse effects are not negligible and must be taken into consideration when it is time to prescribe one of these anti-obesity drugs. In this regard, there is a need for more better tolerated anti-obesity drugs.

1.3. Impact of Sibutramine and Orlistat on Body Weight set Point and Body Energy Loss

One of the objectives of the pharmacotherapy of obesity is to develop new molecules with the hope that they could reduce body energy stores without compromising the ability to maintain energy balance at a satisfactory satiety level. As depicted in Fig. (**5**), pooled results of prospective randomized controlled trials of at least 1-yr duration showed that patients on sibutramine lost 4.3 kg more weight whereas patients on orlistat lost 2.7 kg more weight than those taking placebo [11]. In this respect, treatment with these drugs was able to induce an additional body energy loss of about 25,000-35,000 kcal over the treatment period compared to placebo. However, even though the weight reduction obtained by these two drugs is not negligible, the body weight/fat gain

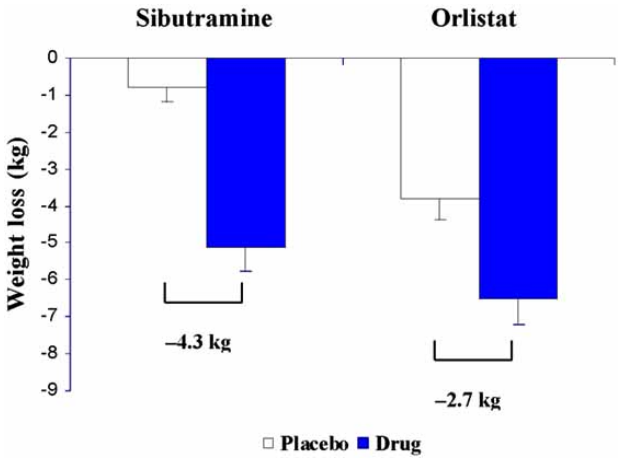

Fig. (5). Potential impact of decrease in body weight set point for sibutramine and orlistat. Data are means ± SEM. Data adapted from Padwal *et al.* [11].

accumulated over years by the affected individuals may be far more important than the potential of these drugs to reverse the accumulated gain. In this respect, the prevention remains very important.

2. NEW MOLECULAR TARGETS FOR POTENTIAL ANTI-OBESITY DRUGS

Over 100 molecules are in various stages of preclinical and clinical development. Table **1** summarizes several potential anti-obesity drug targets, which are discussed in the other articles of this issue.

The rapidly growing science of energy homeostasis gives hope that we are in store for some advances in obesity management. Therapies specifically targeted to newly discovered homeostatic pathways, such as the gut-hypothalamic axis, anorexic and orexigenic hormone receptors within the hypothalamus, effectors of leptin and insulin signal transduction, and central and peripheral nutrient sensing pathways, are possible [25]. Effective weight loss and long-term maintenance of weight loss will probably require multidrug therapy that targets these different regulatory elements. Certain obstacles will, of course, have to be overcome, such as the development of neutralizing antibodies, down-regulation of the targeted receptors, and the counterregulatory changes that occur with weight loss, such as decreased energy expenditure and increased orexigenic signals that drive hunger and favor fat deposition [25]. In giving this new understanding of the regulation of energy homeostasis, we can anticipate that in the future we will probably be able to treat obesity with new pharmacological drugs which will be as effective as those we now have for treating the complications of obesity. Only at that time, the treatment of obesity will dominate the treatment of its complications which will then become a fortunate outcome of weight reduction rather than a primary target of the intervention.

Over the past decade, we have reached consensus that a physiological system exists, the prime function of which is to maintain homeostasis of energy stores in response to variable access to nutrition and demands for energy expenditure. This

Table 1. Some of Potential Targets for New Obesity Treatments

Agonists/stimulators	Antagonists/inhibitors
Adiponectin	Acetyl CoA carboxylase 2
αMSH/MC4R	Agouti-related protein
Apolipoprotein A-IV	11βHSD1
Brain-derived neurotrophic factor/TrkB receptor	Central CPT1
CCK/CCK-A receptor	CRH receptor
CNTF/axokine	DP-IV
Cocaine- and amphetamine-regulated transcript	Endocannabinoid receptor (rimonabant/SR141716A)
GLP-1/exendin-4	Fatty acid synthase (cerulenin; C75)
Human GH fragment (AOD9604)	Galanin
Insulin mimetics	GIP
Leptin; leptin receptor	Ghrelin
Oxyntomodulin	Histamine receptor
PYY	MCH
Phosphatidylinositol 3-kinase	NPY
Somatostatin	Orexin A and B
β3, serotonin, norepinephrine, dopamine receptors	Suppressor of cytokine signaling-3 Tyrosine phosphatase IB

system has both afferent sensing components and efferent effector limbs. The afferent limb of this system includes several kinds of signals. One reflects short-term events such as those related to onset or termination of individual meals; another senses the long-term status of body energy stores. Although these long and short-term signals have often been viewed as operating independently, it now appears that they functionally overlap. Both converge on brain centers, most importantly within the hypothalamus, where the signals are integrated, and the direction and magnitude of efferent responses are determined. The efferent elements of the physiological system include those controlling the intensity of hunger and subsequent food seeking behavior, the level of energy expenditure, including basal and that determined by physical activity, the levels of key circulating hormones such as insulin and glucocorticoids, and factors that influence energy partitioning between lean and fat mass in the body. Some of these signals also influence processes such as reproduction and growth that are linked to nutritional sufficiency.

Since survival is more acutely threatened by starvation than obesity, it should come as no surprise that this system is more robustly organized to galvanize in response to deficient energy intake and stores than to excess energy [26]. Indeed, the efficient storage of energy as fat promotes survival when food supplies are scarce, and evolution would be expected to have favored such "thrifty genotypes" [27]. Nonetheless, increased energy stores promote adaptive responses that resist obesity in experimental animals and humans. These "obesity avoidance" responses are characterized by suppression of appetite and increased energy expenditure [28], and involve the same effector mechanisms that respond in an opposite direction to starvation, as though a switch can be thrown from starvation avoidance to obesity avoidance modes depending on the environment. Unfortunately, circuits that suppress appetite and increase energy expenditure in response to obesity-promoting aspects of the current environment are insufficiently robust to prevent obesity and its complications in a large and increasing fraction of the population. On the other hand, many individuals do resist obesity despite exposure to a common obesogenic environment. The variable susceptibility to obesity in response to environmental influences is undoubtedly modulated by specific genes. Existing knowledge at this interface is still fragmentary and is likely to be an area of great future progress.

2.1. What may we Hope from Pharmacotherapy in the Future?

The future "best" pharmacological agent in obesity management will probably consider the three following aspects in order to improve the chances of success in obesity treatment: 1) having the capacity to spontaneously change the body weight set-point without any specific dietary restriction; 2) being the most specific as possible on the regulation of energy balance; and 3) being well tolerated with the minimum of side effects.

The maximal weight loss achievable with any dietary, physical or pharmacological strategy for treating obesity varies from one to another individual, but generally appears to be no more than 10% of initial weight [a comparison is

made in Fig. (**6**)]. As this threshold is approached, or perhaps as the time spent below initial weight increases, it can be proposed that physiological mechanisms acting to preserve body fat mass cause a progressive increase in appetite and decrease in energy expenditure. These regulatory responses prevent further weight loss and make maintenance of achieved weight loss difficult. It is now appreciated that the long-term regulation of adiposity involves both peripheral signals that relay information about adipose tissue mass to the CNS and opposing circuits in the hypothalamus that control appetite and energy expenditure [29]. To improve the pharmacological options for treating obesity, it will be necessary to intervene at key points within this regulatory network.

Pharmacotherapy in the treatment of obesity must be considered only in a specific part of energy balance regulation and does not take into account the adaptations of human organism with time. These adaptations may potentially induce permanent changes having the potential to be detrimental to the body's functionality and which make more difficult to maintain a reduced-obese state for a long time period. In this regard, reduced-obese individuals are characterized by an increased number of mature adipocytes [30] and a greater body load of organochlorine pollutants as compared to their lean counterparts [31]. These two examples show that body weight/fat gain may lead to permanent changes which may handicap the possibility to return to a complete healthy reduced-obese state as observed in the past. In addition, due to an imbalance in body homeostasis, a physiological vulnerability occurs in a reduced-obese state favoring a body weight/fat regain in order to reequilibrate energy and fat balance. This should confer realism and temper optimism excess for the anti-obesity drug of the future. However, this reinforces the role of prevention in the context of obesity management.

For health professionals, these observations imply that body weight management should be performed with the preoccupation to maintain a reasonable balance between the health benefits of weight loss and its potential inconvenience on the control of energy intake and expenditure. Accordingly, we have to encourage multidisciplinary interventions in the management of obesity by performing progressive personalized tri-therapy (dietary management, exercise program with regular follow-up visits and pharmacological agent), because they had favored a satisfactory benefit-risk profile, as reflected by the enhanced weight loss without the increases in heart rate and blood pressure induced by a sibutramine-based treatment [14].

3. PERSONALIZED TRI-DIMENSIONAL STRATEGY TO LOSE WEIGHT: A CASE-STUDY REPORT

In order to put additional rationale to this multidisciplinary approach, the effect of a personalized 5-year follow-up in a massively obese woman was assessed by our research team at the Clinique Équilibre-Santé of Laval University. Although low-calorie diets, exercise and pharmacological agents have each been shown to play an important role in a weight loss program, no clear evidence exists concerning the sequence in which these strategies should be introduced in the context of a prolonged weight loss program. The present case study addresses this question by having introduced these three strategies of body weight control over a 5-year follow-up in a 35 year-old massively obese woman (156 kg, BMI = 61 kg/m^2). This professional woman had always been slightly overweight but most of her body weight surplus (70 kg) had been gained over a period of 5 years, approximately between 22 and 27 years of age and was mainly a consequence of an excess energy intake.

As shown in Fig. (**7**), dietary modifications constituted the first objective of this weight loss program. Indeed, a low-fat (~30% energy intake), high-carbohydrate (~50% energy intake) diet of 9600 kJ/day was prescribed in order to induce a daily caloric deficit of approximately 2900 kJ. After 5 months of dieting, energy intake was adjusted to the reduced metabolic rate (–836 kJ/day) in order to maintain a 2900 kJ deficit per day. After a 2.5-year follow-up, aerobic exercise was introduced in the intervention program. The subject first walked regularly 3 times a week for 20 min per session. Duration and frequency of walking were then gradually increased until a 45-min walk (increase of 5-10 min per month) was achieved 5-6 times/week. After 4 years of follow-up, the subject had achieved a total weight loss of 20.1

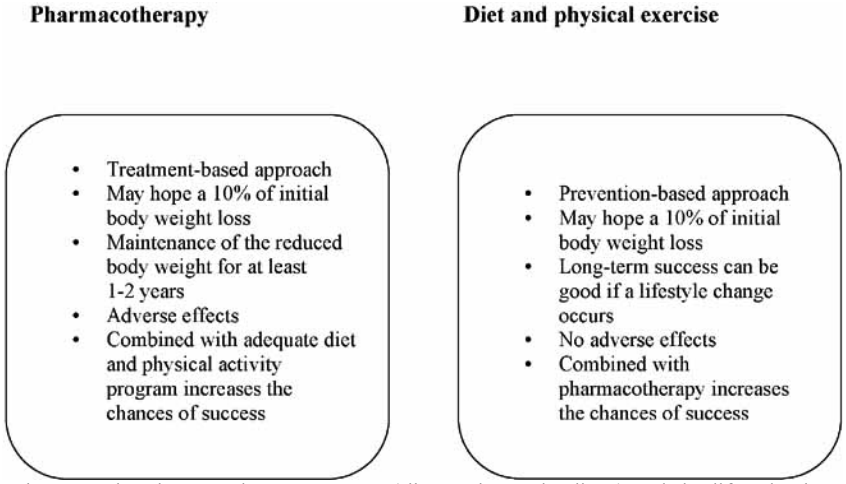

Fig. (6). Brief comparison between the pharmacotherapy strategy (sibutramine and orlistat) and the lifestyle changes approach (diet and physical activity) on body weight loss and long-term success.

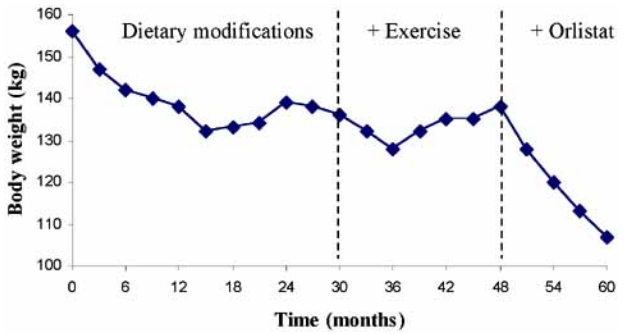

Fig. (7). Body weight changes within a 5-year intervention: a case-study report.

kg but despite this, her level of motivation regarding weight loss was low and the use of another tool was thus necessary. The last part of this intervention included the use of orlistat three times a day (120 mg/day) with each main meal. In this regard, the addition of orlistat as an adjunct to the weight reduction program was successful since an additional weight loss of 27.9 kg was observed over 10 months.

This 5-year intervention led to a total of 48.4 kg weight loss and a decrease of 18.9 units of BMI. As a result of this diet, the subject lost 23 kg in the first 15 months. This is concordant with previous results which demonstrated that a low-calorie and low-fat diet has to be carefully followed to induce and maintain weight loss [32]. In addition, this period of intervention provided results which are concordant with recent studies which suggest that regular long-term contact with the patient facilitates body weight maintenance [33].

In summary, this case-study showed that the gradual integration of a low-calorie, low-fat diet, exercise, and medication respecting the patient's life situation may help to maintain a good level of motivation in obese patients seeking weight loss. These results also confirm that behavior modification combined with pharmacotherapy can improve the treatment of obese patients. Finally, this case-study report provided evidence that substantial weight loss may be achievable in massively obese people if the subject and the health professional work closely together and meet on a regular basis.

4. CONCLUSIONS AND PERSPECTIVES

Sibutramine and orlistat, the only two agents currently approved for long-term treatment of obesity, may induce up to a 10% weight loss when used in combination with dietary, behavioral, and exercise therapy. Although this degree of weight loss may have a salutary effect on medical co-morbidities, there is a need for better tolerated anti-obesity drugs.

Our growing understanding of the physiological mechanisms regulating body fat content will certainly allow the development of such drugs. However, longer and more methodologically rigorous studies powered to examine end points such as mortality and cardiovascular morbidity are needed before more definitive recommendations can be made regarding the role of these medications in the management of obese patients. In the meantime, efforts should focus on the prevention of obesity in those persons who are not obese, and non-pharmacological management should remain the cornerstone of therapy in those with existing disease. Drug therapy should be considered on an individual basis, with stronger consideration given to those individuals with greater degrees of obesity and co-morbid illness. Thus, body weight management imposes a balance between the expectations of a patient and what his/her body biology can tolerate in terms of lifestyle changes.

Altogether, a better understanding of the mechanisms of appetite control and the application of this knowledge as part of evidence-based interventions are leading to a more coherent approach to obesity treatment. Moreover, with the progressive rise in the prevalence of obesity, a relatively small proportion of patients will be treated by intensive behavior therapy, long term supervised drug treatment, or surgery. Therefore, we believe that the most effective long term management of obesity will remain its prevention.

Thus, in a context of preventive medicine, health professionals must consider the obesity problematic in a wider context in order to be optimally managed. In particular, the comprehension of the problem prior to its treatment seems to be a more logical approach before targeting homeostatic pathways which could be irrelevant in some cases.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

BMI	=	Body Mass Index
CCK	=	Cholecystokinin
CNS	=	Central Nervous System
CNTF	=	Ciliary Neurotrophic Factor
CPT1	=	Carnitine Palmitoyltransferase 1
CRH	=	Corticotrophin-Releasing Hormone
DP-IV	=	Dipeptidyl Peptidase IV
EMEA	=	European Medicines Agency
FDA	=	Food and Drug Administration
GH	=	Growth Hormone
GIP	=	Gastric Inhibitory Polypeptide
GLP-1	=	Glucagon-Like Peptide-1
11βHSD1	=	11β-Hydroxysteroid Dehydrogenase Type 1
LDL	=	Low-Density Lipoprotein
MCH	=	Melanin-Concentrating Hormone
MC4R	=	Melanocortin 4 Receptor
αMSH	=	α-Melanocyte-Stimulating Hormone
NPY	=	Neuropeptide Y
PYY	=	Peptide YY_{3-36}
REE	=	Resting Energy Expenditure
RMR	=	Resting Metabolic Rate

SNS = Sympathetic Nervous System

TPD = Therapeutic Products Directorate

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