Pharmacological Treatment of Obesity

revisão

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ABSTRACT

This review offers an overview of physiological agents, current therapeutics, as well as medications, which have been extensively used and those agents not currently available or non-classically considered anti-obesity drugs. As obesity — particularly that of central distribution — represents an important triggering factor for insulin resistance, its pharmacological treatment is relevant in the context of metabolic syndrome control. The authors present an extensive review on the criteria for anti-obesity management efficacy, on physiological mechanisms that regulate central and/or peripheral energy homeostasis (nutrients, monoamines, and peptides), on β-phenethylamine pharmacological derivative agents (fenfluramine, dexfenfluramine, phentermine and sibutramine), tricyclic derivatives (mazindol), phenylpropanolamine derivatives (ephedrin, phenylpropanolamine), phenylpropanolamine oxytrifluorphenyl derivative (fluoxetine), a naftilamine derivative (sertraline) and a lipstatine derivative (orlistat). An analysis of all clinical trials — over ten-week long — is also presented for medications used in the management of obesity, as well as data about future medications, such as a the inverse cannabinoid agonist, rimonabant. **(Arq Bras Endocrinol Metab 2006;50/2:377-389)**

Keywords: Obesity; Treatment; Anfepramone; Mazindol; Sibutramine; Orlistat; Rimonabant

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RESUMO

Tratamento Farmacológico da Obesidade.
Esta revisão faz um apanhado dos agentes fisiológicos e terapêutica atual, bem como de medicações que têm sido usadas extensivamente e de outros agentes ainda não disponíveis ou que são consideradas drogas anti-obesidade não clássicas. Como a obesidade — em especial aquela com distribuição central — representa um importante fator desencadeador de resistência à insulina, o seu tratamento farmacológico é relavente no contexto do controle da síndrome metabólica. Os autores apresentam uma revisão extensa dos critérios de eficácia do manuseio anti-obesidade, dos mecanismos fisiológicos que regulam a homeostase energética central e/ou periférica (nutrientes, monoaminas e peptídeos), dos agentes farmacologicamente derivados dos seguintes produtos: β-fenetilamina (fenfluramina, dexfenfluramina, fentermina e sibutramina), tricíclicos (mazindol), fenilpropanolamina (efedrina, fenilpropanolamina), fenilpropanolamina oxitrifluorofenil (fluoxetina), naftilamina (sertralina) e lipstatina (orlistat). Também é apresentada uma análise de todos os ensaios clínicos com duração maior do que 10 semanas para medicações usadas no manuseio da obesidade, assim como dados sobre medicações futuras, como o agonista canabinóide inverso, rimonabant. **(Arq Bras Endocrinol Metab 2006;50/2:377-389)**

Descritores: Obesidade; Tratamento; Anfepramona; Mazindol; Sibutramina; Orlistat; Rimonabant

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THE PHARMACOLOGICAL MANAGEMENT of obesity has witnessed drastic changes and experienced the development of new products and treatment proposals. Information presented in this review offer an overview of physiological agents, current therapeutics, as well as medications widely used in the past and no longer available.

There is no specific strategy or medication to be recommended on a routine basis. The obese individual must be thoroughly examined regarding improper eating habits and exercising, depression symptoms, obesity-associated complications or conditions, and the possibility of developing side effects. The choice for anti-obesity medications is also based on patients' prior experience and previous therapies, although the failure of a previous treatment does not rule out an agent for later use.

The understanding of some key concepts is crucial in any discussion on the rationale of anti-obesity medications: 1) pharmacological treatment can only be justified when combined with diet and lifestyle changes. Efficacy of all agents depends on patients' compliance to nutritional and behavioral changes; 2) pharmacological treatment does not cure obesity – when discontinued, weight gain is expected; 3) anti-obesity medications must be used under continuous medical supervision; 4) treatment and medication choice are patient-tailored. The risks associated to the use of a drug must be assessed considering the obesity persistence; 5) treatment should be maintained only when considered safe and effective for the patient.

Anti-obesity pharmacological treatment is indicated when body mass index (BMI) is over 30 kg/m^2, or when morbidities are associated to overweight (BMI over 25 kg/m^2) when dieting, physical activities and behavioral changes have proved unsuccessful (1).

Anti-obesity pharmacological agents are not recommended for children, since up to this point in time there is not enough evidence on their effects at this age group.

A useful medication for obesity treatment must: 1) be effective for body weight reduction and result in overweight-dependent conditions improvement; 2) have a long-term efficacy and safety; 3) be related to tolerable or transitory side effects; 4) not be addictive; 5) have known mechanism of action; 6) be reasonably affordable (2).

Obesity is a chronic and stigmatized disease (3) as it is the case of hypertension or hypercholesterolemia (4). Each of these chronic diseases is associated to a number of co-morbidities. Hypertension may cause heart failure and stroke while hypercholesterolemia commonly leads to atherosclerosis and coronary events. For obesity, its main consequences are numerous such as diabetes mellitus, systemic hypertension, dyslipidemia, cardiovascular diseases, certain types of cancer, sleep apnea, ostheoarthritis, among others.

Obesity is recognized as an epidemic condition that affects populations worldwide (1,5). Therefore, the need to improve the quality and efficacy of therapeutics has emerged. The core to current obesity management is based on specific behavioral therapies aiming to change eating habits and raise energy expenditure. Nutritional counseling to lower the intake of calories, particularly fat, associated with increased daily physical activities are highly necessary but compliance are very limited. Pharmacological management is seen as additional tool to this basic therapy.

As obesity — particularly that of central distribution — represents an important triggering factor for insulin resistance, its pharmacological treatment is relevant in the context of metabolic syndrome control.

Pharmacological treatment of obesity is subject to classification according to the mechanisms of action. Knowledge on body adiposity control and regulation had marked improvement in the last decades. One class of anti-obesity agents involves the control mechanism of energy intake. A second strategy against obesity relates to shift the normal nutrient metabolism and a third one to raise energy expenditure.

ANTI-OBESITY TREATMENT: CRITERIA FOR ASSESSING EFFICACY

A number of criteria have been proposed to assess the response to treatments for obesity. Nowadays, the most widely used criteria to assess the efficacy of anti-obesity therapies are those proposed by the Food and Drug Administration (FDA) in the United States, and by the Committee of the European Agency for the Evaluation of Medicinal Products (CPMP) in Europe. According to the FDA, a 5% weight loss significantly higher than placebo is consider response to treatment; CPMP suggests body weight loss over 10% as compared to placebo. In addition, the agencies suggest the inclusion of a run-in period, categoric analysis of the results (patients who have lost over 5% or 10% of their initial weight) and consider the improvement of obesity co-morbidities. Those and other secondary criteria are listed in a recent review (6). The basic difference between the criteria used by the American and the European agencies is the emphasis given to ancillary

recommendations — stronger on the part of the European agency — including behavioral changes following the initial counseling in long-term studies, which raises body weight loss in the placebo group, thus allowing the detection of true effects of the active ingredient. If patients under study lose weight quickly under a behavioral change program or a very low calorie diet, it is harder to keep track of anti-obesity medications additional effects.

The typical body weight history of overweight individuals is an approximate 0.25 kg gain per year (7). A very good objective, under a population point of view, would be the prevention of any kind of additional weight. For obese individuals, a sustained 5% loss may be considered the lowest criterion for success. A 5% to 10% sustained loss as compared to initial weight — associated with partial or no improvement of risk factors — would be from reasonable to good a response, whereas losses over 15% associated with normalization of risk factors and body weight reduction below 25 kg/m² would be excellent and ideal, although hardly ever attainable in clinical practice.

Most studies usually report maximal body weight loss between 20 and 24 weeks of treatment. In a review of clinical trials, Bray calculated that weight loss in weeks 6, 12, and 18 in average corresponded to 44%, 72% and 89% of the 24-week loss (ref).

PHARMACOLOGICAL AGENTS MODULATING ENERGY HOMEOSTASIS

Pre-absortive agents

β-phenethylaminic and phenylpropanolaminic derivates

All central action anorectic medications — except for mazindol — are derived from β-phenethylamine. The β-phenethylaminic skeleton is also the structure of the neurotransmitters dopamine, norepinephrine (NE), and epinephrine (monoamines). Those neurotransmitters are tyrosine-synthetised at nervous terminations, stored in granules and released in the synaptic cleft to act on post-ganglionic receptors. After they act on those receptors, the monoamines may be deactivated through catechol-O-methyltransferase or be reuptaken by the nervous termination (8).

Chemical modifications in the structure of amphetamine (α-methyl-β-phenethylamine) resulted in the synthesis of a range of compounds, with different pharmacological actions and responses. On one end within the pharmacological spectrum, β-phenethylaminic derivates — diethylpropion and phentermine — influence noradrenergic and dopaminergic neurotransmission (stimulating release or blocking reuptake) which results in NE release from the nervous termination, raising the amount of NE interacting with post-synaptic receptors (17). On the other end, the substances affecting serotonin release and reuptake can be found, such as dexfenfluramine and its levorotatory isomer, *l*-fenfluramine or fenfluramine (9). Sibutramine can be found in the middle, blocking NE and serotonin reuptake (10).

Binding studies of [^{3}H] marked phenethylaminic derivates have shown the presence of binding sites of variable affinity in the hypothalamus and in other cerebral regions (11). The binding affinity of the various phenethylaminic derivates is correlated to its anorectic potency, but not to its stimulative ability (20). The binding sites of those substances in the hypothalamus are regulated by glucose level through the action of ionic channels, stimulating sodium-potassium ATPase pump (12).

All β-phenethylaminic derivates have shown to be feeding-reducing in animal studies. Such action is the primary mechanism for weight-loss induction. When feeding is kept constant and paired with control group, weight loss is the same in the group receiving the active substance or placebo. These studies were carried out in animals using amphetamine, and in humans using fenfluramine (in metabolic units) (13,14). The effect is dose-related and takes place immediately after parenteral administrations of the substances (22).

Feeding pattern differs between compounds with primarily noradrenergic or serotoninergic action mechanisms. While amphetamine delays intake outset, fenfluramine does not, but rather anticipates food intake cessation (15). In animals, the administration of serotonin and fenfluramine primarily reduces fat intake (16), whereas NE injection at the paraventricular nucleus affects carbohydrate intake, and noradrenergic medications may have selective action on macronutrient choice (17).

Generally, β-phenethylaminic medications report thermogenic action in animal studies. Mazindol (in this paper, taken together with β-phenethylaminic medications despite a non-β-phenethylaminic derivate) stimulates oxygen consumption (just like diethylpropion) and raises NE stimulation in brown fat (just like amphetamine, fenfluramine, and dexfenfluramine) in rats. Sibutramine — that blocks NE and serotonin reuptake — reduces food intake and also stimulates thermogenesis in brown adipose tissue in animals (18).

Clinical pharmacokinetics

Noradrenergic anorectic medications are usually well absorbed in the gastrointestinal tract, reaching plasma peak levels in the first two hours (table 2). They are removed through metabolization or by hepatic conjugation, which produces active metabolites for some drugs (fenfluramine, dexfenfluramine, sibutramine) (19,29), but deactivates others (amphetamine, phentermine) (20). Half-life is short for most of those medications, and long for fenfluramine, dexfenfluramine and sibutramine metabolites (table 1) (29). Studies indicate that fenproporex is metabolically dealkylated leading to the production of amphetamine in animals (21,22), and its use results in amphetamine positive tests in humans (23). Even so, central nervous system stimulative effects with fenproporex are less notorious in clinical practice than with other agents such as diethylpropion and mazindol. Medical literature is hardly available regarding controlled clinical studies on that substance.

Human studies to assess food intake

Many anorectic medications have been studied to document human feeding reduction action in humans (24-26). It is interesting that *d*-amphetamine effects on appetite are attenuated by ondansetron, a 5-HT_3 receptor antagonist, which suggests that serotoninergic pathways may be involved in the response to noradrenergic action as well (24).

Serotoninergic medications (fenfluramine and dexfenfluramine) reduce carbohydrate intake, although studies have been carried out with carbohydrate and fat-containing foods (25). Other studies have demonstrated that serotonin and fenfluramine led to protein and fat intake reduction, and that ingestion suppression under dexfenfluramine was more effective than under fenfluramine (24-26). Dexfenfluramine leads to meal size reduction and significant reduction in the habit of nibbling (39). Human studies have shown that dexfenfluramine selectively reduces fat intake (27).

Ritanserin, a 5-HT_{2C} serotoninergic receptor antagonist, cancels dexfenfluramine-induced food intake reduction, as well as the increase or prolactin and temperature (28). m-chlorophenylpiperazine (mCPP), a 5-$HT_{1B/2C}$ agonist, was shown to reduce food intake in humans (29); similarly, sumatriptan, a selective 5-$HT_{1B/D}$ agonist, reduced food intake (especially fat intake) and raised plasma GH in a double-blind placebo-controlled study (30). Therefore, serotoninergic receptors 5-HT_{1B}, 5-HT_{2C} e 5-HT_D are candidates for serotonine anorectic effects in humans.

Cardiovascular effects

Sympathomimetic vascular effects are predictable when using β-phenethylaminic substances, since their basic structure is the same of the monoamines NE, adrenaline and dopamine. After acute administration (except for fenfluramine and dexfenfluramine), a small stimulating effect occurs on heart rate and blood pressure (31). Treatment with sibutramine leads to a slight dose-proportional raise, 3–5 mmHg for diastolic blood pressure and 2–4 bpm for heart rate (32). Weight loss leads to blood pressure reduction in quite a number of patients (44) and long-term, clinically significant reductions may be obtained even with modest weight loss (5% reduction) (33). Mechanisms responsible for the hypotensive response to the weight loss are not fully understood, but they probably involve lower insulin level, followed by the reduction of sympathetic nervous system activity and natriuretic effect (34).

Dexfenfluramine and fenfluramine decrease blood pressure in obese patients who are normotensive (35), hypertensive (36), even in short-term studies (37).

Table 1. Pharmacokinetics of anorectic medications available in Brazil and in other countries.

	Peak (hours)	$t_{1/2}$ (hours)	Prescription	Dose (mg/day)
Phentetrazine*	1–2	2–10	—	75
Benzophetamine*	1–2	6–12	—	25–150
Fendimetrazin**	1–2	2–10	—	70–210
Diethylpropion	1–2	4–6	B	75–150
Mazindol	1–2	10	B	1–4
Femproporex	1–2	—	B	25–50
Phentermine**	4–8	19–24	—	15–37.5
Fenfluramine†	2–4	11–30	C	60–120
Dexfenfluramine†	1–8	17–20	C	30
Sibutramine	1–4	16–18	C	5–30‡
Phenylpropanolamin†	1–2	3–4	C	75
Ephedrine†	1–2	3–6	C	75

* not available in Brazil; ** registered at the Ministry of Health but not produced in Brazil (aminorex and mefenorex are also registered, but not marketed in Brazil); † withdrawn from the Brazilian market; ‡ 5 mg capsules not available in Brazil.

Table 2. Selection of studies on β-phenethylaminic medications and respective weight loss.

Active Ingredient	Duration (weeks)	N	Dose (mg/day)	Δ weight		Comments
				Placebo	Active Ingredient	
Diethylpropion	11	46/51	75	+0.3%	-5.1%	Teenagers
	12	25/27	75	-6.3%	-9.4%	Women
	13	53/53	75	+4.8%	+0.7%	Pregnant women
	12	25/25	75	-5.0%	-8.3%	Women
	12	19/22	75	-2.1%	-5.5%	Run-in
	12	40/40	75	-4.4%	-8.0%	Behavioral support
	52	16/16	75	-13.3%	-11.0%	Intermittent medication
	24	10/10	75	-2.8%	-12.3%	
Mazindol	12	20/40	2	-4.1%	-5.8%	NS Δ weight loss;
	12	15/15	3	-3.3%	-11.3%	Versus amfphetamine
	12	58/58	2	-7.0%	-10.9%	Teenagers (11–18 yrs)
	12	33/32	2	-3.0%	-7.7%	Versus amphetamine
	12	20/20	2	-2.2%	-8.0%	Teenagers (12–18 yrs)
	12	20/20	1	-3.0%	-5.1%	Diabetic subjects
	12	20/40	2	-0.5%	-2.7%	Δ weight p< 0.01
	12	25/25	2	-2.1%	-8.1%	Δ weight p< 0.001
	12	30/30	2	-7.7%	-10.3%	
	12	207/207	2	-5.5%	-8.9%	Δ weight p< 0.001
	12	24/22	2	-5.2%	-15.9%	Diabetics
	12	18/18	1.5	-4.6%	-13.8%	Δ weight p< 0.01
Phentermine	14	29/30	30	-2.0%	-8.7%	
	24	15/15	30	-9.2%	-12.6%	Osteoartrosis
	36	36/36	30	-7.6%	-20.5%	Intermittent vs. continuous
Fenfluramine	12	30/30	80	+0.2%	-4.6%	
	12	22/22	60	0	-3.5%	Dyslipidemic subjects
Dexfenfluramine	12	24/26	30	-1.7%	-6.5%	
	12	69/64	60	-4.0%	-9.6%	
	12	16/17	30	-3.0%	-5.8%	Schizophrenic subjects
	12	14/16	30	-1.3%	-6.3%	Borderline hypertensive
	12	24/25	30	-0.7%	-3.9%	Diabetic subjects under oral agents
	12	15/15	30	-0.4%	-4.9%	TEF measured
	12	20/20	30	-0.4%	-3.9%	Diabetic subjects under sulphonylureas
	12	14/15	30	-0.5%	-2.6%	Dyslipidemic subjects
	12	15/11	30	-13.5%	-16.5%	Very low calorie diet
	12	42/42	30	-0.3%	-4.4%	
	24	30/30	30	-1.8%	-6.9%	
	24	30/30	30	-4.9%	-10.4%	1000–1200 kcal/day
	26	22/23	30	-2.7%	-5.3%	Weight maintenance
	52	418/404	30	-7.3%	-10.0%	INDEX Study
	52	39/36	30	-7.3%	-9.6%	
	52	20/20	30	-2.9%	-6.3%	Diabetic subjects
Sibutramine	12	56/47	5	-1.7%	-2.9%	Multicentric study
	12	59/49	10		-6.0%	
	12	62/52	15		-5.5%	
	24	149/95	5	-1.2%	-3.9%	Multicentric phase III study
	24	151/107	10		-6.1%	
	24	150/99	15		-7..4%	
	24	152/98	20		-8.8%	
	24	146/96	30		-9.4%	
	52	161/80	10	-2.5%	-7.1%	
	52	161/93	15		-7.9%	
	52	181/48	10	+0.2%	-6.4%	
	104	352/115	10–20	-4.9 kg	-8.9 kg	STORM Study

N: numbers of subjects in placebo and active ingredient groups; Δ: variation; TEF: thermic effect on food; NS: non-significant. For detailed references of table 2, report to reference 6 of this paper.

Those using blood pressure ambulatory monitoring have shown that the hypotensive effect occurred at daytime but not during the night (50). Dexfenfluramine resulted in plasma renin and noradrenaline reduction that was not dependent of weight loss (50).

Endocrine and metabolic effects

Weight reduction leads to the correction of a number of obesity-associated disturbances. Benefits occur even after modest weight loss (38), although improvement is accentuated as intentional weight loss progress (39).

Some studies have shown that fenfluramine and dexfenfluramine would have hypoglycemic action, which is not weight loss dependent (40,41). In addition, treatment with dexfenfluramine has been associated with visceral fat loss, which is correlated to insulin resistance improvement and intrahepatic fat reduction (55). Dexfenfluramine stimulates fatty acid oxidation and turnover (42). Fenfluramine, but especially dexfenfluramine, are powerful stimulanting factors of prolactin secretion; elevated prolactin levels are attenuated by naloxone (an opioid antagonist) in slim but not in obese women (43). Such elevation is lower in patients with endogenous depression, obsessive-compulsive and panic disorders; under depression therapy, the response this anti-obesity agent is better (44). Amphetamine, in particular, has no influence on prolactin secretion (56). The increase of ACTH and cortisol, detected in obese and non-obese women after naloxone administration, was attenuated by a seven-day treatment with dexfenfluramine (45). The same agent did not affect ACTH and cortisol responses to CRH (58); however, GH response to GHRH was shown to be increased in patients with android obesity, concomitantly with reduction in insulin levels (although the latter may be influenced by dietary habits) (46). Other authors have not detected increase in GH response to GHRH in obese women treated with dexfenfluramine (47).

Mazindol reduces insulin and GH responses to an oral glucose tolerance test, increases T_4 but no change is observed in FSH, LH, testosterone, renin, angiotensin II and 17-ketosteroids levels and in baseline metabolic rate (48).

Weight loss due to sibutramine and energy restriction is associated to better metabolic control in type 2 diabetic obese patients (61,62).

Human studies to assess thermogenic effects

As previously mentioned, different animal studies have shown thermogenic action of various β-phenethylaminic derivates and mazindol (27-29). Their effects in human studies are not so clear, and contrasting results are frequently attributed to the heterogeneity of the obese patients studied.

While some authors have shown higher resting metabolic rate, as well as higher response to feeding after dexfenfluramine administration (49,50), or attenuation of the usual decrease in resting metabolic rate during low-calorie diet in post-menopausal women in a three-month treatment period (51), others have found no difference in 24-hour energy expenditure after 1 week, 3 months (40), or even 13 months under dexfenfluramine or placebo (52).

Human data are also conflicting in sibutramine studies. In one study, no difference was found between baseline metabolic rate and three hours after the administration of sibutramine or placebo, neither after an 8-month treatment with sibutramine (53). However, when calorie expenditure was measured for a 5-hour period, there was an increase in thermogenesis both while fasting and after feeding in the last 3,5 hours after sibutramine administration. Such effect was not observed in the first study (54).

Phenylpropanolamine is an $\alpha_1$adrenergic agonist widely used in the United States for many years. In Brazil, experience with this agent is more limited. Only one study assessing the possible thermogenic effect of phenylpropanolamine did not report any gain in energy expenditure (55), which is consonant with a 12-week study carried out by our group; we evaluated 103 obese women under hypocaloric diet, with 3 daily administrations of capsules containing placebo, yohimbine (8 mg), T_3 (25 µg), phenylpropanolamine (25 mg), or an ephedrine (25 mg) and aminophylline (100 mg) association (56). Only patients receiving phenylpropanolamine had a weight loss significantly higher than the placebo group, even though no difference was observed in resting metabolic rate measured by indirect calorimetry (69).

Ephedrine belongs to the phenylpropanolamines group and stimulates the release of noradrenaline. Structural changes result in increased peripheral action while reducing central action on adrenergic receptors. This made ephedrine prove to be potential treatment for asthma, and actually, for many years ephedrine — either isolated or in combination with teophylline — has been a first choice treatment to treat this disorder. Ephedrine causes a non-selective stimulation of sympathetic nervous system by acting on β-adrenoceptors (β_3 included) and promoting thermogenesis (57).

Ephedrine has been studied in obese women, at 60 mg daily dose for 12 weeks, resulting in baseline metabolic rate increase. At higher doses — 150 mg daily for 30 days — it resulted in weight loss (58).

Ephedrine associated with methylxantins (like caffeine, teophyilline and aminophylline) or aspirin increases the duration of noradrenalin activity. Adenosin and prostaglandins, which decrease noradrenalin activity, are inhibited by caffeine and aspirin. Phosphodiasterase inhibition through caffeine seems to be the most important effect, since that enzyme is responsible for cyclic AMP metabolization, and its inhibition maximizes noradrenalin action (59,60).

Different combinations of caffeine and ephedrine have been analyzed in double-blind studies whose conclusion was that higher synergy occured at the dose of 200 mg caffeine and 20 mg of ephedrine (3 daily administrations) (61). In a randomized, double-blind study conducted by our group, 3 daily doses of a combination of ephedrine 22 mg, caffeine 20 mg and aminophylline 50 mg, resulted in a significantly higher weight loss, as compared to the group of patients not receiving the association, although baseline energy expenditure through calorimetry was not assessed (62). In a more recent study, 17 women with BMI of 34.5 kg/m^2 and body weight of 87.2 kg, treated with 3 daily doses of aminophylline, 300 mg plus ephedrine, 75 mg, reached a weight loss of 5.6 kg (69).

Clinical trials and case reports in humans

Twenty-five years ago, an analysis including over 200 double-blind, controlled studies concerning appetite reduction medications (including amphetamine, phentetrazine, benzophetamine, fendimetrazine, phentermine, chlorphentermine, chlotermine, mazindol, fenfluramine and diethylpropion) was submitted to FDA to justify registrations of new drugs. Ninety percent of them showed a higher weight loss in the group of patients receiving active medication. The withdrawal rate was nearly 24% at first month and approximately 48% at the end of 3-to-8-week long treatments. A total of 4,543 patients were evaluated receiving placebo and 3,182 receiving active ingredients (8).

A review by Bray & Greenway (8) includes a detailed analysis of some of those studies. Table 2 shows a selection of 41 studies on phenethylaminics or tricyclics (diethylpropion, mazindol, phentermine, fenfluramine, dexfenfluramine), which lasted at least 10 weeks. Most of these studies are also described in another review (6).

Those medications fill the criteria currently used for anti-obesity medications, except for fenfluramine and dexfenfluramine. These 2 medications were withdrawn from world market in 1997 due to valvular abnormalities developed under combined therapy of phentermine plus fenfluramine (but not under phentermine monotherapy) (63,64), similar to carcinoid syndrome lesions. An echocardiographic study, including 76 obese women treated with dexfenfluramine for 6 months at the University of São Paulo Clinics Hospital Outpatient Unit, showed a prevalence of valvular injuries of 49%; from 37 women who presented echocardiographic abnormalities, 10 were reexamined 6 months after medication interruption and lesion regression was found in 5 of them (65). A larger prospective study with 1,072 participants did not detect increased risk of valvular injuries in patients using sustained-release dexfenfluramine for less than 3 months (66). A case-control study including 95 patients with pulmonary hypertension and 355 matched controls showed that fenfluramine use was associated with pulmonary hypertension (*odds ratio* [OR] 6.3; 95% CI 3.0–13.2). OR was higher in patients under fenfluramine for less than 12 months (*OR* 10.1; 3.4–29.9) or for a period longer than 3 months (*OR* 23.1; 6.9–77.7) (67).

Only one case of pulmonary hypertension, 12 months after interruption of mazindol therapy in a patient who had received for 10 weeks, was recently reported (68). Isolated cases of pulmonary hypertension (69) and psychosis (70) were associated to diethylpropion.

Although sibutramine is also a phenethylaminic derivate, it does present quite a different profile and much better tolerability. Table 3 summarizes sibutramine studies in which this agent was used for 10 weeks up to two years. References of these studies can be checked in another review published by the authors (6). The most common adverse effects were headache, dry mouth, constipation, insomnia, rhinitis and faringitis, reported by 10–30% of patients under sibutramine. At 5–20 mg daily doses, diastolic and systolic blood pressure increases were in average 1–3 mmHg; heart rate increase was of 4–5 beats per minute (71). For the controlled hypertensive patients, the number who reported clinically significant increase in blood pressure (> 10 mmHg) in 3 successive visits was comparable to sibutramine and placebo groups. Nevertheless, hypertension was seen as its major adverse effect, resulting in discontinuation of patients in the study (72).

In Brazil, when phenylpropanolamine was used, controlled prescription was required. In contrast, for many years, in the US, this was an over-the-counter medication, more widely used than in our country. A case-control study (men and women, age range 18–49 years), reported that when used as anti-obesity medication (opposedly to its use to fight influenza) phenylpropanolamine increased the risk of hemorrhagic

Table 3. Selected studies on the effect of fluoxetine on body weight.

Active Ingredient	Duration (weeks)	N P/AI	Dose (mg/day)	Δ weight (P)	Δ weight (AI)	Comments
Fluoxetine	12	19/23	60	-8.3 kg	-7.3 kg	Crossed study
	12	20/18	60	-2.4 kg	-5.9 kg	MRI-determined visceral faty
	24	24/24	60	-0.8 kg	-4.2 kg	Type 2 diabetic subjects
	24	11/13	60	0	-3.9 kg	Diabetic subjects > 60 yrs
	52	22/23	60	+0.6 kg	-17 kg	Subjects with binge eating disorder
	52	22/23	60	-4.6 kg	-8.2 kg	
	52	228/230	60	-2.1 kg	-1.7 kg	Multicentric study

N: number of patients studied by study group; P: placebo; AI: active ingredient; Δ: variation; MRI: magnetic ressonance imaging. For detailed references of table 3, report to reference 6 of this paper.

stroke in the first 3 days of use (adjusted *OR* 15.9, p= 0.013) (73). Phenylpropanolamine was removed from the American and Brazilian markets in 2001.

Selective inhibitors of serotonin reuptake

Both fluoxetine and sertraline are selective inhibitors of serotonin reuptake despite diverse chemical structure. Fluoxetine is a phenylpropanolamin oxy-3-fluorphenyl derivate and sertraline is a naftilaminic one. Fluoxetine and sertraline inhibit serotonin reuptake at the presynaptic terminal; their main indication is to treat depression and bulimia, and they are not formally indicated to treat obesity. Both agents were found to reduce animal feeding experimentally (74). In humans, weight loss was a common finding during protocols for the approval of those medications as anti-depressants. Under sertraline — which seems to be different from the drug action at muscarinic receptors — weight loss was 0.45–0.91 kg in follow-ups of 8 to 16 weeks.

Human studies to assess food intake

Clinical trials to assess feeding reported the effect of those medications on patients' food intake size (75).

Endocrine and metabolic effects

A study including diabetic subjects reported that fluoxetine treatment was associated with a higher weight loss and their insulin requirements were reduced (76).

Human clinical trials

The key problem involving fluoxetine as anti-obesity agent is weight regain, as detected in long-term studies. In general, after the first 6 months of treatment, body weight is gradually recovered, although medication is maintained.

A study to assess weight loss under sertraline showed no difference when compared to the placebo groups (77). In another, sertraline increased the weight loss of patients under cognitive-behavioral treatment (78). Double-blind fluoxetine studies with at least 10-week duration are shown in table 3. References are detailed in another review published by the authors (6). Fluoxetine therapy for obesity management has been associated with gastrointestinal symptoms, sleep disorders, reduced libido, sweating, amnesia and thirst (79).

Selective inhibitors of serotonin reuptake are not, therefore, efficacious anti-obesity agents, although they may be useful for depressed obese patients, and for patients reporting other comorbidities for which those anti-depressants may be an appropriate treatment - for instance, sleep apnea - since fluoxetine leads to REM reduction, when most episodes of obstructive apnea occur.

Nutrients metabolism post-absorptive modifiers

Lipstatine analogues

Lipstatine is a compound from yeast - *Streptomyces toxytricini*. Orlistat is a stable lipstatine analogue, and partially hydrolized (tetra-hydrolipstatine).

Clinical pharmacokinetics

Orlistat is a powerful inhibitor of gastrointestinal (GI) lipases. Such enzymes catalize hydrolytic removal of triglycerides fatty acids and produce free fatty acids and monoglycerides. Orlistat binds irreversibly to lipase active sites through covalent binding. Approximately one-third of triglyceride intake does not undergo digestion, and is not absorbed by small intestines, crossing the GI tract and being eliminated. Orlistat has no systemic activity, and absorption by GI is minimal when administered up to 800 mg daily, with lipase inhibiting activity pharmacologically irrelevant (from 1,000 to 2,500 times lower than orlistat) (80).

Human studies to assess human intake

Orlistat has no direct effect on appetite regulating neuronal circuits. However, its pharmacological effect

(reflected by the increased amount of fat in feces) stimulates long-term compliance to lower fat content food intake (81).

Cardiovascular effects

Weight loss resulting from orlistat is associated with significant reduction of systolic and diastolic blood pressure as compared to placebo (-4.9 vs -2.4 mmHg and -3.7 vs -1.8 mmHg, $p< 0.05$) (82). A meta-analysis of 5 studies demonstrated that patients reporting isolated systolic hypertension (systolic blood pressure > 140 mmHg) show higher reductions (-10.9 vs -5.1 mmHg, $p< 0.05$) (83).

Endocrine and metabolic effects

As previously mentioned, weight loss leads to the reversion of some obesity-associated disorders. This occurs even with modest weight loss but benefits are improved with intentional weight loss of greater magnitude.

In non-diabetic obese patients, the use of orlistat combined with calorie-fat restriction is associated with significant reductions in insulin (-5.05% vs +19.1%, vs. placebo, $p= 0.001$) and plasma glucose levels (-0.92% vs +2.33%, $p< 0.05$) (84). A one-year study, including controlled diabetic subjects under sulfonylureas, resulted in significant reduction of plasma glucose and glycated hemoglobin levels, as well as in the number of patients discontinuing oral anti-diabetic treatment (85). Those data have been confirmed by a Latin American multicenter 6-month-long trial (86). In our study, the use of orlistat was associated with higher weight loss and marked improvement in fasting ($p= 0.036$) and post-prandial glycemia ($p= 0.05$), and in glycated hemoglobin ($p= 0.04$). In addition, benefits in lipid profile - as seen by total cholesterol ($p= 0.0001$) and LDL-cholesterol level ($p= 0.002$) reductions - and in abdominal adiposity ($p< 0.05$) were observed (88).

Human clinical trials

The first orlistat clinical trials were 12-week long and multi-dosage, at 10 mg, up to 120 mg, 3 times a day (87,88). Another study, six-month long, was carried out at 30, 60, 120, and 240 mg of orlistat, 3 times a day (89). Significant difference in weight loss was reported from 60 mg doses (total daily dose= 180 mg), reaching a plateau at 120 mg (dose total daily dose= 360 mg). Higher doses did not increase the weight loss. Table 4 presents a selection of clinical trials concerning orlistat, also including diabetic subjects. The references of these studies can be checked in another review published by the authors (6). Trials under analysis reported no differences in the frequency of GI adverse effects comparing orlistat and placebo groups. GI effects are related to orlistat mechanism of action (oily stools, increased number of evacuation episodes, flatulence with or without fat discharge, fecal urgency); they are usually short-term and tend to decrease considerably after the first weeks of treatment. Such pattern seems to be related to the long-term patient compliance to low-fat foods.

TREATMENT PERSPECTIVES WITH PHARMACOLOGICAL AGENTS

Associations of two pharmacological agents

Although no randomized trial on the association of sibutramine and orlistat is available, in clinical practice this combination has been used for the management of obese patients, once mechanisms of action are distinctive. The authors evaluated the efficacy and tolerability of sibutramine combined to orlistat at regular doses up to 6 months in 214 patients (121 women and 93 men) (90). A reduction in body weight from baseline of 8% (1.5% to -24%) and -14.9% (-0.4 to -26.6%) was observerd after 3 months (n= 100) and 6 months (n= 36). In this study, the combination of sibutramine and orlistat for obesity management resulted in higher weight reduction when compared to randomized clinical trials, and tolerability was quite reasonable.

The use of pharmacological agents in childhood obesity management

Current clinical approach towards pediatric obesity mainly involves cognitive-behavioral therapies focusing eating and exercising pattern changes.

Foccus on the pathophysiology of obesity may lead to the development of the appropriate medications both for adults and children, possibly from substances regulating metabolic economy physiology. Orlistat already proved to be effective and its use is approved for teenagers. Development of trials in children and teenagers is critical, since one cannot assume that risks and benefits from the use of pharmacological agents in adults will be the same in children (90).

Use of anti-obesity agents in obese type 2 diabetic patients

Weight reduction has been shown to improve glycemic control and cardiovascular risk associated with insulin resistance in obese individuals with type 2 diabetes mellitus. Therapeutic options for these patients include promotion of weight loss (non-pharmacologic and phar-

Tabela 4. Selected studies on the effect of orlistat on body weight.

Active ingredient	Duration (weeks)	N P/AI	Dose (mg/day)	Δ weight (P)	Δ weight (AI)	Comments
Orlistat	12	19/20	150	-2.1 kg	-4.3 kg	First clinical trial
	12	39/37	30	-3.2 kg	-3.6 kg	Dose-range study
		39/45	180	-3.2 kg	-3.9 kg	
		39/47	360	-3.2 kg	-4.8 kg	Δ weight p< 0.01
	24	136/134	90	-6.5%	-8.5%	NS; dose-range study
		136/135	120	-6.5%	-8.8%	Δ weight p< 0.002
		136/136	360	-6.5%	-9.8%	Δ weight p< 0.002
		136/135	720	-6.5%	-9.3%	Δ weight p< 0.002
	52	23/23	360	-2.6%	-8.4%	Δ weight p< 0.001
	52	113/115	360	-5.4%	-8.5%	
	52	186/190	360	-4.6%	-5.9%	Coronary risk
	104	343/345	360	-6.1%	-10.2%	Δ weight at year 1
	104	223/657	360	-4.5%	-7.6%	Δ weight p< 0.001
	104	265/266	180	-4.1 kg	-7.1 kg	Δ weight at year 1
		265/264	360	-4.1 kg	-7.9 kg	
	104	243/242	180	-6.6%	-8.6%	Δ weight at year 1
		243/244	360	-6.6%	-9.7%	
	104	316/359	360	-3.8 kg	-6.7 kg	Progression towards IGT
	104	36/36	360	-8.6 kg	-13.1 kg	
	52	159/162	360	-4.3%	-6.2%	Diabetic subjects, p< 0.001
	24	174/164	360	-3.0%	-4.7%	Diabetic subjects, p< 0.001

AI: active ingredient; t: study time; n: number of patients studied; P: placebo; IGT: impaired glucose tolerance; NS: non significant. For detailed references of table 4, report to reference 6 of this paper.

macologic treatments), which improves glycemic control, as well as treatment of commonly associated risk factors, such as hypertension and dyslipidemia. A recent review provides an overview of anti-obesity drugs used in the treatment of obese individuals with type 2 diabetes. The most widely investigated drugs, sibutramine and orlistat, resulted in modest, clinically worthwhile weight loss, but with marked improvement in several comorbidities, among them, type 2 diabetes. Studies involving these anti-obesity medications in cohorts of obese diabetic patients have been reviewed, as well as involving cathecolaminergic (diethylpropion [amfepramone], fenproporex, mazindol, ephedrine-caffeine combination), serotoninergic agents (fenfluramine, dexfenfluramine, fluoxetine), and others showing any benefit on weight loss (metformin, the anti-epileptic agent topiramate and zonisamide, and the antidepressive bupropion [amfebutamone]). These trials showed variable benefits in terms of effects on glucose metabolism (91). Orlistat was reported to prevent the development of type 2 diabetes in obese patients treated for 4 years (XenDOS study) (92).

Antagonists of endocannabinoid receptors

The ability of marijuana to increase hunger has been noticed for centuries, although research on its action started in the late 1960s. An endogenous neuromodulating system involved in feeding behaviour leads to the therapeutic use of a novel class of drugs, the selective cannabinoid type 1 receptor (CB1R) antagonists, for the treatment of obesity and eating disorders. The experience with the first agent from this class – rimonabant – was recently published. A 1-year blinded randomised clinical trial with doses of 5 mg or 20 mg of rimonabant was found to cause a pronounced reduction in bodyweight (respectively -3.4 kg and -6.6 kg), along with a decrease in waist circumference and a substantial amelioration of the metabolic profile and insulin resistance. Generally, it was well tolerated with mild and transient side effects (mainly nausea) (93).

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