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A Risk-Benefit Assessment of Anti-Obesity Drugs

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Abstract

This review evaluates the benefits and potential health risks of the currently used drugs that are approved for the pharmacological treatment of obesity. Analysis of several long term clinical trials indicates that all of these drugs are efficient in reducing excess bodyweight, and that the majority of them allow the maintenance of the reduced bodyweight for at least 1 year. However, the loss of bodyweight attributable to these drugs is in general rather modest, approaching only 0.2kg per week during the first 6 months of treatment, and at least a partial regain of bodyweight occurs when these drugs are used for periods longer than 1 year.

All of these drugs induce several adverse effects. Although most of these adverse effects are mild and transient, the prolonged use of adrenergic or serotonergic anorectic drugs, or their use as combination treatment, may induce serious and potentially life-threatening complications, such as primary pulmonary hypertension or valvular heart disease. The adrenergic appetite-suppressing drugs are not recommended for the treatment of obesity, since their safety has never been evaluated in long term clinical trials, and because of their stimulatory effects on the cardiovascular and nervous systems. The serotonergic drugs, such as fenfluramine and dexfenfluramine, have been the most widely used during the past decade; however, both these compounds have recently been withdrawn from

the market, since their use was associated with serious cardiovascular complications. The safety of the prolonged therapeutic use of newer compounds such as sibutramine and orlistat has not yet been demonstrated. Therefore, none of the currently available anti-obesity medications meets the criteria of an 'ideal anti-obesity drug' and, if prescribed, these medications should be used with caution and only under careful medical supervision.

Since obesity is recognised as a chronic health-threatening condition, and since classical behavioural therapeutic approaches lack long term efficacy, there is clearly a need for an efficient pharmacological treatment offering an acceptable safety profile. Such a treatment is not available at present. Development of new agents and a more careful assessment of the safety of currently available drugs are needed.

The purpose of this review is to evaluate the benefits of the pharmacological treatment of obesity and to compare them with the adverse effects and health risks that may be related to the use of appetite-suppressing drugs. Several excellent reviews on the pharmacological treatment of obesity have been published in recent years.[1-7] These articles describe in detail the methodology of short- or long term clinical trials of anorectic drugs, the efficacy of the treatment and the adverse effects. Therefore, in the present review the emphasis will be on the comparison of the expected benefits with the potential risks related to the use of anti-obesity drugs.

When approaching this kind of analysis, it is first necessary to define the criteria used to determine the efficacy of pharmacological treatment of obesity. Most previous reviews of the area have considered a treatment to be efficacious if it induces a loss of at least 5 to 10% of the initial bodyweight, and if the prolonged use of the drug allows the maintenance of the reduced bodyweight.[3-7] When compared with the use of placebo plus dietary and behavioural treatment, the benefit of practically all pharmacological treatment of obesity, in terms of additional loss of bodyweight, appears to be rather modest, only 0.2 to 0.3kg per week for most drugs.[1,5,7] However, in the majority of placebo-controlled studies lasting ≥6 months, twice as many patients treated with active drug achieved a loss of >10% of initial bodyweight compared with those who received placebo.

Loss of bodyweight occurs during the first weeks (or months) of treatment and, as a rule, ceases after 6 months of treatment despite continued administration of the drug for several additional months or even years. Several authors emphasise, however, that this apparent lack of long term efficacy cannot be considered as a sign of a tolerance to the action of the appetite-suppressing drug.[1,3,4,6] Indeed, when the drug is withdrawn a rapid regain of bodyweight usually occurs, which clearly indicates that the drug remained active as long as it was administered. Thus, an anti-obesity drug should not necessarily be discontinued because bodyweight reduction has ceased; rather, continuation of treatment should depend on a balance between the health benefits of the maintenance of bodyweight loss and the adverse effects of the drug.[3,5]

The definition of the benefit of anti-obesity treatment should not be restricted to the evaluation of the amount of bodyweight lost during the treatment, but should be extended to the improvement of several comorbid conditions related to obesity, such as hypertension, hyperlipidaemia, coronary heart disease, type 2 diabetes mellitus or sleep apnoea syndrome.[2-5] Indeed, it has been clearly demonstrated that even a modest reduction of excess bodyweight is usually followed by a clear-cut trend towards normalisation of blood pressure, metabolic profile and cardiorespiratory function.[3,5,7] However, these benefits disappear rapidly when

the drug is discontinued because of the ensuing rapid regain of bodyweight.

Thus, the benefit of an 'anti-obesity drug' should be evaluated in terms of its ability to induce a significant loss of bodyweight and to maintain it during the whole period of treatment. These benefits, defined in terms of reduction of the severity of obesity and of its comorbidity, should be balanced against the potential adverse effects and health risks related to the use of a drug. It should also be stressed that all anti-obesity drugs are efficacious in terms of their ability to promote the loss of bodyweight only if they are administered together with effective lifestyle interventions such as an energy-restricted diet, exercise and behavioural modifications.[2,5]

Since obesity is now recognised as a chronic disease, and is the second most frequent cause of preventable death in the US,[8,9] it is obvious that it requires long term treatment. This implies a need for careful assessment of the potential health-threatening effects of the drugs currently used for the pharmacological treatment of obesity.[1-7,9] Because the nonsurgical treatment of obesity, even if it includes diet, exercise and behavioural modification, usually does not allow prolonged reduction of bodyweight, and given the worldwide increase in the prevalence of obesity,[10] there has been a considerable recent increase in the use of appetite-suppressing drugs both in the US and in Europe. This renewed interest in the pharmacological treatment of obesity was stimulated by several long term clinical trials indicating that nonaddictive anorectic medications can promote a prolonged (albeit rather modest) loss of bodyweight with only minor and usually transient adverse effects.[1,3-5,7] The bodyweight-reducing drugs have therefore been increasingly used during the past decade, and administered for prolonged periods of time either alone or in combination in an attempt to increase their efficacy. Given this favourable climate for the pharmacotherapy of obesity, not only have existing drugs been increasingly used but several promising new molecules have been submitted to preclinical and clinical assessment in an attempt to improve the efficacy of obesity treatment.[6,7,11]

The majority of long term clinical trials with the bodyweight-reducing drugs indicated that the adverse effects of currently available agents are in general mild and subside with continued treatment[4-7] or resolve after stopping the medication. For these reasons, in September 1995 the North American Association for the Study of Obesity (NAASO) took an official position in favour of pharmacotherapy of obesity,[2,3] stating: 'There is little evidence that the currently available Schedule IV drugs are addictive or that they have severe side effects. Thus, there is no evident scientific basis for any unusual level of concern about safety.'[3] Unfortunately, shortly after this reassuring official statement was published, several serious and even life-threatening complications such as primary pulmonary hypertension and valvular heart disease were reported.[12,13]

This obviously raises serious concerns regarding the safety of at least some forms of pharmacotherapy of obesity, and makes it necessary to reassess the results of clinical trials with anorectic drugs in an attempt to answer the question of whether the benefits of the use of bodyweight-reducing drugs really outweigh the risks related to their use. The present review will try to provide at least a partial answer to this important question. Before coming to some general conclusions and recommendations, the beneficial effects of different classes of anorectic drugs will be analysed according to the pharmacological profile and the mode of action of these drugs.

1. Catecholaminergic Agents

With the exception of mazindol, all of the currently available compounds belonging to this class of anorectic agents are derivatives of β-phenethylamine.[14] This class includes amphetamine and dexamphetamine, methamphetamine, bezphetamine, phendimetrazine, phentermine, diethylproprion and phenylpropanolamine. Most of these drugs act by releasing noradrenaline (norepinephrine) from presynaptic vesicles in the lateral (prefornical) hypo-

thalamus and some of them, such as mazindol, block the reuptake of noradrenaline by presynaptic neurons. These effects increase the concentration of noradrenaline within the synaptic cleft, which results in stimulation of β_2-adrenergic receptors and powerful inhibition of feeding.

Amphetamines and phendimetrazine are classified by the US Drug Enforcement Agency (DEA) as schedule II, because they have a high potential for abuse, and for this reason are no longer used for the treatment of obesity.[3] Amphetamines, and some amphetamine-like drugs, also block the reuptake of dopamine within the lateral hypothalamus, which reinforces the suppression of hunger; this dopaminergic effect may also account for the high abuse potential of these drugs.[7] Phendimetrazine, listed in DEA schedule III, has a similar pharmacological profile but with somewhat lower abuse potential, whereas diethylproprion and phentermine are much less addictive (DEA schedule IV). Diethylproprion and phentermine are, however, not recommended for a prolonged use because of their amphetamine-like effects on the cardiovascular and nervous systems.[3]

1.1 Diethylproprion and Phentermine

According to the recent review of Bray,[7] and taking into consideration only placebo-controlled studies, the efficacy of diethylproprion administered alone has been evaluated in 7 studies lasting from 6 to 25 weeks. Phentermine has been assessed in 6 studies lasting from 6 to 36 weeks. Although nearly 200 studies dealing with the short term efficacy of diethylproprion were published between 1965 and 1977 (for references see the recent review of Bray[7]), only 2 placebo-controlled trials of diethylproprion lasting longer than 24 weeks have been conducted.[15,16]

In McKay,[16] study patients treated with diethylproprion lost on average 12.3% of their initial bodyweight in 25 weeks, whereas only a 2.8% reduction of initial bodyweight was documented after 16 weeks of placebo administration. The absolute loss of bodyweight averaged 11.7kg for active drug versus only 2.5kg for the placebo-treated group. The drug was therefore efficacious and only minor adverse effects were reported.

The long term efficacy of phentermine was evaluated by Munro and colleagues.[17] In a double-blind placebo-controlled study lasting 36 weeks, there was an average loss of bodyweight of 12.2kg on active drug versus 4.8kg in placebo-treated patients. This indicates a net phentermine-induced additional loss of bodyweight of only 0.2kg per week. However, in terms of modification of initial bodyweight, a 13% reduction occurred in phentermine-treated patients versus 5.2% for placebo. A comparable loss of bodyweight was observed for continuous and intermittent treatment with phentermine.

Similar adverse effects occurred upon prolonged treatment with diethylproprion or phentermine. These included insomnia, nervousness, dizziness, dry mouth, nausea, constipation and depression. Nevertheless, the rise in blood pressure and tachycardia associated with amphetamine and phendimetrazine administration have not been reported in patients treated with either diethylproprion or phentermine. Although no serious adverse effects or life-threatening complications have been reported in these studies, the catecholaminergic agents are contraindicated in patients with hypertension, cardiac arrhythmias, symptomatic cardiovascular disease, glaucoma or in patients with hepatic or renal failure.[5] It is difficult to answer the question whether, in obese patients without these contraindications, the benefits expected from the treatment of obesity with catecholaminergic drugs outweigh the potential risks, since neither the effectiveness nor the potential risk of prolonged treatment with noradrenergic appetite-suppressing drugs have been adequately evaluated.[4-7]

1.2 Mazindol

Mazindol is considered as a catecholaminergic appetite-suppressing drug distinct from the amphetamine-like compounds. It is scheduled by the DEA in class IV, and was recently introduced for therapeutic use in Japan. It exerts at least some of its anorectic effect by inhibiting the reuptake of

noradrenaline in the lateral hypothalamus.[5-7] Mazindol does not inhibit the reuptake of dopamine, and hence has a low potential for abuse. Bray[4,7] evaluated a series of short term clinical trials with mazindol and concluded that both the efficacy and the adverse effect profile of mazindol are similar to those of the other catecholaminergic drugs of schedule IV, except for a higher incidence of insomnia.

The recently reported results of long term treatment with mazindol, lasting for 60 weeks,[18] indicate a rather modest decrease in bodyweight (averaging 6.8kg for the whole period of treatment, thus only 0.2kg per week) and a relatively high drop-out rate (>50%) due to adverse effects or lack of efficacy. This moderate decrease in bodyweight was however sufficient to improve insulin sensitivity, lipid profile and blood pressure control. No serious adverse effects were noted; thirst, constipation and fatigue were the most frequent adverse effects. Mazindol was also effective when administered during or after a very-low-calorie diet to prevent rebound and bodyweight cycling.[18]

1.3 Phenylpropanolamine

Phenylpropanolamine is approved in the US, Europe and Australia for over-the-counter use as a vasoconstrictor and nasal decongestant. It is considered as an unscheduled compound with no abuse potential, and was also extensively used as a bodyweight-reducing drug.[3,7] At least 7 placebo-controlled but short term (lasting from 2 to 12 weeks) studies have evaluated the loss of bodyweight with phenylpropanolamine. Although the mean loss of bodyweight averaged 0.5kg per week, the net reduction of bodyweight attributable to phenylpropanolamine administration was limited to 0.23kg per week.[7,19] The beneficial effect of phenylpropanolamine on bodyweight loss is particularly marked at the beginning of treatment, since in a more recent study lasting only 2 weeks the phenylpropanolamine-treated patients lost 2.6kg whereas those taking placebo lost 1.1kg, a net phenylpropanolamine-induced loss of bodyweight of 0.75kg per week.[20]

Only mild and transient adverse effects have been reported with phenylpropanolamine, but there is some concern about the fact that when used at dosages >75 mg/day phenylpropanolamine can raise blood pressure, especially if combined with caffeine.[21] It has nevertheless been suggested that, if used alone and at a dosage not exceeding 75 mg/day, phenylpropanolamine meets acceptable safety standards to be an over-the-counter appetite suppressant.[19,21]

2. Serotonergic Agents

These compounds suppress feeding and promote the loss of bodyweight by releasing serotonin (5-hydroxytryptamine; 5-HT) and/or inhibiting its reuptake by neurons of several brain areas, but especially within the paraventricular nucleus.[4-7,11]

2.1 Fenfluramine and Dexfenfluramine

The racemic (DL-) form of fenfluramine, and more recently its D-isomer (dexfenfluramine), have been the most extensively studied anorectic drugs of the past 30 years. Although dexfenfluramine was approved for obesity treatment in the US only in April 1996,[5] this drug has been widely used in 65 other countries since 1985 and consequently has been one of the most frequently used anti-obesity treatments over the last decade. Since only the D-isomer of fenfluramine (dexfenfluramine) was thought to have anoretic activity while inducing less adverse effects than the racemic form, only dexfenfluramine was extensively used in clinical trials conducted in recent years. Dexfenfluramine was recognised as an effective drug in reducing bodyweight and abdominal obesity, and was considered to have an acceptable safety profile.[7,11,22,23] It was widely recommended for treatment of refractory obesity,[1,3,5-7,11] especially in patients with hypertension[24] or type 2 diabetes mellitus,[25] or in patients attempting to maintain the loss of bodyweight induced by a very-low-calorie diet.[26]

In the largest placebo-controlled long term study of dexfenfluramine, the International Trial of Long-Term Dexfenfluramine in Obesity (INDEX)

study,[27] the total loss of bodyweight over 12 months was slightly but significantly larger in the dexfenfluramine group than in patients given placebo (9.8 *vs* 7.2kg), and more than twice as many dexfenfluramine-treated as placebo-treated patients achieved a loss of more than 10% of initial bodyweight (35 *vs* 17%). Although the net loss of bodyweight attributable to dexfenfluramine was rather small and occurred exclusively during the first few months of treatment,[27] this small additional bodyweight-reducing effect was associated with other benefits, such as improvements in metabolic profile and in blood pressure control.[1,7,22,23] The adverse effects reported during the long term trials with dexfenfluramine were in general mild and transient, consisting mainly of dry mouth, diarrhoea, tiredness, polyuria and drowsiness.[7,27]

Despite the fact that these serotonergic compounds were in general considered as an efficient and well-tolerated pharmacological treatment of obesity, both fenfluramine and dexfenfluramine were withdrawn from the market in September 1997, because of several reports suggesting the association of these drugs with a risk of primary pulmonary hypertension[12] and of valvular heart disease.[13] The risks of these serious complications in patients treated with appetite-suppressing drugs will be discussed in section 4.

2.2 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, have been approved for the treatment of depression. However, they have not been found to be useful in the long term treatment of obesity, despite the expected serotonergic reinforcement of satiety.[5]

Of the various SSRIs, only fluoxetine has been used for the treatment of obesity, in individuals with or without diabetes mellitus.[1,5-7,28-30] In 2 placebo-controlled studies lasting for 1 year and using fluoxetine dosages 2- to 3-fold higher than the usual dosage for the treatment of depression, the initial moderate loss of bodyweight documented during the first 6 months of treatment was followed by bodyweight regain despite the continuing use of fluoxetine during the following 6 months.[28,29] Moreover, a number of adverse effects were reported during this treatment, such as asthenia, sweating, nervousness, tremor and sexual dysfunction.[29] Although fluoxetine treatment has been reported to improve glycaemic control and lipid profile in obese individuals with diabetes mellitus,[30] the overall benefit was modest and does not outweigh the lack of efficacy during long term treatment. These observations led to the conclusion that serotonin reuptake inhibitors are not useful as pharmacotherapy of obesity, unless there is a short term justification for bodyweight loss.[22] However, fluoxetine is considered as the drug of choice in depressed obese individuals requiring an antiobesity agent and an antidepressant.[22]

3. Combined Drug Treatment of Obesity

Combination treatment of obesity using the simultaneous administration of noradrenergic and serotonergic drugs was introduced several years ago by Weintraub and his colleagues.[31] The goal of combination therapy is to obtain a greater bodyweight loss than is achievable with the maximal dosages of each of these drugs administered alone, while reducing adverse effects. Such treatment, combining phentermine and fenfluramine (or, later, dexfenfluramine) became very popular in the US, and several long term studies using combined administration of phentermine and fenfluramine have been reported.[1,3,5-7,31-35] The results were relatively promising, since an average bodyweight loss of nearly 16kg was reported after continuous 60-week treatment with half-maximal doses of phentermine and fenfluramine, with relatively few adverse effects.[32-34] However, as reported by Atkinson and colleagues,[34] there also occurred some more serious adverse effects, such as depression or short term memory loss in 18% of patients. On the other hand, the expected benefits associated with loss of bodyweight were observed, such as normalisation of blood pressure in previously hypertensive participants and of serum cholesterol

and triglyceride levels in obese hyperlipidaemic patients.[34]

The investigators concluded that combined treatment using phentermine and fenfluramine is generally well tolerated and effective, but remained concerned that there is insufficient knowledge of the long term safety of this combination[34] and that more research is needed to determine the efficacy and safety of the combined treatment if it is continued for more than 3 years.[34] Before this last report appeared in print, several cases of serious valvular heart disease in obese patients undergoing the combined phentermine-fenfluramine therapy were documented.[13]

It has also been reported that the association of fluoxetine and dexfenfluramine administered for 8 months produced a significantly greater loss of bodyweight than fluoxetine plus placebo (13.4 *vs* 6.2kg), and that this combined treatment appeared to be 'safe and well tolerated'.[36] Although no serious adverse effects were reported in this study, the combination of 2 serotonergic drugs cannot be recommended given the potential risk of the 'serotonin syndrome' which may occur in patients receiving SSRIs and other serotonergic medications.[37]

Combination of ephedrine, which stimulates noradrenaline release from sympathetic nerve terminals, with caffeine and/or aspirin (acetylsalicylic acid), to potentiate the thermogenic effect of noradrenaline, represents another type of combined pharmacotherapy of obesity, particularly popular in Denmark.[38] This association of a sympathomimetic agent and methylxanthines such as caffeine was thought to enhance the loss of body fat by inducing a central suppression of hunger concomitant with a stimulatory effect on energy expenditure involving increased fat oxidation.[38] In a study lasting for 6 months, the association of ephedrine and caffeine induced a mean loss of 16.6kg, which was only 3.4kg greater than in the placebo group. The additional bodyweight-reducing effect attributable to this pharmacotherapy was therefore only 0.14kg per week.[39] Although some increase in blood pressure and in heart rate occurred during the first weeks of treatment, this stimulatory effect on cardiovascular function disappeared after 12 weeks of continuous administration of ephedrine plus caffeine.[38,39]

4. Cardiovascular Risks of the Appetite-Suppressing Drugs

4.1 Primary Pulmonary Hypertension

Reversible and irreversible primary pulmonary hypertension has been reported in patients receiving therapy with anorectic drugs, the most frequently used being fenfluramine and dexfenfluramine.[5,12] The incidence of primary pulmonary hypertension in the general population is very low, an annual rate of 1 to 2 cases per million per year. The recent multicentre case-cohort study[12] found that the risk of primary pulmonary hypertension was 23-fold higher in obese individuals taking anorectic medication for ≥3 months than in the general population. Manson and Faich[9] pointed out that, although significant, the absolute risk of this life-threatening complication remains extremely small, amounting to 28 cases per million individuals exposed for 1 year to anorectic drugs. They suggested that if one takes into account the potential life-saving benefits of bodyweight reduction in obese individuals and a 50% mortality rate for patients with primary pulmonary hypertension, treatment with appetite-suppressing drugs still presents a benefit : risk ratio of 20 : 1 (280 lives saved as compared with 14 deaths caused by primary pulmonary hypertension). This kind of speculation remains, however, purely theoretical.

The association of appetite-suppressant drugs with primary pulmonary hypertension is probably not limited to dexfenfluramine. Indeed, fatal pulmonary hypertension has been recently reported after the short term use of fenfluramine and phentermine, with clinical and anatomopathological features quite similar to the pulmonary hypertension caused by aminorex in Switzerland, Germany and Austria 35 years ago.[40,41] This clearly indicates that the risk of primary pulmonary hypertension is not limited to the serotonergic

appetite-suppressing drugs, but the role of other amphetamine-like anorectic agents remains unclear.[12,40] Another vascular complication reported recently after combined fenfluramine and phentermine treatment consisted of ischaemic colitis resulting from local vasoconstriction, reminiscent of the postulated vasoconstrictive effect of anorectic medications on the pulmonary arteries.[42]

4.2 Valvular Heart Disease

More recently, investigators from the Mayo Clinic reported on 24 women in whom valvular heart disease, associated in several patients with pulmonary hypertension, developed after a mean period of 12 months of combined administration of fenfluramine plus phentermine.[13] Several additional cases were reported quite recently in the US, either after combination treatment with fenfluramine plus phentermine[43] or after dexfenfluramine administered alone.[44] The median duration of therapy before diagnosis of valvular disease was 10 months, and 6 patients underwent valve-replacement surgery, of whom 1 died. The mitral valve was most frequently affected in this study (86%); aortic valve insufficiency was documented in 68% of patients, and tricuspid valve insufficiency in 39%.[43] Left-sided valves were involved in all cases, and 3 of the women also had pulmonary hypertension.

Somewhat discrepant results have been published as to the incidence of cardiac valve abnormalities in patients treated with appetite-suppressing drugs. The first large echographic evaluation involved 271 patients who had taken the combination of fenfluramine and phentermine for 6 to 24 months and it indicated that 86 patients (32%) had aortic valve insufficiency with significant regurgitation.[45] A similar incidence was reported more recently by Wadden et al.[46] in 21 patients after 2 years of continuous treatment consisting of fenfluramine 60 mg/day and phentermine 15 mg/day. However, no comparison was made in these studies with the prevalence of cardiac valvulopathy in obese patients who had not been treated with anoretic drugs, making it difficult to evaluate the risk of cardiac valve abnormalities attributable to the appetite-suppressing drugs.

This issue was recently addressed by Khan and colleagues,[47] who evaluated the prevalence of cardiac valvular insufficiency in 257 obese patients who had taken dexfenfluramine alone, dexfenfluramine and phentermine or fenfluramine and phentermine for various periods, and in 239 control obese patients, who were matched for age, gender and body mass index. Valvulopathy was found in only 1.3% of controls, while 22.7% of patients previously treated with anoretic drugs had cardiac valve abnormalities; aortic valve insufficiency was the most common abnormality. The odds ratio for valvulopathy was 22.6 for all treated patients; the odds ratio was 12.7 for dexfenfluramine alone, 24.5 for the combination of dexfenfluramine and phentermine and 26.3 for the combination of fenfluramine and phentermine. It should be noted, however, that these differences in the risk of valvulopathy were also related to duration of treatment.

The importance of duration of treatment with anoretic drugs as a risk factor for cardiac valvulopathy was also indicted by the findings of a recent, large, population-based study conducted in the UK by Jick et al.[48] In this study, the 5-year cumulative incidence of idiopathic cardiac valve disorders with regurgitation was 0 per 10 000 patients in obese individuals who had never taken appetite suppressants and among those individuals who took phentermine alone. However, the incidence of valvulopathy was 7.1 per 10 000 patients among patients treated with fenfluramine or dexfenfluramine for <4 months and 35 per 10 000 patients among those who received either of these medications for ≥4 months.[48] It is noteworthy that this incidence was lower than that suggested by other studies.[43-47] Finally, it may be of interest to note that in a recent study no significant difference in the incidence of cardiac valvular regurgitation was seen between obese individuals treated with either placebo or dexfenfluramine for 2.5 months.[49] Therefore, short term exposure to anoretic drugs is probably not associated with a significant risk of cardiac valvular disease, but this risk clearly in-

creases with increasing duration of treatment, mainly in patients taking fenfluramine and dexfenfluramine, either alone or in combination with phentermine.

It has been suggested that this valvular disease was induced by increased plasma serotonin levels in patients taking the association of fenfluramine and phentermine. This is because of the similarity of the morphological features of cardiac valvulopathy documented in these patients with the valvular disease observed previously in patients given serotonin-like drugs such as ergotamine, or in those with carcinoid disease which is associated with high circulating serotonin levels.[12] This pathophysiological mechanism involving serotonin cannot be excluded, since 10- to 100-fold normal plasma serotonin levels have been documented in patients with primary pulmonary hypertension and who had previously been treated with fenfluramine.[50] In addition, we have observed that even in the absence of any sign of pulmonary hypertension, 6 months of treatment with dexfenfluramine was associated with a 2-fold increase in plasma serotonin levels, whereas the platelet serotonin content was decreased (J. Kolanowski, J.P. Thissen, M. Moriau; unpublished observation).

5. New Anti-Obesity Drugs

5.1 Sibutramine

Sibutramine, recently approved for management of obesity in the US and currently awaiting approval in Europe, suppresses feeding by inhibiting noradrenaline and serotonin reuptake within the hypothalamic areas involved in the regulation of eating behaviour.[51] Sibutramine acts through the generation of 2 active metabolites which inhibit both noradrenaline and serotonin reuptake without any direct influence on neuronal noradrenaline, dopamine and serotonin release, which clearly differentiates its pharmacological action from those of anorectic drugs such as fenfluramine and the amphetamine-like agents.[51] The bodyweight-reducing effect of sibutramine may result both from enhancement of satiety and from a stimulatory effect on thermogenesis and thus on energy expenditure. While is has been documented that sibutramine exerts a dose-dependent reduction in food intake even in nondieting obese individuals,[52] which may obviously promote bodyweight loss, the resting metabolic rate is not affected by sibutramine in obese individuals taking an energy restricted diet.[53] Sibutramine has no potential for abuse, and its bodyweight-reducing efficacy is comparable with that of appetite-suppressant noradrenergic and serotonergic compounds.[5,7]

Long term clinical trials indicate that sibutramine given for 6 months induces a significant dosage-dependent reduction in bodyweight,[54] which for dosages ranging from 10 to 20 mg/day was 3 to 5kg greater than the loss of bodyweight with placebo.[54,55] In the study conducted by Bray and colleagues,[54] 38% of patients taking sibutramine 20 mg/day over a period of 24 weeks lost at least 10% of the initial bodyweight, whereas none of the placebo-treated patients achieved such a reduction in bodyweight. In this study the net additional loss of bodyweight attributable to sibutramine was clearly dosage-dependent, and for 20 mg/day averaged 0.33kg per week. The most frequently reported adverse events included dry mouth, anorexia, constipation, insomnia, dizziness and nausea, but also, paradoxically, an increase in appetite was reported in 9% of patients (and in 3% of patients treated with placebo).[55]

Sibutramine slightly increased blood pressure and heart rate in normotensive obese individuals, whereas mean blood pressure was reduced by about 4mm Hg in hypertensive individuals. It is noteworthy, however, that this beneficial influence of bodyweight loss on blood pressure was more pronounced in placebo-treated hypertensive obese patients.[55] This observation is not surprising since, when administered to healthy individuals, sibutramine induced a significant increase in systolic and diastolic blood pressure, as well as in heart rate.[56] Since these effects were completely prevented by concomitant administration of atenolol, the cardiovascular effects of sibutramine are

probably mediated through a sympathetic mechanism potentiating the effects of circulating catecholamines.[56] The safety of prolonged sibutramine administration and potential hazards related to this treatment remain to be established.

5.2 Orlistat

Another new drug, orlistat (tetrahydrolipstatin) has been approved in some countries. It is an inhibitor of gastric, carboxyl-ester and pancreatic lipase, which reduces by about 30% the intestinal absorption of fat by inhibition of triglyceride hydrolysis.[57,58] In a double-blind placebo-controlled study conducted for 12 weeks, total bodyweight loss averaged 4.3kg in the orlistat group versus 2.1kg in the placebo group, a net additional loss of bodyweight limited to 0.18kg per week.[57] The reported adverse effects consisted of abdominal pain, liquid stools, faecal incontinence with oily stools, nausea, vomiting and flatulence, but these symptoms were in general mild and transient. There was also some trend towards a decrease in lipid-soluble vitamin levels, but only the decrease in vitamin E levels was statistically significant.[57]

More recently, a multicentre placebo-controlled study was designed to assess the efficacy and tolerability of orlistat administered for 52 weeks.[59] The preliminary data indicate that at 6 months the orlistat-treated patients lost 8.6kg, versus 5.5kg on placebo, a net additional loss of bodyweight of only 0.13kg per week. However, during the remaining 6 months of treatment a clear-cut regain of bodyweight occurred in the placebo group, whereas patients from the orlistat-treated group maintained their bodyweight loss, achieving an 8.4% reduction of their initial bodyweight at 52 week of the study.[59] Analysis of the 1-year placebo-controlled trial with orlistat[59,60] indicates that 55% of patients taking this drug lost >5% of bodyweight; a similar bodyweight loss was achieved by only 33% of patients taking placebo. Corresponding figures for bodyweight loss >10% of the initial bodyweight were 25% and 15%, respectively. As an additional benefit, there was a decrease in cholesterol levels, which may explain the concomitant decrease in serum vitamin E concentration. The investigators came therefore to the conclusion that orlistat, when used with a health-promoting low-fat diet, may be a useful addition to the pharmacological management of obesity.[59]

These conclusions are supported by the results of 3 recent multicentre studies conducted in Europe[61,62] and in the US.[63] In all these studies, twice as many orlistat-treated patients lost >10% of their initial bodyweight compared with placebo-treated patients, and this significant weight-reducing effect was associated with an improvement of cardiovascular risk factors and in metabolic profile. In the 2-year randomised, double-blind, placebo-controlled trial with orlistat conducted recently by Sjöström and colleagues,[61] 38.8% of patients treated with orlistat lost >10% of their initial bodyweight versus 17.7% in the placebo group. However, as emphasised by the authors, 'the use of orlistat beyond 2 years needs careful monitoring with respect to efficacy and adverse events'.

6. Conclusions

Analysis of clinical trials using different types of anti-obesity drugs for prolonged periods of time indicates that pharmacotherapy for obesity, when combined with appropriate behavioural approaches, is in general efficient in promoting the loss of bodyweight during the first months of treatment, and allows the maintenance of bodyweight loss for at least 1 year.[1-7] This analysis indicates, however, that the additional loss of bodyweight attributable to the currently used anorectic drugs is in general very modest. If treatment is continued for 2 or 3 years, there is usually at least a partial regain of the bodyweight lost at the beginning of treatment.[1,7,33,35] Even if the adverse effects associated with these prolonged treatments have been considered as 'mild and transient',[3,5] some adverse effects of adrenergic sympathomimetic drugs, even those from DEA schedule IV and thus having a low potential for abuse, should be considered as potentially health-threatening, especially in older patients with hypertension and coronary insufficiency, or in patients with psychological dis-

orders and depression. In addition, no information is available as to the safety of prolonged administration of these drugs.

According to the opinion expressed by Bray:[64] 'The ideal anti-obesity drug should be safe and acceptable for long term administration, as established by data documenting 6 months of efficacy and 2 years of safety.' This obviously raises the question of whether the anti-obesity drugs should be held to higher standards than other drugs used long term, such as antihypertensive or antidiabetic medications. The answer to this important question is not obvious since, at least theoretically, reduction of bodyweight can be obtained by non-pharmacological (behavioural) approaches which, even if complied with, are frequently insufficient to normalise blood pressure and blood glucose levels. At present, the regulatory agencies require at least 1 year of clinical trial of a new anti-obesity drug for efficacy and 1 year of data for safety.[3]

As to the risk-benefit assessment of the serotonin-releasing drugs, such as fenfluramine and dexfenfluramine, the prevailing opinion was that the risks related to very rare but nevertheless serious complications such as primary pulmonary hypertension[12] were outweighed by the benefits of this treatment and by the risk of remaining overweight.[3-5,9,23] This rather positive judgement about the usefulness of fenfluramine and dexfenfluramine for the pharmacological treatment of obesity was obviously modified by the possible involvement of these drugs in the development of valvular heart disease.[13] The recent withdrawal of these drugs from the market, a step taken by the manufacturer, is the best expression of the opinion that, at least at present, the therapeutic benefits of fenfluramine do not outweigh the potential hazards. Compounds influencing eating behaviour through a specific inhibition of serotonin reuptake (such as fluoxetine) are not effective in the long term treatment of obesity,[22,28,29] but they may help some obese depressive participants to comply with diet. As for combined therapy with phentermine and fenfluramine or dexfenfluramine, it should no longer be used because of a clearly increased risk of cardiovascular complications.[13,41-44] The association of ephedrine and caffeine should be used with caution, especially in obese patients at risk of cardiovascular complications.

There appears to be no reliable method allowing the identification of patients in whom the administration of an anorectic medication is likely to produce a substantial loss of bodyweight.[5,22] However, several studies have found that the magnitude of the bodyweight loss during the first weeks of treatment with a given drug predicts further responsiveness to the drug.[5,29,65] This implies that, even if a drug is well tolerated, it should be withdrawn if there is no significant reduction of bodyweight during the first month of treatment.

Analysis of the results of clinical trials of drugs approved for the treatment of obesity and widely used over the past few years clearly indicates that none of these compounds corresponds to the definition of an 'ideal anti-obesity drug'[3-5] where the health benefits clearly outweigh the adverse effects and potential risks. It appears therefore that the presently available appetite-suppressing drugs do not have a convincingly favourable benefit : risk ratio and, if prescribed, they should be used with caution and under strict medical supervision.

Assessment of the benefit : risk ratio of the new anti-obesity drugs, such as sibutramine and orlistat, is not possible at present because of the lack of long term evaluation of the safety of these drugs. Despite the fact that sibutramine has a pharmacological profile distinct from the effects of combined phentermine and fenfluramine administration, its noradrenergic and serotonergic effects must inevitably raise some concerns about its long term safety.

Since obesity is now recognised as a health-threatening chronic condition, and given the lack of long term effectiveness of nonsurgical and non-pharmacological treatments of obesity, there is clearly a need for an efficient pharmacological bodyweight-reducing treatment that can be used long term with an acceptable safety profile. Such a treatment is not available at present. The development of new compounds acting on different mech-

anisms involved in bodyweight control, such as eating behaviour and energy expenditure, is urgently required. In all likelihood, such compounds will be used as combined treatments, influencing simultaneously the mechanisms controlling nutrient ingestion, absorption and partitioning, as well as thermogenesis.

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