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HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

Pharmacologic Treatment Options for Obesity: What Is Old Is New Again

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Abstract After a long period of failure in development, two new medications (phentermine/topiramate ER – Qsymia™ and lorcaserin – Belviq®) have been approved by the US Food and Drug Administration for long-term weight management in persons with obesity (BMI≥30 kg/m^2) or in overweight persons (BMI≥27 kg/m^2) with comorbidities. Another medication, bupropion/naltrexone, is undertaking a cardiovascular outcomes trial and an analysis in 2014 will determine its approval and release. The most widely prescribed drug for obesity, phentermine, used since 1959 for short-term weight management, has been released in a new formulation. This paper reviews these new medications, and other important events in the landscape for management of obesity, with an eye to the interests of physicians who manage hypertension. All the new drugs under discussion are re-fittings of old agents or fresh approaches to old targets; thus, what is old is new again in the pharmacotherapy of obesity.

Keywords Obesity · Hypertension · Pharmacotherapy · Obesity treatment · Medications for obesity · Phentermine · Topiramate · Topiramate ER · Lorcaserin · Naltrexone · Bupropion · Qsymia · Belviq · Contrave · Suprenza

Introduction

Recent events have changed the landscape for managing obesity. First, there is a growing appreciation that modest weight loss (5–10 % from baseline) is achievable, sustainable and is associated with health benefits. With observation of more than 2,500 diabetic subjects in a intensive lifestyle intervention, Look AHEAD has demonstrated the ability to produce modest weight loss and sustain it over four years [1, 2]. That weight loss had benefits regarding risk factors [1, 2], sleep apnea [3], urinary incontinence [4], mobility [5] and symptoms of depression [6]. Further, the intervention reduced medication use and costs [7]. In response to a growing appreciation of the impact of obesity on morbidity and health care costs, and the health and potential cost benefits of modest weight loss, the Center for Medicare Services (CMS) announced in 2012 that reimbursement would be provided for up to 14 sessions of intensive behavioral therapy for obesity, when delivered by primary care physicians [8]. Surgery for obesity is being more widely implemented across the US; The Swedish Obese Subjects study has shown that compared to usual care, bariatric surgery is associated with long-term reduction in overall mortality, and decreased incidence of diabetes, myocardial infarction, stroke and cancer in women [9]. The diabetes remission or "reversal" rate following various types of bariatric surgeries has garnered attention [10–12] in the face of a diabetes epidemic, and this treatment may be implemented more often for patients with that disease. And, finally, at long last, there appears to be a new appreciation of the need for medications to aid patients in their attempts to achieve weight loss and related health benefits and the US Food and Drug Administration (FDA) approval and release of two new medications for weight loss in 2012.

Medications for the treatment of obesity have an unfortunate history that has been a barrier to rapid development of safe and effective drugs [13]. The "halo" around using medications to help patients lose weight has been tarnished on account of these events. Sibutramine was removed from the market in 2012 because of increased risk for cardiovascular events in patients with pre-existing cardiovascular disease. Fenfluramine and dexfenfluramine were associated with cardiac valvulopathy and removed from the market in 1997. Many drugs failed in development for lack of efficacy

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(i.e. NPY antagonists, leptin) or safety (i.e. cannabinoid receptor antagonists, ecopipam). In part, the problem has been that the paradigm for developing drugs is to push the dose to achieve weight loss that might be cosmetically desirable. This strategy inevitably produces side effect profiles that are unacceptable. When smaller doses of medications are given in combination, side effects are minimized and cumulative weight loss can be satisfactory. A major trend is that the approach to medicating for obesity seems to follow the approach in hypertension, i.e. to use combinations of medications to achieve good control with minimization of side effects, and to use the medications chronically. Another emerging trend is that physicians should prescribe long term for obesity much like they prescribe for hypertension, except that the drugs should be prescribed to assist a lifestyle prescription, and antihypertensives are rarely prescribed with lifestyle recommendations. Medications for treatment of obesity should be viewed as adjuncts to lifestyle changes and may help more patients succeed in achieving and maintaining weight loss sufficient to achieve health benefits. Pharmacotherapy can augment weight loss through reduction in food intake brought about by reductions in appetitive signals, supporting behaviors to eat less by reducing hunger and increasing satiety.

In recent years, the regulatory environment has improved for obesity drugs and the FDA has signaled a desire to help provide safe drugs and devices to be prescribed as adjuncts to lifestyle intervention, for patients who would derive health benefits from weight loss [13]. Two new medications, phentermine/topiramate ER combination and lorcaserin, were finally released on the market in 2012 after more than a decade without new drugs, and a third drug combination, naltrexone/bupropion, is undertaking a premarketing trial to assure cardiovascular safety. There is even a new formulation available for the old compound, phentermine, which was released in 1959. This review will focus on these four compounds—lorcaserin, phentermine/topiramate ER combination, naltrexone/bupropion combination and phentermine, with a focus on research results of the last three years. The similarities are that they are based on agents that have been around so long as to be off patent (phentermine, topiramate, bupropion and naltrexone), or are a modern take on an old target (5HT2c receptor, with lorcaserin being the targeting agent.) So for all these drugs, what is old is new again. This review will focus on those four agents, with an emphasis on items of interest to those interested in hypertension.

Phentermine/Topiramate ER, Marketed as Qsymia™ in the US

The combination phentermine/topiramate ER (PHEN/TPM ER) is marketed as Qsymia™ by Vivus Inc., and is the first new drug approved for chronic weight management in overweight and obese persons in more than a decade. The combination uses lower doses of phentermine (3.75 mg in the starting dose, 7.5 mg in the recommended dose and 15 mg in the full dose) than are usually prescribed when phentermine is a single agent. The topiramate is an extended release formulation, not available other than in this combination and the dose of topiramate in the combination (23 mg in the starting dose, 46 mg in the recommended dose and 92 mg in the full dose) is also lower than that when topiramate is used for migraine prophylaxis or seizure control. In terms of mechanism of action, phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus and topiramate's appetite reducing mechanism is not thoroughly understood, although it may be through its effect on GABA receptors.

Efficacy of PHEN/TPM ER

Two clinical studies [14•, 15•] provided efficacy and safety data that formed the basis [16, 17••] for approval of the medication. EQUIP [14•] enrolled subjects≤70 years of age with BMI≥35 kg/m^2. That study required blood pressure to be controlled (≤ 140/90 mmHg using 0–2 antihypertensive medications), fasting blood glucose≤110 mg/dL and triglycerides≤200 mg/dL using 0 or 1 lipid lowering medication. CONQUER [15•] enrolled adults≤70 years of age with BMI≥27 and≤45 kg/m^2, but for patients with type 2 diabetes, no lower BMI limit was required. CONQUER also required patients to have two or more of the following comorbidities: hypertension, hypertriglyceridemia, dysglycemia (impaired fasting glucose, impaired glucose tolerance or type 2 diabetes) or an elevated waist circumference (≥ 40 inches for men or≥35 inches for women). Thus, the patient population in these two studies represents those with higher risk profiles from the consequences of excess weight. A titration period is required for PHEN/TPM ER, starting at a dosage of 3.75/23 mg. In these studies, the titration period was 4 weeks, while the recommendation for use is at least 2 weeks. All subjects in these studies received a lifestyle modification program based on the LEARN manual [18]. The weight loss results are shown in Table 1. This combination medication has produced the largest weight losses, approaching 10 % on average, observed in clinical trials of obesity medications.

The CONQUER study was extended for a second year of observation, with patients keeping their treatment assignment. This has been published as the SEQUEL study [19••]. At the end of the second year of treatment, patients completing the trial taking the recommended dose (7.5 mg/46 mg) maintained a weight loss of 9.3 % below baseline, and those on the top dose maintained a 10.7 % weight loss from baseline.

Table 1 Weight loss efficacy of phentermine/topiramate ER (PHEN/TPM ER) and lorcaserin at 1 year

Drug, Study and Treatment	Mean Weight Loss (%) (ITT-LOCF)	Percent of Patients Losing >5 % of Body Weight
PHEN/TPM ER (Qsymia™)		
EQUIP		
PHEN/TPM ER 15 mg/92 mg	10.9 %	67 %
Placebo	1.6 %	17 %
CONQUER		
PHEN/TPM ER 7.5 mg/46 mg	7.8 %	62 %
PHEN/TPM ER 15 mg/92 mg	9.8 %	70 %
Placebo	1.2 %	21 %
LORCASERIN (Belviq®)		
BLOOM AND BLOSSOM, combined		
LORCASERIN 10 mg BID	5.8 %	47 %
Placebo	2.5 %	23 %
BLOOM-DM		
Lorcaserin 10 mg BID	4.5 %	38 %
Placebo	1.5 %	16 %

The weight loss with PHEN/TPM ER is accompanied by improvements in risk factors. In the CONQUER study [15•], there were clinically and statistically significant improvements in blood pressure, glycemic measures, HDL cholesterol and triglycerides with both the recommended and the top doses of the medication. We provide in Fig. 1 the effects of blood pressure in the CONQUER, which will be of particular interest to readers of this journal. In the EQUIP, CONQUER and SEQUEL studies, improvements in risk factors were related to the amount of weight loss, with greater benefit being observed with greater weight loss. Further, a population with abnormal risk factors is more likely to demonstrate improvement in those risk factors. PHEN/TPM ER has also been studied in patients with sleep apnea and been shown to reduce the severity of symptoms from sleep apnea [20].

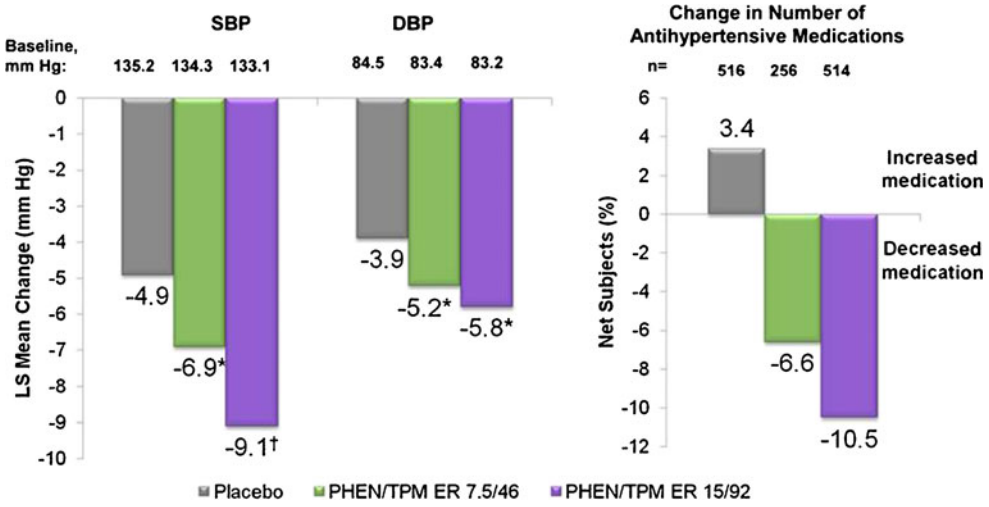

Fig. 1 CONQUER study: blood pressure change and medication change from baseline at week 56 in subjects with hypertension (intention to treat, last observation carried forward analysis). There are statistically significant reductions in both systolic and diastolic blood pressure for patients treated with either dose of medication and the lifestyle program compared to placebo and lifestyle program. While there was a net increase in blood pressure medications for subjects receiving placebo plus lifestyle intervention, subject on either dose of medication plus lifestyle intervention experienced a net decrease in blood pressure medication. Reprinted from The Lancet, 377, Gadde et al. [15•], Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial,1341-1352, 2001, with permission from Elsevier. SBP=systolic blood pressure; DBP=diastolic blood pressure. *P<0.05 vs placebo; $^{+}$ P<0.0001 vs placebo

Safety Profile of PHEN/TPM ER

The most commonly observed side effects in the clinical trials were paraesthesia, dizziness, dysgeusia (altered taste), insomnia, constipation and dry mouth (Qsymia® Prescribing Information). These side effects are related to the constituents of PHEN/TPM ER or, in the case of constipation, to weight loss per se. Phentermine, as a sympathomimetic agent, causes insomnia and dry mouth, usually early in treatment, which then resolve. Topiramate is a carbonic anhydrase inhibitor, and it is associated with altered taste for carbonated beverages and tingling in fingers, toes and perioral areas and may lead to mild metabolic acidosis.

Safety concerns (Qsymia™ Prescribing Information) with PHEN/TPM ER are also associated with the two components. Weight loss is contraindicated in pregnancy, as are all weight loss medications. Topiramate is associated with oral clefts if used during pregnancy and PHEN/TPM ER is pregnancy Category X. A rare side effect of topiramate is acute glaucoma, and the drug is contraindicated in glaucoma. PHEN/TPM ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors (MAOIs), and in patients with hypersensitivity to any of the ingredients in the medication. Because of the risk of oral clefts, a negative pregnancy test before treatment and monthly thereafter and use of effective contraception is required. If a patient becomes pregnant while taking PHEN/TPM ER, treatment should be immediately discontinued. Other potential issues, although rare, include risk of kidney stones (associated with topiramate) and increased heart rate in patients susceptible to sympathomimetic drugs (associated with phentermine).

Lorcaserin, Marketed as Belviq® in the US

Lorcaserin (Belviq®, Arena Pharmaceuticals and Esai Pharmaceuticals) has recently been approved by the US FDA for chronic weight management. Serotonergic drugs have been used in the past for obesity treatment (fenfluramine and dexfenfluramine), but have been removed from the market, because their action on the 5-hydroxytryptamine (5 HT, serotonin) 2b receptor was associated with damage to the heart valves [21]. Lorcaserin selectively targets the serotonin 2c receptor, which when activated in the hypothalamus is associated with reduced food intake [22], and to avoid the serotonin-2b heart valve target. Lorcaserin is prescribed at 10 mg twice daily (Belviq® Prescribing Information).

Efficacy of Lorcaserin

Three clinical studies provided evidence [23] for approval of lorcaserin, and their effect on weight loss at 1 year is displayed in Table 1. Two of these studies, BLOOM [24••] and BLOSSOM [25•], enrolled volunteers who were obese or had BMI≥27 kg/m^2 with one comorbidity. The third study, BLOOM DM [26•], enrolled diabetic patients with hemoglobin A1C 7–10 % and BMI 27–45 kg/m^2. In this study, all patients (including the placebo group) received counseling in diet and physical activity. As demonstrated in Table 1, the weight loss with lorcaserin at 1 year is more modest than with the combination PHEN/TPM ER. There were improvements in cardiovascular risk factors in these studies, most prominent in the BLOOM DM study, where the patient population was more likely to have abnormal risk factors at baseline. In that study, HbA1c decreased 0.9±0.06 with lorcaserin BID, in those treated with the recommended dose, compared to and 0.4±0.06 with placebo ($P<0.001$) and fasting glucose decreased 27.4±2.5 mg/dl compared to a decrease of 11.9±2.5 mg/dl for placebo ($P<0.001$). The drug has also been evaluated for 2-year efficacy in BLOOM. In that study, weight maintenance was demonstrated with a small amount of regain.

Safety Profile of Lorcaserin

Lorcaserin was scrutinized for potential effects on heart valves during Phase III studies where echocardiograms were done on more than 5,200 subjects. Figure 2 shows the 2-year echocardiogram results for the BLOOM study. There is no statistically significant increase in FDA-defined valvulopathy with drug treatment as compared to placebo. In the briefing report [23] using combined data on all patients who were exposed to lorcaserin or to placebo in the three studies, the relative risk of FDA-defined valvulopathy in lorcaserin-treated participants, as compared with those who received placebo, was reported as 1.16 (95 % confidence interval [CI], 0.81 to 1.67), which is not statistically significant. However, since lorcaserin has much greater selectivity for the 5-HT2c receptor than the 5-HT2b receptor, it is very unlikely that lorcaserin increases the risk of valvulopathy in humans, and the FDA has not recommended routine echocardiography for prescription of lorcaserin.

Another issue with lorcaserin was the preclinical observation of an increased numbers of brain and mammary tumors in rats in toxicology studies. These were reanalyzed, and there were fewer malignant tumors than first thought [23]. Additionally, the drug does not have high levels in the central nervous system of humans, whereas it does in rats [23].

Lorcaserin is well tolerated. The most common adverse events in clinical trials were headache, nausea, dizziness, fatigue, dry mouth, and constipation (Belviq® Prescribing Information). But these were mild and resolved quickly. However, a primary concern is that the drug should not be used with selective serotonin reuptake inhibitors (SSRIs) or with monoamine oxidase inhibitors (MAOIs), because of the risk of serotonin syndrome.

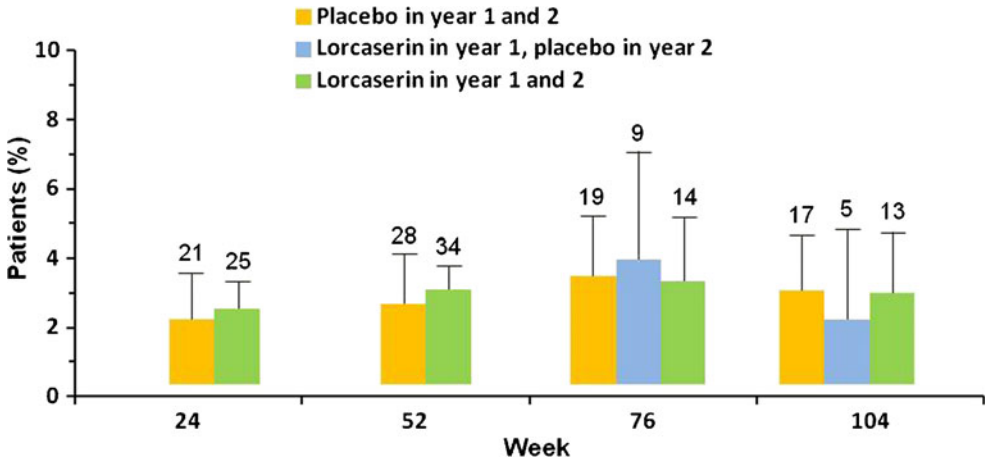

Fig. 2 Echocardiography findings over two years of treatment with lorcaserin or placebo. All patients received lifestyle intervention and were randomized to receive either lorcaseing or placebo. At week 52, the lorcaserin patients were re-randomized to either placebo (lorcaserin in year 1, placebo in year 2) or lorcaserin (lorcaserin in year 1 and 2). The bars represent the mean percentage of patients who met echocardiographic FDA criteria for cardiac valvulopathy; the number of patients in each group with valvulopathy is shown above each bar. *From* New England Journal of Medicine, Smith et al. [24], Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management, 363:245–56, © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

In summary, the value of lorcaserin seems to be not in the magnitude of its weight loss efficacy, but in its safety and tolerability. The only issue is the risk of serotonin syndrome and because the background use of SSRI antidepressants is so high, physicians should be watchful and not prescribe in that group of patients.

Naltrexone/Bupropion (NB) Combination, Not Yet on the Market, (Tentatively Named Contrave)

The combination of bupropion and naltrexone was favorably reviewed by an FDA Advisory Panel in 2012 [27]. However, bupropion (an inhibitor of the reuptake of norepinephrine and dopamine) increases pulse and both bupropion and naltrexone increase blood pressure. Additional concerns were raised by effects of the combination on pulse and blood pressure in the phase III studies. Thus, the FDA has required a pre-marketing study of the combination drug with assessment of cardiovascular outcomes. There will be an interim analysis of the trial and the FDA may allow the marketing of the combination as Contrave as early as 2014, provided the cardiovascular outcomes are acceptable.

We include a brief discussion of this combination because journal readers may be interested in the issue of mixed risk factor effects with weight loss medications, and especially the blood pressure effects of naltrexone/bupropion in Phase III studies.

Weight loss with the naltrexone/bupropion combination at one year was intermediate to that of PHEN/TPM ER and lorcaserin. This produced improvement in risk factors. However, in the two studies that comprised the Phase III trials of naltrexone/bupropion, called the COR [28] and COR BMOD trials [29], the effect on blood pressure is not as great as one would expect with this degree of weight loss.

What is of concern is the outlier effect of NB, not the mean blood pressure effect, which is reduced, albeit not as much as expected. In the COR BMOD trial [29], the authors describe a post hoc subgroup analysis of 50 individuals who had systolic blood pressure≥130 mmHg at baseline. For individuals who received NB32/360 + BMOD, mean systolic blood pressure declined at all visits with mean reductions 3.4 to 11.4 mmHg. In this same set of subjects, mean diastolic blood pressure also declined by 1.0 to 6.5 mmHg. This would seem to indicate that there was no increased risk for those with higher blood pressure who take the drug. However, neither of the reports [28] provides data on blood pressure responses of outliers. Furthermore, in the COR I trial [28], there were transient increases in mean blood pressure of 1.5 mmHg systolic, while the placebo-treated group had transient decreases of 1.5 mmHg. The amount of weight loss may modify the blood pressure response. In the COR BMOD trial [29], the authors report that change in blood pressure in the NB 32/360 + BMOD group was correlated with weight loss.

If the cardiovascular outcome trial shows no increased risk for cardiovascular events with naltrexone/bupropion, this drug could be a valuable addition to the therapeutic toolbox in obesity. There are some tolerability issues, chiefly nausea on initiating the drug [27], and potential issues with SSRIs or MAOIs [27], but the medication could offer another prescribing option in an uncrowded field.

Phentermine, Marketed with Various Trade Names

We include a brief discussion of phentermine, which, as a single agent, remains the most often prescribed drug for weight loss in the United States. Because phentermine was approved in 1959 for short-term use for weight loss, there is little current data to evaluate its long-term efficacy. In 2011, the FDA approved a new formulation of the drug [30] as Suprenza, and Akrimax Pharmaceuticals, LLC, is the marketer of the drug. Since the FDA only approved the new orally disintegrating formulation, there was no clinical weight loss data submitted with the NDA application. However, several studies are worthy of note because they provide recent data on safety and efficacy of phentermine as a single agent.

Efficacy of Phentermine as a Single Agent

A study of 6 six months duration that was presented to the FDA in the briefing document [31] for topiramate/phentermine combination had four treatment arms and 200 subjects, with 158 subjects completing the 6 months. For the phentermine 15 mg daily treatment group, weight loss at 6 months was 4.6 %, compared to a loss of 2.1 % for placebo. Another phentermine study that is relatively current was presented as a poster at the European Congress of Obesity in 2009 [32]. This study also explored phentermine topiramate combination and overall had seven treatment arms among 756 subjects; it is thus one of the largest studies of phentermine alone at two doses (> 100 subjects per dose) with over 6 months of observation. In that study, at 28 weeks, completion rates were 65 %. Weight loss at 28 weeks for the placebo group was 1.7 % from baseline; for phentermine 7.5 mg/d it was 5.5 %; and for phentermine 15 mg/d it was 6.1 %. Finally, a report from Korea [33] evaluated a diffuse, controlled release form of phentermine at 30 mg (n=37) versus placebo (n=37). At 12 weeks, mean weight loss was 8.1 +3.9 kg for drug treated patients versus 1.7 +2.9 kg for placebo patients. The conclusion is that the degree of weight loss with phentermine is dose-related.

Safety Profile of Phentermine as a Single Agent

The sympathomimetic drugs produce central excitation, manifested clinically as insomnia and in some individuals as nervousness. This effect is most obvious shortly after the drug is started and wanes substantially with continued use. Dry mouth is among the most common side effects. To a variable extent, these drugs may also increase heart rate and blood pressure. The prescribing information usually recommends that the drugs not be given to individuals with a history of cardiovascular disease. Unfortunately, because both drugs were approved for short-term use more than 50 years ago, and since they were not intended for long-term use, the issue of impact on cardiovascular events was not considered.

There is little evidence of quantitative effects on blood pressure and pulse, especially over the longer term (6 months or more). A short-term study evaluating phentermine and taranabant [34] administered singly or together for up to 28 days, showed that there were no significant differences in blood pressure and heart rate versus placebo in that study. In a 12-week study [35] from Korea, 68 obese individuals were randomized to either phentermine HCL 37.5 mg per day or placebo. There were no significant differences in mean blood pressure changes between groups at 12 weeks, although the phentermine group lost significantly more weight on average (7.2 +2.7 kg vs. 1.9 +2.7 kg, P<0.001). In the Korean study [33] of a new formulation of phentermine (diffuse controlled release; not marketed in the US), at twelve weeks, mean weight loss was significantly greater in the phentermine group (8.1 +3.9 vs. 1.7 +2.9 kg, P<0.001). However, there were no significant differences in systolic and diastolic blood pressure. Despite clinically significant weight loss, one does not observe expected decreases in blood pressure. Furthermore, the phentermine group had a mean increase in heart rate of 2.7±11.4 beats/minute, compared to a decrease of 4.3±12.5 beats/minute in the placebo-treated subjects [33].

Lacking good quantitative measures of the effects of phentermine on heart rate and pulse, we recommend caution in prescribing the drug. It should not be prescribed to persons with a history of cardiovascular disease. The blood pressure and pulse should be monitored while taking phentermine. Even though there is no convincing evidence of mean blood pressure increases, the lack of the expected reductions in blood pressure with weight loss is an indication that the drugs do have some stimulatory effect on blood pressure. Should these drugs have come before the FDA today for approval for long-term use, the Agency would undoubtedly require a cardiovascular outcome study.

Conclusion

It has been a bumpy road developing safe and effective medications for obesity. The lessons of the past are several. First, we learned that prescribing for obesity, like prescribing for hypertension, is a chronic disease management paradigm. Drugs must be prescribed over the long term for chronic weight management; they don't produce permanent weight loss. Second, we learned the importance of understanding the mechanism by which drugs produce weight loss, so that the medication can be prescribed along with appropriate instruction in diet and physical activity. Third, safety and tolerability are key factors. By increasing doses of a single agent to maximize weight loss, adverse

consequences arise. Thus, combination therapy using lower drug doses are carrying the day. Last, we've learned the hard lessons of unexpected consequences. Because one can never predict these, the current trend is to prescribe for patients with health consequences of their weight status, who will benefit from weight loss. Prescribing for cosmetic weight loss is unacceptable, given the wide margin of safety required for cosmetic intervention. The new medications for obesity take advantage of old targets, old compounds and old principles learned from chronic disease management. In obesity pharmacotherapy, what is old is new again.

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