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WEIGHT LOSS MEDICATIONS IN THE TREATMENT OF OBESITY AND HYPERTENSION

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Abstract

Purpose of Review: Weight loss is strongly associated with improvement in blood pressure; however, the mechanism of weight loss can impact the magnitude and sustainability of blood pressure reduction.

Recent Findings: Five drugs—orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion—are currently approved for weight loss therapy in the United States. Naltrexone/bupropion results in an increase in in-office and ambulatory blood pressure compared to placebo. Other therapies are associated with modest lowering of blood pressure, and are generally well-tolerated; nonetheless, evidence is limited regarding their effect on blood pressure, particularly longitudinally, in individuals with hypertension.

Summary: Although weight loss medications can be an effective adjunct to lifestyle modifications in individuals with obesity, there is limited evidence regarding their benefit with regard to blood pressure. Future studies evaluating the effectiveness of weight loss medications should include careful assessment of their short- and long-term impact on blood pressure in individuals with hypertension.

Keywords

Obesity; Hypertension; blood pressure; weight loss; weight loss medication; weight loss pharmacotherapy

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Compliance with Ethics Standards

Conflict of Interest

Dr. Cohen has no financial conflicts of interest to disclose.

Human and Animal Rights and Informed Consent

This review article does not contain any studies with human subjects or animals performed by any of the authors.

Epidemiologic association between obesity and hypertension

Obesity is a critical epidemic with a growing global burden over the past several decades. In the United States (US), the prevalence of obesity has been increasing in adults since the 1980s. Analyses from the most recent National Health and Nutrition Examination Survey from 2015–2016 estimated that 39.6% of US adults are obese (body mass index [BMI] ≥30 kg/m^2), compared to 33.7% in 2007–2008 and 7.7% of adults are severely obese (BMI ≥40 kg/m^2), compared to 5.7% in 2007–2008 [1]. Based on pooled international data, there are approximately 603.7 million adults with obesity worldwide, with accelerating rates of obesity in many countries [2].

The rising rates of obesity worldwide pose a serious economic and public health threat [3]. Over 7% of deaths and almost 5% of disability globally are attributed to excess body weight [2]. Much of the increased morbidity and mortality in individuals with obesity is due to adverse metabolic effects of adipose tissue. Excess adiposity is strongly associated with increased risk of type 2 diabetes, cardiovascular disease [4], and end stage kidney disease [5]. In turn, many of the cardiometabolic consequences of obesity have a reciprocal relationship with hypertension. Almost three-quarters of individuals with hypertension in the US are overweight or obese [6]; correspondingly, higher rates of hypertension are observed in individuals with obesity compared to normal-weight individuals [7]. Obesity has several causal links with hypertension and, consequently, the end organ effects of hypertension. Adipose tissue possesses pathophysiologic properties that affect vascular behavior, sodium handling, and liver and kidney function, resulting in elevations in blood pressure and complicating the medical management of hypertension [8]. Obesity is often associated with lifestyle factors that drive hypertension, such as high sodium intake [9] and insufficient physical activity [10]. Additionally, measurement of blood pressure can be significantly complicated by large body habitus [11], further hindering the management of hypertension in obesity.

Pathophysiology of hypertension in individuals with obesity

Mechanisms of elevated blood pressure due to excess adipose tissue

A number of interrelated pathophysiologic mechanisms stimulate the development of hypertension in obesity. Hypertension is most often driven by vascular aging, which is accelerated in individuals with obesity. This accelerated vascular aging is likely in part due to concomitant inflammation, oxidative stress, and insulin resistance [12–14]. Individuals with obesity also experience increased neurohormonal (i.e. sympathetic nervous system) and humoral (i.e. renin-angiotensin aldosterone system) activity [15, 16]. Elevated renin-angiotensin aldosterone system activity in individuals with obesity is likely stimulated by adipokine activity [17], and does not seem to be systemically regulated. The combined neurohormonal and humoral dysfunction results in impaired vasodilation, increased sodium reabsorption by the kidney, reduced natriuresis, and volume expansion [18, 19], further precipitating elevated blood pressure.

Challenges in the treatment of hypertension in individuals with obesity

Taking into account the pathophysiologic drivers of elevated blood pressure due to adipose tissue, individuals with obesity experience several challenges in the management of their hypertension (Table 1). Individuals with obesity are at greater risk of treatment-resistant and treatment-refractory hypertension [20, 21], and experience higher rates of end organ damage from hypertension (i.e. cardiovascular disease and end stage renal disease) [4, 5], compared to normal-weight individuals. As a result, individuals with obesity often require a greater number of antihypertensive medications to achieve adequate blood pressure control compared to normal-weight individuals, exposing them to higher risk of adverse effects from medications. Excess adipose tissue also alters the pharmacokinetic and pharmacodynamic handling of many medications. The mechanisms driving altered medication handling in the setting of excess adipose tissue include expanded volume of distribution, altered hepatic metabolism (due to nonalcoholic fatty liver disease) [22], renal hyperfiltration (or alternatively, impaired renal clearance due to chronic kidney disease) [18, 19], and increased sympathetic activity [23, 24]. Together, these mechanisms result in altered plasma concentrations of certain medications (particularly lipophilic medications) in obese compared to normal-weight individuals [24, 25].

Several antihypertensive medications have altered treatment effects in individuals with obesity compared to the general population. Individuals with obesity seem to have exaggerated hemodynamic responses to medications inhibiting the sympathetic nervous system and renin-angiotensin aldosterone system [26–29], potentially increasing the risk of organ ischemia [30]. Nonetheless, in individuals with obesity, inhibition of the renin-angiotensin aldosterone system may reverse some of the pathophysiologic mechanisms driving end organ damage in this population. Small studies in humans have demonstrated that renin-angiotensin aldosterone system blockade may reduce insulin resistance [31], endothelial dysfunction [32], and aldosterone production [33] in individuals with obesity.

Effect of weight loss on blood pressure and end organ effects of hypertension in individuals with obesity

Dose-response relationship between weight loss and blood pressure

Epidemiologic data consistently demonstrate a direct linear relationship between elevated body mass index and blood pressure: as weight increases, blood pressure increases. Correspondingly, the blood pressure lowering effect on weight loss also appears to be linear, with higher achieved weight loss resulting in greater decline in blood pressure. Meta-analyses of older randomized controlled trials (RCTs) of lifestyle modifications (i.e. diet and exercise) demonstrate that every 1 kg of weight loss corresponds to a short-term (2–3 year) decline in systolic blood pressure of 1 mm Hg [34, 35]. A more recent trial of the effect of the comparative effectiveness of lifestyle modifications vs. bariatric surgery demonstrated that participants randomized to bariatric surgery were on 20–30% fewer antihypertensive medications during the first four years of follow up [36]. This difference is likely, at least in part, due to substantially greater weight loss observed individuals who underwent bariatric surgery compared to lifestyle modifications (mean 21.8% vs. 9.6% at five years).

Weight loss due to bariatric surgery in hypertension

Surgical interventions have a more substantial and lasting effect on weight loss than lifestyle modifications. Considerable weight loss after bariatric surgery corresponds to high rates of remission of hypertension. In a recent trial in which participants were randomized to Roux-en-Y gastric bypass vs. medical management of hypertension, Schiavon et al. found that 84% of participants who underwent bariatric surgery experienced a ≥30% reduction in the total number of antihypertensive medications, compared to 13% of participants randomized to medical management [37]. Over half of participants who underwent bariatric surgery had complete remission of hypertension as measured by office blood pressure (46% by ambulatory blood pressure), in contrast to zero participants randomized to medical management. By meta-analysis, 75% of individuals randomized to bariatric surgery with diagnosis of hypertension prior to surgery experienced complete remission of hypertension [38]; however, such high rates of hypertension remission are not consistent across all studies [39]. Mechanistically, bariatric surgery is associated with persistent declines in plasma leptin and muscle sympathetic activity, likely contributing to the observed decline in blood pressure [40].

Of note, compared to non-surgical weight loss, bariatric surgery is associated with significantly higher rates of perioperative adverse events such as surgical complications, reoperation, acute kidney injury, and mortality [38], in addition to longitudinal gastrointestinal complications [36]. The absolute rates of serious adverse events are low relative to the reduced comorbidity burden attributable to bariatric surgery.

Lifestyle modifications with and without weight loss in hypertension

Weight loss resulting from dietary modifications with or without increased physical activity has the potential to significantly reduce blood pressure [34, 35]. However, there are much lower rates of sustained weight loss due to lifestyle modifications than bariatric surgery [36]. Weight loss by any method is associated with significant decline in sympathetic and renin-angiotensin aldosterone system activity, likely playing a substantial role in blood pressure reduction [41–44]. Several studies evaluating the effects of behavioral counseling along with diet, exercise, or both demonstrate initial weight loss associated with improvement in blood pressure; however, upon longitudinal follow up, participants fail to demonstrate maintenance of weight loss beyond one year, with no long-term reduction in cardiovascular morbidity from any temporary reduction in blood pressure [45–47].

In a trial randomizing individuals with obstructive sleep apnea to non-surgical weight loss, continuous positive airway pressure (CPAP) therapy, or both, Chirinos et al. found that all participants achieved clinically significant declines in blood pressure with weight loss; the greatest reduction in systolic blood pressure (14.1 mmHg) was observed with a combination of weight loss and continuous positive airway pressure [48].

With regard to lifestyle modifications independent of weight loss, sodium restriction significantly reduces blood pressure in individuals with hypertension [49]. Evidence suggests that the Dietary Approaches to Stop Hypertension (DASH) diet (which is rich in fruits, vegetables, and low-fat dairy products and encourages reduced sodium intake) seems

to reduce blood pressure most effectively among dietary interventions for hypertension [50]. The combination of sodium restriction and DASH diet is more effective than either sodium restriction alone with regard to blood pressure lowering [51]. Additionally, a randomized control trial comparing the DASH diet alone vs. the DASH diet in combination with exercise and weight loss demonstrated a 4.9/2.4 mmHg ($p<0.001$) larger blood pressure reduction with the addition of exercise and weight loss [52]. Effective non-dietary lifestyle approaches to improving blood pressure in individuals with obesity include reduction of alcohol intake [53] and smoking cessation [54].

End organ effects of weight loss in hypertension

Despite demonstrating significant short-term blood pressure reduction, weight loss due to lifestyle modifications does not seem to be associated with improvement in cardiovascular outcomes [55]. Based on observational evidence, weight loss following bariatric surgery compared to usual care is associated with lower risk of cardiovascular disease and mortality [56]. In contrast, in randomized controlled trials, weight loss following bariatric surgery reduces all-cause mortality, although there is no clear effect on long-term cardiovascular events [57]. Regarding renal outcomes, both lifestyle modification with diet and exercise and bariatric surgery are associated with improvement in kidney function and reduction of proteinuria, although bariatric surgery demonstrates more consistent improvement [58]. Weight loss after bariatric surgery is also associated with slower progression of kidney disease, and reduced incidence of end stage kidney disease [59].

Pharmacotherapy for weight management

Pharmacotherapy is indicated for patients with a BMI of ≥30 kg/m^2, and those with a BMI >27 kg/m^2 with weight-related comorbidities, who have failed to achieve adequate success with lifestyle interventions [60]. Antiobesity drug therapy may also be helpful for maintenance of initial weight loss achieved with diet and exercise [61]. Four drugs – phentermine, diethylpropion, phendimetrazine, and benzphetamine – have been available in the US for over 5 decades for short-term treatment of obesity. With the understanding that long-term weight management is imperative for achieving clinically meaningful health benefits, US Food and Drug Administration (FDA) now requires demonstration of weight loss efficacy over a minimum of 1 year for approval of antiobesity drugs [62]. Five drug therapies – orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion - are currently approved in the US for long-term weight management. Of these, liraglutide, administered as daily subcutaneous injections, is approved at the 1.8 mg dose for diabetes and 3.0 mg dose for obesity. Since antiobesity drugs are indicated as adjuncts to diet and exercise, typically an ancillary lifestyle intervention is provided to all participants in RCTs assessing the efficacy of these drugs. Over 1 year, weight loss achieved with these drugs, above and beyond weight loss with lifestyle counseling alone, ranges approximately from 3% to 9% of initial body weight [63]. The rate of weight loss in the first 3–4 months is the only consistent predictor of weight loss over a year. Therefore, it would be prudent to discontinue the antiobesity drug and switch to a different treatment in the absence of significant weight loss early in treatment [61]. With the exception of orlistat, which works

by reducing fat absorption in the gut, all currently approved antiobesity drugs promote weight loss by increasing satiety and decreasing hunger [60].

Short- and long-term effects of antiobesity drugs on blood pressure

Despite the availability of 5 drugs approved for long-term weight management, phentermine, first approved in 1959, remains the most prescribed antiobesity drug in the US, accounting for >75% of prescriptions filled [64–66]. FDA-approved phentermine prescribing information [67] reads: “use caution in patients with even mild hypertension (risk of increase in blood pressure)”; yet, there is no compelling evidence from RCTs to support this warning. In a recent RCT, phentermine was associated with mean systolic and diastolic blood pressure decreases of 3.5 mm Hg and 0.9 mm Hg, respectively, at 28 weeks [68]. However, the highest dose of phentermine used in this study was 15 mg, whereas the most commonly prescribed dose in clinical practice is 37.5 mg. There are no published RCTs that examined the effect of phentermine on body weight over at least 1 year. More importantly, there is lack of knowledge from RCTs regarding the time-course of the effects of phentermine on blood pressure and the level of safety monitoring that might be needed for patients newly prescribed phentermine.

Table 2 shows weight loss and blood pressure changes relative to placebo at 1 year for antiobesity drugs approved for long-term weight management [69–73]. Phentermine/topiramate combination therapy is associated with robust weight loss and clinically meaningful reduction in systolic blood pressure. The only other drug therapy that met the FDA’s stringent primary efficacy criterion [74] of 5% or greater weight loss than placebo was liraglutide, which also reduced blood pressure. Orlistat, lorcaserin, and naltrexone/bupropion are associated with marginal to moderate weight loss.

Among the pharmaceutical interventions currently approved for long-term weight management, the combination drug therapy of naltrexone/bupropion is the only one that raises blood pressure. In phase 3 trials, naltrexone/bupropion was associated with placebo-adjusted systolic and diastolic blood pressure changes of +1.5 mmHg and +1.2 mmHg, respectively, at 1 year [75]. The blood pressure increases were greater at week 8 for naltrexone/bupropion with mean placebo-adjusted systolic and diastolic blood pressure changes of +2.4 mmHg and +2.1 mmHg, respectively, suggesting that this combination drug therapy raises blood pressure to a greater degree early in treatment before weight loss has occurred. Furthermore, an ambulatory blood pressure monitoring (ABPM) substudy revealed that naltrexone/bupropion was associated with placebo-adjusted 24-hour average systolic and diastolic blood pressure changes of +2.9 mmHg and +3.0 mmHg, respectively, at 6 months and corresponding changes of +2.6 mmHg and +2.9 mmHg at 1 year, suggesting that elevation in 24-hour blood pressure persists over long-term exposure [75]. Unfortunately, after an inappropriate public disclosure of confidential interim data by the study sponsor, the naltrexone/bupropion cardiovascular outcomes trial was terminated early [76]; thus, the cardiovascular safety of this drug therapy remains uncertain.

Effects of antiobesity drugs on blood pressure among patients with hypertension

Blood pressure reduction associated with weight loss is typically more pronounced in the subset of patients with hypertension. In the largest RCT [77] of phentermine/topiramate in which 52% of the patients had high blood pressure or were receiving two or more antihypertensive medications at baseline, the subgroup of hypertensive patients had placebo-subtracted systolic and diastolic blood pressure reductions of 4.2 mmHg and 1.9 mmHg, respectively, despite baseline average blood pressure not being very high at 133/83 mmHg.

Orlistat, approved in the US in 1999, has been the best studied antiobesity drug among people with hypertension. A recent meta-analysis [78] that included 4 RCTs of orlistat in patients with hypertension estimated that the drug was associated with placebo-adjusted systolic and diastolic blood pressure reductions of 2.5 mmHg and 1.9 mmHg, respectively. In contrast, when all randomized subjects, regardless of baseline blood pressure status, were included in another meta-analysis, orlistat was associated placebo-adjusted systolic and diastolic blood pressure reductions of 1.1 mmHg and 1.1 mmHg, respectively [72].

The effects of lorcaserin, liraglutide 3.0 mg, and naltrexone/bupropion on blood pressure have not been specifically studied in RCTs among patients with obesity and hypertension. In a cardiovascular outcomes trial involving 12,000 overweight/obese subjects of whom 90% had co-existing hypertension at baseline, lorcaserin was associated with placebo-adjusted weight loss of 2.8 kg and systolic and diastolic blood pressure reductions of 0.9 mmHg and 0.8 mmHg, respectively, after a median follow-up of 3.3 years [79].

Antiobesity drug selection for weight loss among overweight/obese patients with hypertension

Orlistat is a good choice to assist in achieving weight loss among patients with hypertension and obesity, as its efficacy and safety has been examined well in this population [78]. However, it yields an average of 3% or less weight loss, relative to placebo, after 1–2 years, thus not inspiring the enthusiasm of patients to continue the treatment for long periods. Furthermore, approximately 8% of patients discontinued orlistat in clinical trials due to gastrointestinal adverse effects [63]. Nevertheless, for patients who are able to tolerate orlistat, it is a reasonable therapeutic option.

Although there are no RCTs that specifically examined the efficacy of phentermine/topiramate in patients with obesity and hypertension, data from the subset of patients with hypertension [77] support its use in this patient population. On the negative side, it raises pulse rate slightly (average of 1.6 beats per minute at 1 year), requires a negative pregnancy test prior to initiation of treatment and monthly thereafter for women of childbearing potential due to increased risk of oral clefts among babies born to mothers who were exposed to topiramate during first trimester of pregnancy, and is associated with significant adverse effects including paresthesia, insomnia, depression, anxiety, and memory problems [63]. Thus, initiation and continuation of phentermine/topiramate requires a skilled and well-informed clinician and close monitoring of tolerability and safety.

Despite yielding marginal weight loss, lorcaserin is tolerated well and is associated with a small decrease in blood pressure. Lorcaserin may be a suitable drug for the small percentage

of patients who achieve ≥5% weight loss with it in the first 3 months, as these initial responders seem to have a greater chance of continued success. Although there are no published RCTs of liraglutide 3.0 mg specifically among patients with obesity and hypertension, it was associated with reduction in blood pressure in phase 3 trials among patients with obesity [Table 2]. Furthermore, liraglutide's cardiovascular safety has been demonstrated at the dose of 1.8 mg among patients with type 2 diabetes [80]. Naltrexone/bupropion should be avoided in patients with hypertension.

Limitations of currently available antiobesity drugs for patients with hypertension

Whereas a small degree (2–5%) of weight loss, if maintained for 2 years, can significantly reduce the risk of type 2 diabetes among patients with overweight/obesity and weight loss of 5–10% significantly improves glycemia in patients with type 2 diabetes, reductions in blood pressure are less significant and vary with mild to moderate weight loss [81]. Unlike bariatric surgery, which is associated with significant reduction in blood pressure and antihypertensive medication use for most patients [37, 38], antiobesity drugs, while generally improving glycemic outcomes, have not yielded consistent and clinically significant improvement in blood pressure.

Gaps in research and future directions

With the exception of orlistat, the currently approved antiobesity drugs have not been studied well among patients with overweight/obesity and hypertension. There are no published RCTs of the short- and long-term effects of phentermine on blood pressure, the #1 prescribed antiobesity drug, accounting for 3 of 4 prescriptions for all drugs in this class, with >8 million Americans exposed to the drug yearly. This is a major therapeutic gap and an unmet need. With the exception of naltrexone/bupropion, the currently approved antiobesity drugs have not been tested for short- and long-term changes in ambulatory blood pressure, which provides a better assessment of hypertension than office blood pressure alone [82] and is superior to office-based measurements in predicting cardiovascular events and target organ injury [83–85]. Furthermore, ABPM gathers a wealth of information including 24-hr, daytime, and nighttime averages of systolic blood pressure, diastolic blood pressure, mean arterial pressure, the degree of nocturnal dipping, and morning surges, and the proportions of recordings with values higher than the established cut-off values [86–90]. Therefore, an ABPM substudy should be incorporated into the portfolio of phase 2 and phase 3 trials included in every new drug application of an antiobesity drug seeking FDA approval.

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Table 1.

Challenges in the management of hypertension in individuals with obesity

Barriers to accurate blood pressure measurement
Need for large and extra-large cuff sizes
Body habitus-associated poor cuff fit
High prevalence of vascular disease
Comorbidity burden
High prevalence of drug resistant hypertension
Polypharmacy
Concomitant lifestyle factors driving hypertension
Low physical activity
High sodium intake
Pathophysiologic attributes of adipose tissue driving hypertension
Increased vascular stiffness
Impaired natriuresis
Altered pharmacologic handling of medications
Increased volume of distribution
Altered hepatic enzyme activity
High prevalence of nonalcoholic fatty liver disease
Glomerular hyperfiltration
High prevalence of chronic kidney disease

Table 2

Changes in weight and blood pressure relative to placebo following 1-year treatment with drugs approved for long-term weight management

Drug	% Weight change	SBP change, mmHg	DBP change, mmHg
Orlistat *	−3.0 (~)	−1.1	−1.1
Lorcaserin	−3.3	−0.7	−0.6
Liraglutide 3.0 mg	−5.2	−2.8	−0.9
Phentermine/Topiramate	−8.9	−3.1	−1.0
Naltrexone/Bupropion	−4.2	+1.5	+1.2

* Orlistat-associated weight change: Approximate estimate based on various meta-analyses and systematic reviews that included different RCTs of various durations [69–71]; Orlistat-associated change in blood pressure is based on a recent meta-analysis [72]. For all other drugs, the results are based on pooled data of phase 3 RCTs in patients with obesity without diabetes as drawn from the FDA advisory committee briefing documents [73]. When more than one dose was studied, results shown are the ones for the most effective dose.