Treatment of Obesity With “Combination” Pharmacotherapy

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The increasing prevalence of obesity in the United States is widely recognized as a complex problem with significant public health implications, morbidity, mortality, and costs. Pharmacotherapy can contribute to the treatment of obesity. The regulation of appetite and body weight involves multiple parallel neuronal and bodily mechanisms. Not surprisingly, experience has shown that a medication that targets any one mechanism produces weight loss of 5%–10%. Although weight loss of this magnitude may produce significant reductions in risk factors associated with cardiovascular morbidity and mortality, patients expect cosmetically meaningful reductions in weight (~20%–25%). Combining 2 medications that work via different mechanisms, that is, “combination pharmacotherapy,” is an approach to obtaining cosmetically relevant reductions in weight. The most effective example of this approach was the combination of phentermine and fenfluramine. This article will describe a novel combination pharmacotherapy developed in clinical practice: the combination of phentermine with the serotonin precursor L-5-hydroxytryptophan plus the peripheral decarboxylase inhibitor, carbidopa. Observational data on the efficacy and safety of this combination pharmacotherapy will be presented. In conclusion, combination pharmacotherapy can make important contributions to the treatment of obesity. Controlled clinical trials should be done before such combination treatments are widely adopted.

Keywords: obesity, appetite, craving, phentermine, carbidopa, L-5-hydroxytryptophan, nutrition, diet

INTRODUCTION

Epidemiological data indicate that the prevalence of obesity is increasing in the United States. As is well known, obesity brings with it considerable morbidity, mortality, and costs to the health care system. The causes of obesity include biological, genetic, psychological, and social factors. As fittingly stated by Bray and Champagne, “obesity is a chronic, relapsing, stigmatized, neurochemical disease.” Diet and exercise are the primary treatment approaches to obesity, although for many patients, the results are disappointing and patients often, over time, regain the weight they have lost. Numerous patients also cycle (“yo-yo”) through periods of dieting and weight loss, followed by weight regain. Pharmacotherapy can be a crucial component of a weight loss program. In support of this idea, a recent study reported that pharmacotherapy combined with lifestyle modification is more effective than lifestyle modification alone.

Several recent publications provide excellent reviews on the medications currently used, or under investigation, for the treatment of obesity. Because obesity is a chronic relapsing disorder, many specialists in obesity believe that chronic treatment with antiobesity medications is appropriate to help patients maintain a lower weight. The brain utilizes multiple mechanisms, often working in a “parallel” manner, to regulate appetite and weight. This is the likely reason why a medication that targets 1 mechanism produces a relatively small degree of weight loss (~5%–10%). Although weight loss of this magnitude can produce significant reductions in risk factors associated with cardiovascular morbidity and mortality, patients expect cosmetically meaningful reductions in weight (~20%–25%). Combining 2 medications that work via different mechanisms, that is, “combination pharmacotherapy,” is an approach to obtaining cosmetically relevant reductions in weight. The most effective example of this approach was the combination of...
phentermine and fenfluramine.17–21 This particular approach was compromised by the valvulopathy associated with the use of fenfluramine, an effect likely caused by the agonist actions of norfenfluramine, the major metabolite of fenfluramine, at the 5-HT₂B receptor.22,23 However, the lesson that combination pharmacotherapy can help provide enhanced weight loss remains valid. Thus, this article will describe a novel combination pharmacotherapy developed in clinical practice: the combination of phentermine with the serotonin precursor L-5-hydroxytryptophan (L-5-HTP) plus the peripheral decarboxylase inhibitor, carbidopa. Observational data on the efficacy and safety of this combination pharmacotherapy will be presented. The present article will focus on the results obtained in the first 4 weeks of treatment. Subsequent communications will focus on observations of long-term treatment.

BACKGROUND

The biosynthesis of 5-hydroxytryptamine (5-HT) in the brain proceeds from the uptake of dietary tryptophan by the neuron, followed by its conversion to 5-HTP by an enzyme called tryptophan hydroxylase.24 L-5-HTP is the immediate precursor of serotonin (5-HT). When administered to animals or humans, L-5-HTP is rapidly decarboxylated by an enzyme called aromatic L-amino acid decarboxylase (AADC, E.C.4.1.1.28) also commonly called 5-hydroxytryptophan decarboxylase.25 Tryptophan hydroxylation is the rate-limiting step in the biosynthesis of 5-HT. Administration of L-5-HTP bypasses this rate-limiting step and can increase synaptic 5-HT levels. Numerous studies document that medications that increase synaptic brain 5-HT, such as fenfluramine, are effective anorectic agents that help obese patients lose weight and that also decrease craving for sweets and carbohydrates.26,27 Thus, there is interest in using L-5-HTP for this purpose.28

Pharmacokinetic studies show that the bioavailability of L-5-HTP is about 70%–29 and that the plasma half-life is about 4.3 hours with a time to peak concentration of 1–2 hours.29 This reflects in part the rapid metabolism of 5-HTP to 5-HT by AADC, which is localized throughout the body, including the adrenal glands, kidney, liver, pancreas, gastrointestinal tract, and lungs.30,41 As noted by Turner et al.,28 this rapid metabolism of 5-HTP outside of the brain means that very little of an administered dose actually reaches the brain. Importantly, the 5-HT resulting from administration of L-5-HTP does not cross the blood–brain barrier. The concentration of plasma 5-HT is maintained at subnanomolar concentrations by active uptake into platelets and lung endothelial cells by the 5-HT transporter33 and by metabolism by monoamine oxidase. Interestingly, L-5-HTP is rapidly metabolized to 5-HT in the kidney, followed by the prompt excretion of 5-hydroxyindoleacetic acid in the urine.34 L-5-HTP is available for human use as an over-the-counter supplement and has been administered for the treatment of depression, obesity, and insomnia.28,35–38 L-5-HTP has not been associated with dangerous side effects or toxicity, including the eosinophilia–myalgia syndrome (EMS) and the serotonin syndrome.28,39 The EMS was first reported in 1989 and is reviewed by Das et al.29 Briefly, EMS includes a striking eosinophilia along with severe myalgias. Other symptoms include weakness, oral ulcers, abdominal pain, skin rash, increased serum aldolase, and leukocytosis. A comprehensive investigation of EMS ultimately demonstrated that it was caused by a contaminant present in a single source of L-tryptophan [1,1’-ethyldenebis (tryptophan)]. This contaminant resulted from the particular manufacturing methods used by the company. The occurrence of an EMS-like illness in a woman exposed to 5-HTP (1 case report) led to a series of investigations of possible contaminants in commercially available 5-HTP. This investigation focused on “peak x,” a trace chromatographic peak. The extremely low concentration of this impurity, the fact that it may arise from analytical artifacts, the fact that since 1998 suppliers of 5-HTP are required by the Food and Drug Administration to produce 5-HTP without “peak x,” and the fact that only one possible case of an EMS-like illness has been reported fully support the safety of 5-HTP.39

Carbidopa is an inhibitor of AADC. The plasma half-life of carbidopa is 1–2 hours, but it may exert inhibitory effects for more prolonged periods.29 According to “Martindale—The Complete Drug Reference,” carbidopa has “little or no pharmacological activity when given alone in usual doses.” Carbidopa does not enter the brain, and thus administration of carbidopa selectively blocks the conversion of L-5-HTP to 5-HT in the periphery but not in the brain. Co-administration of carbidopa with L-5-HTP can be used to increase brain 5-HT.25,40,41 Co-administration of carbidopa (50 mg) with L-5-HTP (100 mg) increased the plasma L-5-HTP levels 15.4-fold and increased the plasma half-life 2-fold.42 Thus to achieve the desired effect of increasing brain 5-HT with low doses of L-5-HTP, it is necessary to co-administer an inhibitor of the enzyme peripheral decarboxylase along with the L-5-HTP.

As noted above, L-5-HTP is available as a widely promoted over-the-counter supplement and has not been associated with significant toxicity.28,39 According to some theories of the pathogenesis of fenfluramine-associated valvular heart disease (VHD),33 increases in plasma 5-HT might increase the risk of VHD.

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Administration of L-5-HTP would predictably cause small transient increases in plasma 5-HT, especially when not coadministered with carbidopa. Thus, there is a theoretical concern that L-5-HTP administration could increase the risk of VHD. However, as pointed out in a recent article, this is highly unlikely, since plasma 5-HT levels are maintained at subnanomolar concentrations, and ultra-high 5-HT concentrations (500 nM) are required to produce valvulopathy in carcinoid syndrome. Modest 2- to 3-fold elevations of plasma 5-HT, such as those occurring with the prescribed use of lithium and monoamine oxidase inhibitors, are not associated with VHD. Thus, it is unlikely that small and transient increases in plasma 5-HT that might occur with L-5-HTP administration would increase the risk of VHD.

The best way to determine the safety of a medication is a long-term (multi-year), prospective, randomized, placebo-controlled clinical trial. These types of studies are rarely done and will never be done with phentermine (or L-5-HTP) because they are generic medications. In the absence of this type of data, one must rely on clinical experience to ascertain the safety of long-term phentermine use. Phentermine has been in clinical use since the late 1950s, and as far as this author knows, there are no long-term adverse effects that have emerged from its use, such as, for example, heart attacks from the use of Vioxx. A cursory examination of the medical literature reveals a link between “appetite suppressants” or “anorectics” with primary pulmonary hypertension, but the link is actually with fenfluramine, the medication that was removed from the market in 1997, not phentermine. In addition, epidemiological investigations do not link phentermine to an increased risk of stroke. Although the labeling of phentermine classifies it as an appetite suppressant, it is in fact a stimulant similar in many respects to the stimulants used to treat attention deficit disorder, such as d-amphetamine and methylphenidate. For many decades, patients with attention deficit disorder have been taking stimulants on a long-term basis to control their disorder without suffering long-term adverse effects. These reasons and the author’s personal experience indicate that phentermine is a safe medication if used appropriately.

**CLINICAL EXPERIENCE WITH PHENTERMINE PLUS 5-HTP/ CARBIDOPA**

Basic concept of the combination treatment

The foregoing information derived from the author’s treatment of obese patients with the combination of phentermine and L-5-HTP + carbidopa (abbreviated “5-HTP”). Ideally, this treatment should be subjected to a randomized placebo-controlled clinical trial. However, few resources are available to support such research, especially because these are generic medications without significant intellectual property protections. Thus, the data to be presented are by necessity uncontrolled.

Figure 1 summarizes the basic concept of the combination treatment. The primary action of phentermine administration is to increase norepinephrine release in the brain. This generally reduces appetite and food craving and increases satiety. However, these therapeutic effects are often accompanied by stimulant side effects, such as nervousness, irritability, insomnia, and increases in heart rate and blood pressure. Administration of 5-HTP increases synaptic 5-HT in the brain. This generally reduces appetite and food craving, especially for sweets and carbohydrates, and increases satiety. Combining phentermine and 5-HTP generally results in greater weight loss than would be observed with either medication alone. Importantly, fewer stimulant side effects occur in patients treated with phentermine and 5-HTP. This is not unexpected, as both rat and human studies demonstrate that increasing brain 5-HT releases decreases stimulant-induced side effects (for review, see Rothman et al).

**Clinical procedures**

New patients fill out standard demographic and medical history forms. They are weighed, have a 3-lead electrocardiogram taken (rhythm strip), and meet with a nutritional counselor who discusses an individualized diet and exercise plan. New patients read and sign a consent form. A medical provider takes the pulse and blood pressure, reviews the medical history,
takes electrocardiogram, and performs a focused physical examination. The medical provider discusses the risks and benefits of the medication and, if no contraindications exist, prescribes diet, exercise, and medication. New patients are typically seen twice in the first 4 weeks (initial visit and 1 week later). Afterward, patients are typically seen every 4 weeks.

At each return visit, patients fill out a return questionnaire, which inquires about side effects, compliance with the diet and exercise plan, changes in medications prescribed by other physicians, and also about any problems the patients may be having. Return patients are weighed and typically meet with the nutritional counselor. Return patients then meet with the medical provider, who measures pulse and blood pressure and assesses reports of side effects, weight loss, compliance with the exercise and diet, and other relevant items. Medications are then typically prescribed at each return visit. Medication dosing is individualized with a dose-to-effect method. Most prescriptions are filled at an on-site compounding pharmacy.

At every visit, the patient’s weight, pulse, blood pressure, and prescribed medications are entered into a FileMaker Pro computer database. One record is generated for each prescription. One patient visit can generate more than 1 record—this can make extracting information more difficult. This database lets easily us extract certain types of information, which will be presented in the following sections.

**Clinical results**

Starting in November 1998, most patients were treated with phentermine plus 5-HTP. In 2005, the initial body mass index (BMI) was 33.5 ± 0.3 (mean ± SD), and 89% of patients had an initial BMI > 27, whereas 67% had an initial BMI > 30. Most patients are female and are in treatment for several months to perhaps 1 year.

5-HTP is compounded in 4 dose strengths. All 4 strengths have 5 mg of carbidopa, with the amount of 5-HTP set at 5 mg ("5-HTP"), 10 mg ("5-HTP-DS"), 15 mg ("5-HTP-TS"), or 25 mg ("5-HTP-5S"). The terms "DS," "TS," and "5S" refer to double, triple, and 5 times the standard 5-mg 5-HTP dose. Phentermine is also provided as a compounded product. PHEN 20 and PHEN 40 refer to capsules that contain 20 and 40 mg of phentermine HCl, respectively. These compounded phentermine capsules approximate the commercially available 15 and 37.5 mg phentermine formulations. Adjunctive medications are sometimes used to treat side effects. Trazodone, typically at a 50-mg dose, is used to treat insomnia. Occasionally (<0.1%), a patient will clench the jaw or grind teeth during sleep. This stimulant side effect also responds nicely to trazodone administration. In some cases, propranolol is used when patients (without asthma) experience nervousness, irritability, or mild increases in blood pressure or pulse. A typical starting dose for a new patient is PHEN 20 + 5-HTP with breakfast, PHEN 20 + 5-HTP with lunch, and 5-HTP after dinner.

To determine the typical weight loss in the first 4 weeks of treatment, the author selected, via chart review, 91 new patients treated by the author in the period February 2003 through March 2004. The basic criterion for selection was compliance with our usual treatment schedule for the first 4 weeks. The initial weight was 214 ± 54 lbs (± SD, range 147–387). As reported in Figure 2, patients lost (values are ± SEM) a mean 5.2 ± 0.30 lb in the first week and 10.1 ± 0.43 lb after 4 weeks. Expressed as a percentage of initial body weight, patients lost 4.7 ± 0.17% of their initial weight in the first 4 weeks. As described in Figure 3, weight loss in the first 4 weeks ranged from 2 to 23 lb. The distribution of weight loss appeared to be Gaussian, and this was confirmed by the Kolmogorov–Smirnov test (Prizm version 4.0). The bell-shaped curve of the weight loss observed in these 91 new patients indicates that although the patients were not randomly selected, the selection was not biased toward selecting patients who did well in terms of weight loss. The pounds lost

![Weight Loss in the First Four Weeks of Treatment](image)
(r = 0.56) in the first 4 weeks but not the percentage of initial body weight lost (r = 0.037), significantly correlated with the initial weight.

The daily medication doses (±SEM) are reported in Figure 4. The initial phentermine and 5-HTP doses were 41 ± 1 and 11.4 ± 0.4 mg, respectively. At the second visit 1 week later, medication doses were often increased, resulting in significantly increased mean daily doses of 55 ± 2 mg for phentermine and 22 ± 1 mg for 5-HTP. These phentermine doses are within the dosage range used by physicians who specialize in the treatment of obesity (Hendricks et al., Obesity 2009, in press). There were no statistically significant alterations in the systolic and diastolic blood pressure or in the heart rate (Figure 5). Because all these patients were concurrently prescribed 5-HTP, these data do not address the effect of phentermine dosage on vital signs in the absence of 5-HTP. However, from 1995 to 1996, most patients were treated with phentermine alone, and we did not note significant changes in vital signs.

Ideally, it would be of interest to compare the efficacy of the phentermine/5-HTP method with that of phentermine alone or the phentermine/fenfluramine treatment. This would obviously require controlled trials. As a first approach to these questions, a chart review identified 27 patients who had been treated with phentermine/fenfluramine. These same patients returned some time later for treatment with phentermine/5-HTP. As reported in Figure 6, the results plotted as either pounds lost in 30 days or as a percentage of initial body weight loss were similar. We similarly identified a set of “good responder” patients who had been treated first with phentermine alone and then subsequently with phentermine/5-HTP. The patients treated with phentermine only (n = 28) lost approximately 10.8 lb in the first 4 weeks, as compared with approximately 17 lb lost by patients treated with phentermine/5-HTP (n = 36).

CONCLUSIONS

Numerous reviews and commentaries document the growing “epidemic” of obesity and the challenges of
developing medications to help treat this disorder.\textsuperscript{51–53} As described by Staten,\textsuperscript{52} the blemished history of antiobesity drugs, as exemplified by fenfluramine-associated VHD, can reasonably diminish the enthusiasm of pharmaceutical companies for investing vast sums of money to develop a new medication for treating obesity. Moreover, although combination pharmacotherapy will likely be very useful for the clinical treatment of obesity, as it is for the treatment of hypertension and diabetes,\textsuperscript{54–56} there are significant regulatory hurdles that must be overcome to achieve Food and Drug Administration approval for a combination treatment.\textsuperscript{53} Despite these hurdles, certain smaller pharmaceutical companies are exploring the use of 2 medications in combination as treatments for obesity.\textsuperscript{8}

To the author’s best knowledge, this communication is the first report in the peer-reviewed literature of the use of phentermine with l-5-HTP/carbidopa for the treatment of obesity. The author’s patent related to this approach (Pharmaceutical combinations for treating obesity and food craving. US Patent 6,207,699. March 27, 2001) concerns the concurrent use of pindolol with phentermine and 5-HTP/carbidopa and not the use of phentermine with l-5-HTP/carbidopa.

The focus of the present communication was to provide retrospective data on the short-term efficacy of combination pharmacotherapy with phentermine plus 5-HTP/carbidopa for the treatment of obesity. The data clearly show that the combination is safe and effective. Importantly, our clinical experience and some retrospective analysis indicate that the combination is more effective than treatment with phentermine alone. Clinical results observed with long-term treatment will be the subject of a future publication. The ability of medications that increase 5-HT release (fenfluramine) to decrease stimulant effects is now well documented.\textsuperscript{57–59} Although not directly quantitated in this study, we also observe that patients treated concurrently with phentermine plus l-5-HTP/carbidopa experience fewer stimulant side effects than those treated with phentermine alone.

In conclusion, the preliminary and uncontrolled data reported here support the hypothesis that combination pharmacotherapy can make important contributions to the treatment of obesity. Controlled clinical trials should be done before such combination treatments are widely adopted.

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