

How Physician Obesity Specialists Use Drugs to Treat Obesity

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Specialist physicians may have prescribing habits that are different from nonspecialist physicians. Little is known about the prescribing habits of physicians specializing in the treatment of obesity. An anonymous survey was given to the physician members of the American Society of Bariatric Physicians (ASBP). There was a 35% response rate (266 physicians) to the questionnaire that was represented nationally. Almost all prescribed medications and all of them recommended phentermine. The average maximal dose of phentermine was above that approved in the package insert, and these physicians disagreed with the National Institutes of Health (NIH) Obesity Treatment Guidelines. Phendimetrazine, metformin, and phentermine plus L-5-hydroxytryptophan (5-HTP) with carbidopa were all used more frequently than either orlistat or sibutramine. The combination of sibutramine and orlistat as well as 5-HTP/carbidopa were prescribed by 14 and 20%, respectively. As 5-HTP-carbidopa was a combination not previously reported for the treatment of obesity, a retrospective chart review was performed in a single obesity practice, which may not be representative. Twenty-two subjects had a 16% weight loss with phentermine over 6 months and an additional 1% weight loss with the addition of 5-HTP/carbidopa for an additional 6 months. One subject who started on 5-HTP/carbidopa alone lost 24.4% of initial body weight over 6 months. This questionnaire revealed that 20% of the obesity specialists responding to the survey used phentermine plus of 5-HTP/carbidopa, an unreported combination. A controlled, randomized, clinical trial to evaluate the safety and efficacy of this combination in treating obesity should be considered.

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INTRODUCTION

Drugs have been used in the treatment of obesity since the discovery of thyroid hormone at the end of the 19th century (1). Most of the literature concerning obesity drugs relate to clinical trials, and this literature has been repeatedly reviewed in refs. 2,3. As physicians can use medications approved by the Food and Drug Administration for purposes other than their approved use, and as they can use dietary herbal supplements without a prescription, the use of drugs by physicians to treat obesity may deviate from the drugs approved indications. In addition, some obesity drugs were approved prior to 1985 when the United States National Institutes of Health (NIH) declared obesity to be a chronic disease (4). Drugs approved prior to 1985 were tested and approved for use up to 12 weeks, on the basis that obesity was caused by bad habits, and that bad habits could be retrained in ≤ 12 weeks. The pattern of use for these older drugs, in the light of obesity being a chronic disease, is unclear.

In any area of medicine, specialists often discover and use medications differently than the nonspecialists for the diseases in which they specialize. Thus, obesity specialists might

be expected to use obesity medications differently than the descriptions in the package inserts, or use medication without an official indication for use in treating obesity. Despite the fact that much could be learned by studying the prescribing habits of specialists in any disease, there are no descriptions that we could find in the medical literature that shed light on the prescribing habits of physicians, who specialize in the treatment of obesity. These physicians refer to themselves as bariatricians and have a society called the American Society of Bariatric Physicians (ASBP). This report will describe the prescribing habits of bariatricians belonging to that society, who responded to a questionnaire about these habits.

METHODS AND PROCEDURES

In an effort to define the prescribing habits of bariatricians in practice, we asked the members of the ASBP to complete an online questionnaire. Although only members of the society had access to the questionnaire, the questionnaire was anonymous and did not identify the individual physicians. This anonymity undoubtedly insured more honest answers from the respondents, but prevented us from following up on any answers received. The survey (**Table 1**) was put on the web with access only by members of the ASBP, a group with 757 physician members,

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Table 1 The questionnaire completed by the obesity specialist physicians

1. In your bariatric practice, how many individual patients do you treat/year?
2. How many years have you been in bariatric practice?
3. What percentage of your practice is bariatrics?
4. Please indicate where you practice. (US by Census Regions)
5. In your bariatric practice, do you employ any prescription pharmacologic agents to specifically treat obesity?
6. Do you prescribe or dispense any of the following for obesity treatment? Check all that apply
 - None, I never employ pharmacotherapy
 - Phentermine
 - Diethylpropion
 - Phendimetrazine
 - Amphetamine or methamphetamine
 - Sibutramine
 - Orlistat
 - Topiramate
 - Zonisamide
 - 5-HTP/carbidopa
7. How long do you use the drugs for an individual patient?
8. Do you prescribe or dispense drug combinations in any patient specifically for treating obesity?
9. Do you prescribe drugs to treat obesity that are not FDA approved for that purpose?
10. Do you ever prescribe obesity drugs for patients whose BMI is lower than the NIH guidelines stipulate?
11. Do you prescribe obesity drugs for adolescents?
12. Do you prescribe obesity drugs for patients on antidepressants?
13. If you have prescribed obesity drugs and antidepressants together, have you ever seen problems or complications due to the combination? What problems?
14. If you use sibutramine, what are the lowest and highest doses you prescribe, and for what percentage of your patients do you prescribe sibutramine?
15. If you use orlistat, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe orlistat?
16. If you used phentermine, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe phentermine?
17. If you used diethylpropion, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe diethylpropion?
18. If you used phendimetrazine, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe phendimetrazine?
19. If you used 5-HTP/carbidopa, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe 5-HTP/carbidopa?
20. If you used zonisamide, what are the lowest and highest doses you prescribed, and for what percentage of your patients do you prescribe zonisamide?
21. In the last year did you use any of these combinations of drugs specifically for treating obesity?
 - Caffeine and ephedrine
 - Sibutramine and orlistat
 - Phentermine and 5-HTP/carbidopa
22. Have you ever been questioned about your obesity treatment prescribing practices by any of the following?
 - Federal Drug Enforcement Administration
 - State Medical Board
 - Law enforcement personnel
 - Attorneys
 - Pharmacists
 - Patients
 - Malpractice insurance
 - Health insurance

5-HTP, 5-hydroxytryptophan; FDA, Food and Drug Administration; NIH, National Institutes of Health.

and they were encouraged to complete the survey. The responses were tallied and were reported.

RESULTS

A total of 266 physicians out of a membership of 757 answered the questionnaire, a 35% response rate. Three physicians reported seeing 50,000, 43,450, and 17,280 patients per year, respectively. This probably represents patient visits rather than patients seen. As this was an anonymous survey, it is impossible to confirm this presumption. Nevertheless, a member who has one of the more active practices in the society with two practice locations sees only 2,596 individual patients, but this translates into 12,708 patient visits per year. Four of the physician respondent to the survey have treated <10 obese patients per year. This is such a low number that it is probably not representative of the true obesity specialist. For both of these reasons it was decided to trim the data set to two standard deviations from the mean to eliminate the 2.5% outliers on each end of the distribution. Although this trimming was done to make the data reflect more accurately the practice patterns of the obesity specialists, the trimmed data looked very similar to the untrimmed data.

Thirty-four percent of the physicians had been in practice for <3 years, 50% had been in practice for a period between 3 and 20 years, and 16% had been in practice for >20 years. Thirty-two percent of the physicians devoted <50% of their practice in treating obese patients and 9% devoted <10% of their practice in treating obese patients. On the other hand, 68% of the responding physicians had a majority of their practice devoted to the treatment of obesity, and 36% completely limited themselves to the treatment of obesity. The responding physicians were distributed throughout the different census regions in the United States: New England 4%, Mid-Atlantic 10%, South-Atlantic 29%, East North-Central 10%, East South-Central 5%, West North-Central 4%, West South-Central 12%, Mountain 11%, Pacific 13%, and 2% resided outside the 50 states of the United States.

Ninety-eight percent of the physician respondents used medications in their treatment of obesity, and 97% of those that used medication used phentermine. One can see a breakdown of the medications used in this physician population in [Table 2](#). Although orlistat and sibutramine are both approved for long-term use, only 33 and 32% of the physicians use these drugs for as long as they and their patients feel that the drugs are still helpful to them in furthering their weight-loss goals. By contrast phentermine, diethylpropion, and phendimetrazine, which are all approved for only short-term use, are continued as long as the physicians and their patients feel that the drugs are still helpful to them in furthering their weight-loss goals by 56, 48, and 39% of the physicians, respectively.

In descending order, the percentage of patients treated by the average physician answering the questionnaire in their practices was: phentermine 50%, phendimetrazine 18%, diethylpropion 15%, metformin 15%, 5-hydroxytryptophan (5-HTP)/carbidopa 12%, orlistat 8%, bupropion 7%, and sibutramine 4%.

Table 2 The obesity medications prescribed by physician obesity specialists and the percentage of the physicians that used the respective medications in their practices

Medication	% Frequency of use
Phentermine (Adipex)	97
Diethylpropion	64
Phendimetrazine	60
Methamphetamine (Desoxyn)	3
Sibutramine (Meridia)	49
Orlistat (Xenical)	43
Topiramate (Topomax)	50
Zonisamide (Zonegran)	9
5-HTP/Carbidopa	20

5-HTP, 5-hydroxytryptophan.

The majority of respondent physicians (83%) occasionally or frequently prescribed combinations of medications to treat obesity, and 65% of the physician respondents occasionally or frequently prescribed combinations of medications to treat obesity that are not approved for obesity treatment. Only 1.4% used the combination of caffeine with ephedrine whereas 14% used the combination of orlistat with sibutramine. The surprising finding was that 20% used the combination Phen/5-HTP, a combination not reported either in the literature or indexed on PubMed, for the treatment of obesity.

The National Heart, Blood, and Lung Institute of the United States NIH published guidelines for the evaluation and treatment of obesity in 1998 (ref. 5). This report described four types of evidence to support the guidelines. Evidence classified as A or B was based on randomized clinical trials, evidence classified as C was based on nonrandomized trials and observational studies, and evidence classified as D was based on consensus judgment of the expert panel. Thus, although some of these guideline recommendations were made on evidence short of randomized clinical trials, the guidelines represented consensus on evaluation and treatment based on the best evidence available in 1998. The guidelines suggest, based on category C evidence, that medications should be reserved for the patient with a BMI over 30 kg/m² or over 27 kg/m² if the obesity is accompanied by medical problems that are likely to improve with weight loss (dyslipidemia, diabetes, hypertension, or sleep apnea). In fact, the majority (62%) of the obesity specialists that responded to this survey deviate from these guidelines occasionally (41%) or frequently (21%).

The treatment of adolescents with drugs for obesity is more controversial than the treatment of adults, but the obesity prevalence is growing in children and adolescents in a similar manner to adults. The majority (56%) of physician specialists who responded to this survey treat adolescents with drugs for obesity. There has been concern in some quarters regarding the concomitant treatment using antidepressants and obesity drugs, but this is something that is done by 97% of the physician respondents to this survey and 84% of these have not seen any problems in doing so. The problems described by the other

16% were typical of antidepressant medications, rather than those typical of the weight management medications.

Some of the physician obesity specialists responding to this survey used all of the approved obesity drugs and some also used zonisamide, bupropion, and metformin, which are approved for epilepsy, depression, and diabetes, respectively, but have been associated with weight loss. With the exception of phentermine, diethylpropion, and sibutramine, the highest average doses used by those surveyed conform to the recommended doses for the drugs. The highest average doses of diethylpropion and sibutramine used by the respondents of the survey were only slightly higher than the recommended doses, 77 and 17 mg/d used vs. 75 and 15 mg/d recommended. The exception was phentermine. The maximum recommended dose of phentermine is 37.5 mg/d and the average highest dose of phentermine used was 56 mg/d, almost twice the upper limits of the recommended dose (Table 3).

The percentage of those responding to this survey, 5, 8, 3, and 7%, have been questioned about their prescribing habits by the Drug Enforcement Administration, their State Medical Board, law enforcement personnel, and attorneys, respectively. Questioning by any of these entities could potentially result in punitive action that would jeopardize their ability to continue practicing their specialty. The percentage of respondents to this survey, 25, 32, 12, and 12% were also questioned by pharmacists, patients, malpractice carriers, and health insurance carriers, respectively.

DISCUSSION

This survey included >250 practicing obesity specialists that had a varying amount of time in practice and represented all areas of the United States. Almost all of these specialists used medications and those that did so used phentermine. The average maximal dose of phentermine used by the respondents to this survey was almost twice the maximal amount recommended by the package insert. In addition, although phentermine is only approved for use up to 12 weeks, more than half of the obesity

specialists responding to this survey (56%) used phentermine as long as they and their patients felt it was helpful in achieving the weight-loss goals or the weight-maintenance goals, whereas only 32–33% of the respondents did so with orlistat or sibutramine, which are approved for long-term use. Thus, in the context of an obesity specialty practice, there seems to be a great deal of comfort with the use and safety of phentermine.

The frequency with which the obesity specialist physicians use the different available medications was somewhat surprising. Phentermine was by far the most commonly used obesity medication despite it being in Drug Enforcement Administration category 4 and approved only for short-term use. Even phendimetrazine, which is in Drug Enforcement Administration category 3 and only approved for short-term use, was more popular than either of the two obesity medications approved for long-term use—orlistat and sibutramine. Orlistat seemed more popular than sibutramine despite meta-analyses that show orlistat to be less effective than sibutramine. Sibutramine, in the same meta-analysis, was the most effective obesity drug, giving a placebo subtracted weight loss of 4.5%, except for topiramate, which gave a weight loss of 6.5% in excess of placebo (6). The cost of the medications may be playing a factor in their use, as obesity medications are infrequently covered by third party payers, and the older generic drugs are considerably less expensive. This cannot be the reason for using orlistat in preference to sibutramine, however, as they both are similar in price. Metformin, which only gives a 2 kg weight-loss (7) and bupropion, which only gives a 2.8% weight-loss, were used more frequently than sibutramine that gives a 4.5% weight-loss in excess of placebo (6). This may be due to the obesity specialist physicians treating concomitant diseases that frequently accompany obesity with drugs for diabetes and depression that give some measure of weight loss, but the questionnaire did not address that possibility.

The most surprising finding was the more frequent use of Phen/5-HTP than either of the two obesity medications approved for long-term use despite the lack of any reports on PubMed of the use of this combination for the treatment of obesity, although we know of a manuscript in press on the use of this combination to treat obesity (8). It appears from this data that sibutramine is not highly valued by obesity specialists, but the reason for this is not clear from the questionnaire.

The majority of the obesity specialist physicians who responded to this survey used combination drugs to treat obesity. Surprisingly, only 1.4% used the combination of caffeine and ephedrine, which was approved as a combination obesity medication in Denmark for more than a decade with a good record of safety and efficacy (9). It was also surprising that 14% used the combination of sibutramine and orlistat, which has been shown in four consecutive studies to give no better weight loss than sibutramine alone (10–13). Most surprising, however, was that 20% of the responding obesity specialists used a combination of 5-HTP and carbidopa, a combination upon which no articles indexed on PubMed exist for the treatment of obesity. This finding prompted the retrospective chart review in the practice of one of the members of the ASBP comparing weight

Table 3 The highest and lowest average doses of obesity medications used by physician obesity specialists compared to the doses approved in the package inserts

Medication	Highest average dose (mg/d)	Lowest average dose (mg/d)	Approved dose
Sibutramine	17	9	10–15 mg/d
Orlistat	271	138	360 mg/d
Phentermine	56	17	15–37.5 mg/d
Diethylpropion	77	27	75 mg/d
Phendimetrazine	122	38	35–210 mg/d
5-HTP/Carbidopa	82	21	N/A (≤400 mg/d)
Zonisamide	95	35	N/A (≤400 mg/d)
Bupropion	288	14	N/A (≤400 mg/d)
Metformin	1,662	527	N/A (≤2 g/d)

5-HTP, 5-hydroxytryptophan; N/A, not available.

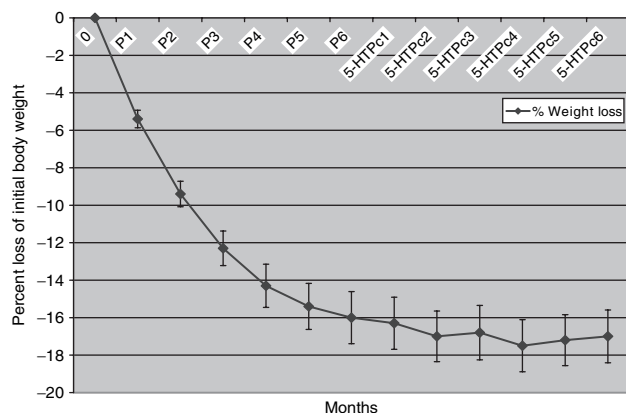


Figure 1 Monthly weight loss in 22 subjects who took phentermine for 6 months followed by phentermine plus 5-HTP/carbidopa for an additional 6 months. 5-HTP, 5-hydroxytryptophan.

loss after taking phentermine alone for 6 months or longer to a second 6 months with the combination of phentermine plus 5-HTP/carbidopa (Figure 1).

Although the practice selected may not be an appropriate representative, it seemed important to collect some data on this previously unreported obesity treatment. Twenty-three subjects were included in the retrospective chart review. They had a weight of 93.7 ± 20.7 kg (mean \pm s.d.). Weight loss during the 6 months on phentermine was $16 \pm 6.5\%$ of initial body weight. At the end of the second 6 months on phentermine plus 5-HTP/carbidopa the subjects had lost $17 \pm 6.6\%$ of initial body weight. Four of the subjects had the 5-HTP/carbidopa added after being on phentermine for an average of 8 years (range 4–11 years). These four subjects maintained a $6.23 \pm 9.24\%$ weight loss, but actually gained 6% of initial body weight during the 6 months after adding 5-HTP/carbidopa. The weight loss from baseline in this group on long-term phentermine was significantly less than the rest of the group ($P < 0.002$). One subject in the practice started on 5-HTP/carbidopa without prior treatment with phentermine. That subject lost 24.4% of initial body weight over 6 months.

The 16% loss of initial body weight with phentermine alone was remarkably robust compared to clinical trials in the peer-reviewed literature (6). It is possible that this unexpected weight loss may relate to the higher doses of phentermine used by this group of physician obesity specialists. An article recently reported a 14% weight loss with a low calorie diet combined with phentermine up to 75 mg/day, which is consistent with the findings in our retrospective chart review (14). The addition of 5-HTP/carbidopa to this remarkable weight loss resulted in an additional 1% weight-loss over the ensuing 6 months. Wadden *et al.* reported a trial in which a 11% weight-loss was induced over 1 year with sibutramine. At the end of that year subjects were randomized to continue sibutramine or to have orlistat added to sibutramine. There was no additional weight loss during this 16-week study (10). As weight loss was greater with phentermine in this retrospective review than with sibutramine in the Wadden study, and as there was some additional weight loss in

this retrospective review, it suggests that 5-HTP/carbidopa may be more effective in giving weight loss than orlistat. The 24.4% weight-loss in the subject given 5-HTP/carbidopa alone for 6 months would be consistent with that contention.

The four subjects who took phentermine for an average of 8 years and achieved a 6% weight-loss at the end of that period represent a select group. There is a report of eight subjects who took pharmacologic treatment, primarily phentermine, for obesity over an average of 19 years and on an average gained less than a kilogram (15). Judging by the upward weight trajectory in both the placebo and active group in the third year of a long term clinical trial with phentermine and fenfluramine, it would appear that obese subjects may have a gradual progressive weight gain over time (16). Thus, these subjects with long-term phentermine treatment appear to respond differently than subjects who take phentermine over a less prolonged period. Even maintenance of weight over 19 years or maintenance of a 6% loss over an average of 8 years represents a success.

Phentermine, one component of the phentermine/5-HTP-carbidopa combination, is a sympathetic amine anorectic agent that releases norepinephrine in the central nervous system. Phentermine is approximately sevenfold less potent in releasing dopamine than norepinephrine, and data gathered in baboons indicate that large intravenous doses of phentermine do not release central dopamine (5). Consistent with its lack of activity on the dopamine system at clinical doses, phentermine has less potential for addiction than amphetamine (6).

5-HTP is the precursor of serotonin, while carbidopa is a peripheral decarboxylase inhibitor that inhibits conversion of 5-HTP to serotonin outside the brain. The use of oral 5-HTP is known, in high doses (900 mg/d), to induce weight loss, but the use of 5-HTP in such high doses has been limited due to a 20% incidence of nausea as a consequence of peripheral 5-HTP conversion to serotonin (7). Administration of carbidopa with 5-HTP inhibits decarboxylation of serotonin in the periphery, which limits side effects while allowing the 5-HTP to reach the central nervous system, where it is converted to serotonin.

The observations made in this retrospective chart review suggest that the Phen/5-HTP combination has potential for causing weight loss. It is hoped that these uncontrolled retrospective observations are sufficiently encouraging that a randomized and controlled clinical trial of Phen/5-HTP for the treatment of obesity will be initiated. This combination seems to be popular in the treatment of obesity by obesity specialists. Importantly, as recently reviewed, the dietary supplement 5-HTP has been used extensively in treating obesity and depression for over 30 years and the combination of 5-HTP/carbidopa has been used in treating depression and, only minor adverse side effects have been reported (17). In these settings, the most common adverse effects are nausea, vomiting, and diarrhea related to the conversion of 5-HTP to serotonin in the gastrointestinal tract (18). Less common side effects include headache, insomnia, and palpitations. More serious side effects of theoretical concern include the eosinophilia myalgia syndrome, the serotonin syndrome, cardiac valvulopathy, and pulmonary hypertension. Eosinophilia myalgia syndrome has

never been reported to be associated either with 5-HTP or with serotonin syndrome (17).

The obesity specialist seems to feel that the published guidelines do not reflect their experience in practice with the low risk-benefit ratio of using doses of phentermine higher than those recommended and using them for longer than their indicated use. They also feel that the published guidelines are too restrictive in their relegation of obesity drug use to particular BMI categories. Their feelings about both these issues may, at least in part, emanate from their society treatment guidelines (19). Although these guidelines mention the BMI as one consideration to be factored into decisions to treat patients with anorectic medications, in the ASBP clinical guidelines, clinical judgment is emphasized and over-rides the BMI in importance, which contrasts to the NIH guidelines that relies on the BMI for these treatment decisions (9). The ASBP guidelines also permit the use of anorectic medications at doses higher than recommended in the package insert based on the observation that only short-term studies of these drugs have been reported and that higher doses, based on clinical judgment, may be needed for long-term treatment (19). The degree of regulatory scrutiny seems to be greater in the obesity field than in other medical specialties, judging by the number of diverse agencies and businesses that have questioned these obesity specialists. The level of BMI recommended in the NIH guidelines, the length of time for the recommended use of phentermine and dose of phentermine recommended in the package insert seem to be the three things, which these specialists seem to find the most limiting to the way they wish to practice.

Rheumatologists sometimes use minocycline for the treatment of rheumatoid arthritis, and cardiologists sometimes use antibiotics for the treatment of atherosclerosis (20,21). Both of these drug treatments are deviations from the standard treatment guidelines and represent off-label use (22,23). Thus, obesity specialists, like other medical specialists, seem to deviate from generally accepted guidelines for treatment and engage in off-label medication use. In doing so, the ASBP seems to have discovered a previously unpublished and potentially effective combination medication for the treatment of obesity. Viewed collectively, these considerations suggest the need for a randomized controlled clinical trial to test the safety and efficacy of Phen/5-HTP for the treatment of obesity.

DISCLOSURE

R.B.R. holds an issued US patent on the combination of phentermine-5HTP/carbidopa for use in the treatment of obesity.

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