Research Review Speaker Series™

Phentermine: the American experience (GPCME Rotorua)

Making Education Easy

June 2016

About the speaker

Dr Ed J. Hendricks, MD, is a Fellow at the Obesity Medicine Association and a Diplomate for the American Board Obesity Medicine. He has practiced in bariatric medicine in Roseville and Sacramento, USA, since 1989. His expertise in caring for patients with weight problems is well known in Northern California and internationally. He is widely regarded as an expert in bariatric medicine across the globe due to his research activities, his published scientific papers on obesity treatment and his many lectures and presentations. He was an appointee to the US FDA Endocrine and Metabolic Drug Advisory Committee from 2010 to 2015. He can be contacted at edhendricks@surewest.net or ed@hendricksforhealth.com.

Abbreviations used in this review

AF = atrial fibrillation
BMI = body mass index
BP = blood pressure
CV = cardiovascular
HDL = high-density lipoprotein

This publication is a summary of a workshop at the 2016 GP CME Rotorua on June 10 by Dr Ed J. Hendricks, who spoke on the role phentermine has played in the successful management of excess adiposity in the US. His presentation included the history of phentermine and observations from his own clinical experience and research, and those from the literature, on the efficacy and safety of phentermine. He also highlighted the importance of focussing on the impact of weight loss on obesity-associated comorbidities. In addition to this Speaker Series, Research Review has also published a Product Review for phentermine (Duromine™).

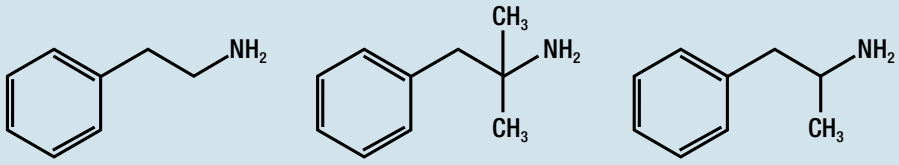
MEDICAL MANAGEMENT OF EXCESS ADIPOSITY

Successful management of obesity requires frequent visits by the patient in order to effect changes in their eating and exercise behaviours and to monitor pharmacotherapy. A low-carbohydrate, ketogenic diet is preferred. Dr Hendricks also uses pharmacotherapy in 90–95% of his patients, mostly phentermine.

Phentermine

Phentermine is a phenethylamine with a structure similar to amphetamine (figure 1);[1] however, the small primary structural difference (one methyl group) changes the three-dimensional structure significantly, resulting in changes to its pharmacological properties. Of note, the two agents perform quite differently in the clinic setting despite assumed similarities by US regulators. For example, the stimulant effect of phentermine in biological systems is ~10% of that seen with amphetamine when milligram equivalents are compared. The formulation of phentermine used in the US includes an HCl (hydrochloride) group, which is absent from the formulation available in NZ, Duromine™. The resultant differences in molecular weight mean that Duromine™ doses are 80% of the phentermine-HCl doses.

Figure 1. Molecular structure of phenethylamine (parent), phentermine and amphetamine



Phenethylamine | Phentermine (Duromine™) | Amphetamine

Phentermine pharmacokinetics

After an oral dose of phentermine 15mg, the maximum concentration of ~65 ng/mL is reached ~3 hours postdose, and the half-life is ~24–25 hours, although variability among individuals is seen.[1,2] The agent is deaminated in the liver, but 70–80% is excreted unchanged in the urine. The amount of urinary excretion of methamphetamine is affected by urinary pH, with greater excretion rate with a lower (acidic) pH reducing the half-life to 7–8 hours.[3] This has not been investigated for phentermine, due to lack of fundamental research for the agent driven by the assumption from regulatory authorities that these two agents possess the same or very similar characteristics.

Approvals

Phentermine was first approved for managing obesity in 1959; amphetamine had been approved in 1943 for depression, narcolepsy, hay fever and alcoholism, and then for obesity in 1947.[4] Within a year of its approval for treating obesity, phentermine had become the most widely used agent for this indication. In 1963, the US Food and Drug Act was amended to include efficacy as well as safety, and new phentermine trials were undertaken in the 1970s. In 1973, the US FDA reapproved phentermine for short-term (12 weeks) use.

PHENTERMINE TREATMENT FOR OBESITY

Duromine™ is initiated at 15mg or 30mg per day as part of a comprehensive bodyweight reduction programme.[1] Candidates for treatment are patients aged >12 years with a BMI ≥30 kg/m^2 who have not responded to an appropriate bodyweight reduction regimen and overweight patients with a lower BMI at increased risk of morbidity due to other medical conditions (e.g. sleep apnoea, diabetes, high CV disease risk); Duromine™ is not indicated for patients aged ≤12 years. Secondary organic causes of obesity should be excluded prior to initiating Duromine™.

Most adults are able to tolerate starting Duromine™ at 30 mg/day, but for individuals with known sensitivity to stimulants, starting at 15 mg/day followed by titration to the higher dosage as tolerated should be considered.[1] Treatment duration is 12 weeks, after which treatment should be stopped if weight loss does not exceed 5%.

Treatment with phentermine may be continued for responders provided the patient continues to be monitored and maintains their weight loss.[1] Patient revisits should be frequent, and should include evaluations for side effects (table 1) and effectiveness in terms of changes in eating behaviours and bodyweight loss. Vigilance is necessary for early loss of appetite to the point where the patient may not be eating enough to maintain a good nutritional status – the extent of this usually diminishes over time.

Table 1. Side effects of phentermine

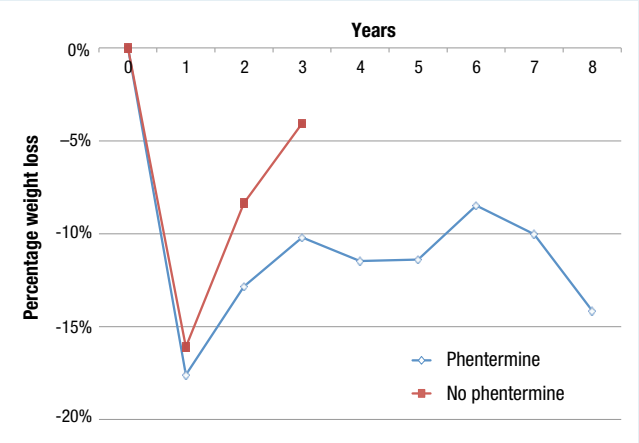
Common	Dry mouth (usually tolerable – encourages water intake) Insomnia (typically fades quickly – melatonin can be helpful) Increase energy/mood elevation (can have positive effect on exercise behaviours) Mild anticholinergic effects (e.g. constipation)
Less common	Impotence/decreased sex drive in men (~2%) Irritability Slowing of micturition

Clinical trials of phentermine of 12–24 weeks duration have reported average bodyweight losses of ~7% across the trials – there have been no long-term RCTs on the effects of phentermine on weight loss. A paper published in 2004 reported good results and few problems in eight patients who had elected to continue phentermine for weight loss/management for >10 years.[5]

Observational data

Dr Hendricks and colleagues conducted a retrospective observational study of patients with mean BMI of ~36 kg/m^2 who had started a very low carbohydrate ketogenic diet (≤40g carbohydrates per day) and had undergone regular assessments; 269 patients received continuous phentermine (drug hiatus of <1 year was allowed) and 31 were treated with diet and lifestyle modification only.[6] Compared with phentermine nonrecipients, those who received the agent had a statistically significantly greater weight loss at 52 weeks (–17.6% vs. –16.1%), although clinically this difference is not so important. Average weight loss among phentermine recipients was 17.3kg, and 10% weight loss at 1 year was achieved by 83%. An important finding is that patients who received phentermine were able to maintain weight loss better than those who did not receive the agent (figure 2). It should also be noted that during the analysis period, after 6–12 months when attempts to reintroduce more carbohydrate into the patients' diets were tried most patients gained weight. Dr Hendricks now believes that most obese patients have a persistent low tolerance to carbohydrates and will regain weight if they increase carbohydrate intake beyond their individual tolerance level at any time, but especially after weight loss (as evidenced in the data after the first year in figure 2). He therefore recommends that patients remain on a low carbohydrate/ketogenic diet during maintenance while receiving treatment with phentermine.

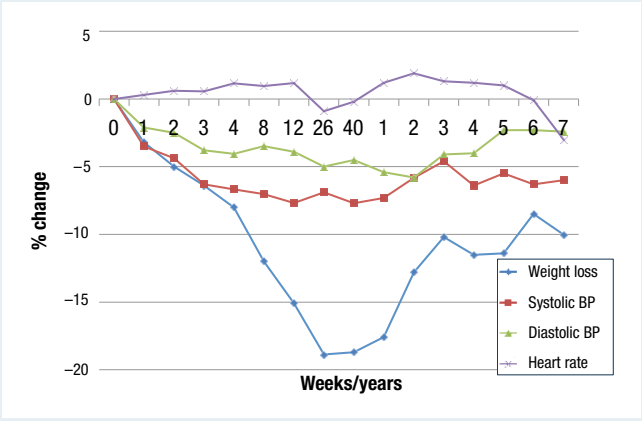
Figure 2. Average weight loss per year in phentermine recipients and nonrecipients[6]



Effects on BP

Just over half of candidates for phentermine treatment at Dr Hendricks' practice are prehypertensive, around one-third have hypertension and the remainder (~14%) have optimal BP. It is well established that as BMI increases, the proportion of patients with prehypertension increases. Dr Hendrick's group found decreases in systolic and diastolic BP within the first few weeks of treatment with phentermine, and these were maintained while weight loss was maintained (figure 3).[6]

Figure 3. Changes in bodyweight, BP and heart rate during treatment with phentermine[6]



Prehypertension typically progresses to hypertension at a rate of ~6–9% per year,[7–9] but the rate of such progression was 1% in the study by Dr Hendricks et al.[6] Additionally, none of the participants progressed from normal BP to hypertension, compared with the expected rate of 3% per year, and three of 22 with normal BP progressed to prehypertension; there were no data on the expected rate for the latter. It therefore appears that long-term phentermine does not have an adverse impact on BP. When study participants were stratified by hypertensive status, those with hypertension had greater decreases in systolic and diastolic BP, and this is consistent with data from another trial investigating the combination of phentermine and extended-release topiramate (Qsymia®).[10]

Study conclusions

- Long-term phentermine therapy can be effective for weight loss and weight loss maintenance.
- Phentermine-induced elevations in BP or heart rate are rare.
- Phentermine-treated overweight patients with hypertension and prehypertension typically have significant decreases in BP and sustained CV benefits.
- Long-term phentermine, by improving maintenance, may help retard the natural progression from normal BP to prehypertension to hypertension in obese patients.
- Bodyweight loss, sustained by phentermine, may substantially reduce CV disease mortality in obese patients with prehypertension or hypertension.

Adverse effects

There is no real evidence in the literature for any of the following suspected adverse effects, some of which have been anecdotally reported: pulmonary hypertension, cardiac valvulopathy, arrhythmias, BP elevations, hypertension, CV disease contraindication and sudden cardiac death. Despite this, Duromine™ remains contraindicated in patients with some of these conditions.[1] Phentermine is not recommended in patients with uncontrolled hypertension, but it does appear to be safe and possibly beneficial when hypertension is controlled. Palpitations do occur at a low rate and are often benign premature ventricular contractions.

There is no association between phentermine use and the most common arrhythmia AF, whereas known risk factors for AF are present in many obese patients as they include obesity, diabetes, hypertension, hyperlipidaemia, low HDL cholesterol level, advancing age, female sex and family history. In addition, bodyweight loss lowers the risk of AF. Overall, it appears that phentermine is associated with CV benefits due to reduced stress on the CV system from bodyweight loss.

Recommendations in patients with hypertension

Phentermine should not be started in new patients with a BP >140/90mm Hg. These patients should initially commence a low-carbohydrate ketogenic diet, and if BP does not decrease, then antihypertensive medication should be considered. Once the patient's BP is <140/90mm Hg, phentermine therapy can be started. If BP subsequently increases, phentermine should be withheld until BP control is regained.

Addictive potential of phentermine

Due to its stimulant effects in rats, phentermine was considered to have addictive potential in 1959 due to the belief that all stimulants were addictive at that time. Dr Hendricks and a colleague in 2010 reviewed the literature for evidence of addiction in humans. With the exception of a couple of anecdotal reports that were subsequently retracted, there were no reports of phentermine addiction and no investigations of its addiction potential. In addition, no evidence of addiction has been seen in clinical observations. There have been reports of nonprescribed use by polydrug users and long-haul truck drivers seen in clinical trials.[11,12] Surveys of US emergency rooms and addiction treatment centres have also failed to identify any evidence of phentermine addiction.

Dr Hendricks and colleagues conducted pilot and clinical trials to confirm the lack of addictive potential with phentermine.[13,14] Using an adapted validated cocaine addiction scale, withdrawal symptoms were assessed in patients who had stopped phentermine in the pilot study. The sole finding was that appetite increased after stopping treatment. The clinical trial used an amphetamine addiction assessment tool in 269 patients treated with phentermine for ≤21 years. No evidence of addiction was seen.

Other benefits of phentermine

Improvements in a number of obesity-associated conditions (e.g. type 2 diabetes, sleep apnoea, congestive heart failure, polycystic ovary syndrome, arthritis, nonalcoholic steatohepatitis, metabolic syndrome, etc.) are often seen with small decreases in bodyweight, and focussing on these conditions has its merits. In addition to maintenance of weight loss and arresting slow progressive weight gain, use of phentermine can also be considered to counteract the effects of weight gain secondary to the use of other drugs (e.g. prednisone, psychotropic agents).

Behavioural changes

As an agent that essentially alters behaviours, phentermine elicits improvements in compliance with diet, with better control of eating. These improvements include less emotional and stress eating, reduced cravings and better eating restraint. Phentermine recipients also often have more energy, which they can channel into more frequent and/or higher intensity exercise.

Typical patient responses to the question 'What is the effect of the drug?' include: i) 'I don't eat as much'; ii) 'I can stop eating'; iii) 'I don't graze all day and night'; iv) 'I'm not hungry as soon as I stop eating'; and v) 'I'm normal' (in respect to eating). Dr Hendricks and colleagues developed an eating behaviour questionnaire (EBQ) consisting of ten questions graded on a visual analogue scale (see below), which they administered to 197 phentermine-treated patients and 217 untreated patients. Compared with the untreated patients, the treated patients had a significantly lower mean score (36.9 vs. 62.0; figure 4), indicating improved control of eating behaviours.

EBQ: Eating behaviour questionnaire

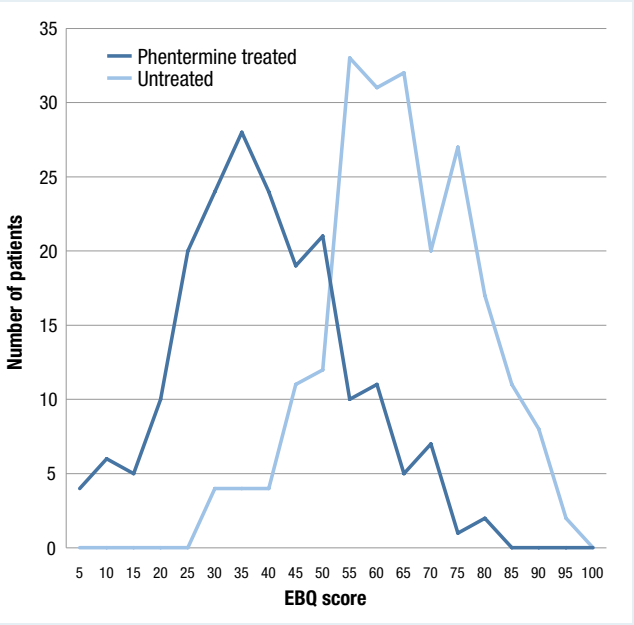
1. Are you preoccupied with thoughts of food or eating?
2. Do you eat to comfort yourself?
3. Do you crave any specific foods?
4. Once you start eating, do you find it hard to stop?
5. Do you find it difficult to stick to an eating plan?
6. Do you eat rapidly, more rapidly than those around you?
7. Do you 'graze' or eat continually during any part of a 24-hour day?
8. Are you in control of your eating?
9. Do you eat more when under stress?
10. Do you eat more during highly emotional times?

The EBQ (designed by Dr Hendricks) is protected by copyright, and can be purchased online.

This product also comes with a supplemental spreadsheet that allows for easy data collection and tracking of how your treatment affects patients' responses to the EBQ.

Proceeds from the sale of this product will go directly to The Obesity Treatment Foundation, a nonprofit organisation whose purpose is to foster, fund and enable research in the field of obesity medicine and educate the public, professionals and government in the nature of obesity, including its aetiologies, prevention, diagnosis, consequences and treatment.

Figure 4. Distribution of eating control questionnaire (EBQ) scores in 197 phentermine-treated and 217 untreated patients



TREATMENT RECOMMENDATIONS AND SUMMARY

- Management of obesity includes three behavioural components (what to eat, exercise/activity and managing harmful eating – frequent visits are important), implementation of a low-carbohydrate ketogenic diet and pharmacotherapy
  - It appears that a low-carbohydrate diet and phentermine act synergistically to enhance weight loss.
  - Of the drugs available for treating obesity, phentermine appears to provide the greatest benefit (80–90% response rate) with minimal risk.
- Early treatment with focus on comorbidities is recommended, remembering that BMI is a very insensitive indicator of obesity-associated problems.
- Lifelong management is usually required, and ideally this includes phentermine when prescribed.
  - While the Duromine™ datasheet indicates 12 weeks of initial treatment, it does allow for continued treatment provided the patient continues to be monitored and weight loss is maintained.[1]
- It is important that a low carbohydrate diet is maintained during long-term treatment with phentermine, as many patients have a very low tolerance to carbohydrates.

REFERENCES

1. Medsafe NZ. Duromine® New Zealand Data Sheet, 2015. Downloaded on July 6, 2016
2. Addy C et al. Pharmacokinetics, safety, and tolerability of phentermine in healthy participants receiving taranabant, a novel cannabinoid-1 receptor (CB1R) inverse agonist. J Clin Pharmacol 2009;49(10):1228–38 (Abstract)
3. Beckett AH & Rowland M. Urinary excretion of methylamphetamine in Man. Nature 1965;206(4990):1260–1 (Abstract)
4. Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. Ann Intern Med 2005;143(5):380–5 (Full text)
5. Frank A. The long-term management of obesity with continuing pharmacotherapy. Obes Res 2004;12(11):1821–7 (Full text)
6. Hendricks EJ et al. Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity. Obesity 2011;19(12):2351–60 (Full text)
7. Brown CD et al. Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res 2000;8(9):605–19 (Full text)
8. De Marco M et al. Cardiovascular and metabolic predictors of progression of prehypertension into hypertension: the Strong Heart Study. Hypertension 2009;54(5):974–80 (Full text)
9. Liu L-K et al. Prehypertension among middle-aged and elderly people in Taiwan: a five-year follow-up. J Atheroscler Thromb 2010;17(2):189–94 (Full text pdf)
10. Davidson MH et al. Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index ≥27 kg/m^2. Am J Cardiol 2013;111(8):1131–8 (Full text)
11. Couper FJ et al. Prevalence of drug use in commercial tractor-trailer drivers. J Forensic Sci 2002;47(3):562–7 (Abstract)
12. Bryman D et al. Incidence of addiction and abuse due to phentermine, diethylpropion, and phendimetrazine in the United States. Unpublished manuscript, 2013.
13. Hendricks EJ & Greenway FL. A study of abrupt phentermine cessation in patients in a weight management program. Am J Ther 2011;18(4):292–9 (Abstract)
14. Hendricks EJ et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. Int J Obes 2014;38(2):292–8 (Abstract)

Radiant Health