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SPEAKER SERIES

What do we really know about phentermine?

Making Education Easy 2022

About the speaker

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Abbreviations used in this review
BMI = body mass index
BPM = beats per minute
CV = cardiovascular
MAOI = monoamine oxidase inhibitor
RCT = randomised controlled trial

This publication summarises an Obesity Medicine Association webinar by Assistant Professor Deborah Bade Horn who provided an overview of the recent literature on phentermine safety, efficacy and dosing as well as the current biases surrounding phentermine and the prescribing of anti-obesity medicines. This write up was supported by an educational grant from Radiant Health.

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The full webinar and CME quiz can be found here (obesitymedicine.org):
Academy: 800,000 Rx's Per Month: What Do We Really Know About Phentermine?

Introduction

Phentermine has been used as an anti-obesity medicine in the United States for decades where it is prescribed approximately 800,000 times a month. Dr Bade Horn outlined what is known about phentermine as well as where further research is required. The presentation's objectives were to:

1. Review the safety, efficacy and factors limiting the use of phentermine with long-term data focussed on the last three years
2. Discuss the current bias towards phentermine and anti-obesity medicines in general and the effect this has on clinical practice
3. Discuss individualised clinical decision making with patients
4. Help to provide colleagues and patients with information to build confidence and expand referral networks

The safety and efficacy of phentermine

To achieve Dr Bade Horn's first objective, a 5-year retrospective literature review was performed at the University of Texas. The review identified 197 publications focussed on phentermine, including 112 reviews, 17 RCTs, 16 retrospective trials and 21 case studies.

Phentermine's anti-obesity mechanism of action occurs predominately via upregulation of noradrenaline. Weak upregulation of serotonin and dopamine also occurs but this is likely to be clinically insignificant. Phentermine causes appetite suppression via activation of neurons in the arcuate nucleus of the hypothalamus.

The optimal dosing regimen for phentermine is not known. Dr Bade Horn's literature review revealed minimal information on weight-based dosing and there was no response-specific data, other than classifying patients as responders or non-responders after 3 months of treatment. There was a small amount of information on gender dosing (see below). The half-life of phentermine is approximately 20 hours, and it is excreted in the kidney.

Discussion on contraindications to phentermine

The most significant contraindication for phentermine use is CV disease (**Table 1**), which as Dr Bade Horn noted, is important due to the association between obesity and CV disease.[1]

There is little data on the use of the phentermine with other anti-obesity medicines, therefore combining these medicines requires careful consideration. There have been rare instances of primary pulmonary hypertension, mainly relating to the combination of phentermine and fenfluramine which is no longer prescribed after fenfluramine was withdrawn.[1] Dr Bade Horn pointed out that concerns about phentermine abuse relate to the potential for abuse based on experiences with amphetamines.

Table 1: Contraindications and precautions to phentermine use[1]

Contraindications	Precautions
• Pulmonary artery hypertension • Existing heart valve abnormalities or heart murmurs • Moderate to severe arterial hypertension • Severe cardiac disease including arrhythmias • Cerebrovascular disease • Advanced atherosclerosis • Known hypersensitivity to sympathomimetics • Hyperthyroidism • Agitated states or a history of psychiatric illness (including anorexia nervosa and depression) • Glaucoma • A history of drug or alcohol dependence • Concomitant treatment with an MAOI or within the last 14 days	• Primary pulmonary hypertension • Valvular heart disease • Avoid during pregnancy and lactation • Alcohol may increase central nervous adverse effects • Ability to operate machinery may be impaired*

*Dr Bade Horn has seen no clinical data to demonstrate this

Additional information on safety and efficacy

Later in the talk, Dr Bade Horn presented additional information on the safety and efficacy of phentermine:

- **The addiction potential of phentermine has been studied and no evidence of abuse or psychological dependence has been found**. Hendricks *et al* (2014) performed a clinical intervention trial with interruption of long-term phentermine treatment in 269 patients.[2] Interviews, severity of dependence scales and questionnaires assessing craving and withdrawal found that abuse or psychological dependence does not occur when phentermine is taken as an anti-obesity medicine.
- Additionally, Hendricks and Greenway (2011) found that abrupt cessation of long-term phentermine treatment did not induce amphetamine-like withdrawal and that cravings for phentermine were entirely absent.[3] These studies suggest that although phentermine may be structurally similar to other sympathomimetic drugs the pharmacological effects of phentermine may be different.
- **There is no data to support the development of tolerance** in patients taking phentermine.
- **A review found no evidence of hepatotoxicity** associated with phentermine use, unlike some other sympathomimetic medicines, and the reviewers concluded that:

  "*…small structural differences can lead to drastically different pharmacological/toxicological profiles, and one should not assume that all sympathomimetic agents are hepatotoxic. Such assumptions could lead to diagnostic errors and incorrect or insufficient treatment.*"[4]
- **Dose reductions of phentermine may be appropriate in patients with renal impairment**, particularly older patients, as phentermine is predominantly excreted by the kidneys. If a patient has an eGFR of 15-29 mL/min/1.73m^2 they should not exceed 15 mg phentermine per day.
- **Phentermine reduces the incidence of prediabetes converting to type 2 diabetes**, most likely as a function of weight loss.[5]

In New Zealand, phentermine is available in 15 mg and 30 mg modified-release capsules that are approved for adults and children aged ≥ 12 years.[1] The usual starting dose is 30 mg daily, but in lighter framed people or where adverse effects occur, 15 mg daily is recommended.

Dr Bade Horn noted the optimal timing of administration of phentermine is not well studied. It is generally recommended to take phentermine in the morning to avoid sleep disruption, although some people take phentermine in the afternoon without it negatively affecting their sleep.

Dry mouth is easily the most common phentermine-related adverse effect encountered in Dr Bade Horn's practice. Additional adverse effects occurring in ≥ 5% of patients include, headache, increased blood pressure, tachycardia, palpitations, dysgeusia, insomnia, anxiety and constipation.

Longer-term safety and efficacy

Dr Bade Horn discussed a retrospective study by Lewis *et al* (2019) that used health records to compare the safety and efficacy of short and longer-term phentermine use.[6] The authors assessed whether adults who were prescribed phentermine > 12 weeks experienced greater weight loss or changes in heart rate, blood pressure or increased risk of CV risk or death, compared to patients taking phentermine for < 12 weeks.

The study identified 13,972 adults who had first used phentermine between 2010 and 2015.[6] The health records of patients were assessed 6, 12 and 24 months after initiating phentermine. The study cohort was 84% female, 45% Caucasian, and the mean age at baseline was 43 years with a mean BMI of 37.8 kg/m^2. There was no placebo group in the study, therefore short-term users of phentermine were defined as the reference group and used as a comparator for other treatment groups (**Table 2**).

Table 2: Treatment groups for short, medium and long-term use of phentermine in Figure 1 from Lewis *et al* (2019)[6]

Treatment group	Colour code	Definition
Short-term (reference)		Phentermine use ≤ 112 days continuously and no subsequent use
Short-term intermittent		Phentermine ≥ 2 treatment episodes with no episode exceeding 112 days
Medium-term continuous		Phentermine use > 112 days to 1 year continuously and no subsequent use
Medium-term intermittent		Phentermine ≥ 2 treatment episodes with at least one episode exceeding 112 days
Long-term continuous		Phentermine use ≥ 1 year continuously in a single episode

Dr Bade Horn presented data from the set of patients who responded to phentermine treatment (**Figure 1**), as this more accurately aligns with what is seen in clinical practice. Responders were defined as patients with ≥ 3% weight loss after 12 weeks of treatment.[6]

Overall, a longer duration of phentermine use was associated with greater weight loss. Patients who responded to phentermine and continued to take phentermine for ≥365 days experienced a -10.7% decrease in body weight from baseline at 24 months.[6] Furthermore, long-term continuous users of phentermine lost -7.4% more percentage bodyweight than the short-term reference group at 24 months (p<0.001).

Lewis *et al* concluded that long-term continuous treatment with phentermine was required to produce successful results. It was also noted that discontinuation of phentermine consistently resulted in weight regain.

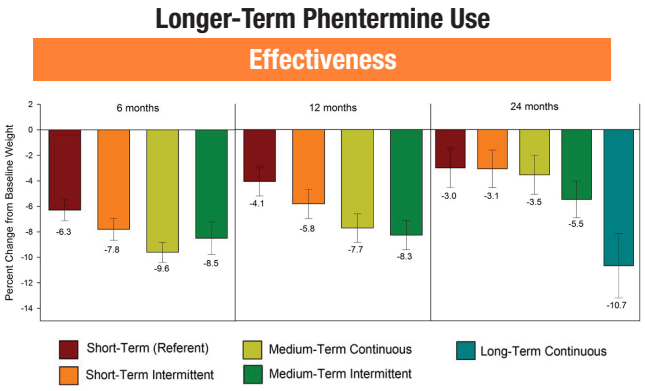

Figure 1: Percent weight loss from baseline at 6 months, 12 months and 24 months in responders losing ≥3% bodyweight after 12 weeks of phentermine treatment, adapted from Lewis *et al* (2019)[6]

Cardiac function and longer-term phentermine treatment in the Lewis study

There was no change in heart rate from baseline at 6, 12 or 24 months for short-term users of phentermine (reference group, **Table 3**).[6] There were small but significant increases in bpm at 6 months in medium-term continuous users and at 12 months in medium-term intermittent users, compared to the reference group. The slight increase in heart rate is consistent with noradrenaline driving phentermine's mechanism of action.[7]

Table 3: Changes in heart rate (bpm) following phentermine treatment in Lewis *et al* (2019)[6]

Treatment group	Change in heart rate (bpm)
Short-term (reference)	No change at 6, 12 or 24 months
Medium term continuous	1.6 bpm higher at 6 months
Medium-term intermittent	1.1 bpm higher at 12 months
All groups	No change at 24 months

The systolic blood pressure of patients in the reference group was stable at 6 and 12 months but increased by 1.8 mmHg at 24 months relative to baseline.[6] There was no difference in systolic blood pressure between the comparison groups and the reference group at 6 months. Dr Bade Horn noted that the comparison groups had lower systolic blood pressure than the reference group at 24 months; most likely because they had lost more body weight.

In patients with baseline hypertension, the systolic blood pressure of long-term phentermine users was lower than short-term users with baseline hypertension. Dr Bade Horn hypothesised that the most likely reason for this was a greater reduction in body weight in patients taking phentermine for longer.

The diastolic blood pressure in the reference group was stable from baseline at 6, 12 and 24 months and there was no significant difference between the comparison groups and the reference group over the course of the study.[6]

The cardiovascular safety data from Lewis *et al* are similar to those of an earlier phentermine study conducted by Hendricks *et al* (2011) that found no change in heart rate and both diastolic and systolic blood pressure declining in both phentermine and non-anti-obesity medicine users whilst participating in a behavioural weight management programme.[8] Dr Bade Horn acknowledged the value of retrospective studies but pointed out that a long-term RCT was needed to gain a fuller understanding of phentermine.

Cardiovascular risk and longer-term phentermine treatment

Lewis *et al* (2019) created a composite measure for CV risk by looking for patients who had experienced a myocardial infarction, stroke, angina, coronary artery bypass, carotid artery intervention or had died up to 3 years after starting phentermine.[6] The composite adverse marker occurred in 41 (0.3%) of 13,972 patients. Dr Bade Horn highlighted that no qualifying CV events or deaths occurred in the long-term continuous group, therefore the authors grouped the long-term and medium-term users for this analysis (**Table 4**). There was no significant difference in CV risk or death between the groups in the 3 years following phentermine initiation.

Table 4: Hazard ratio for composite outcome of incident myocardial infarction, stroke, CV disease intervention, or death up to 3 years after phentermine initiation, adapted from Lewis *et al* (2019)[6]

	Hazard ratio	CI
Short-term (referent)	Reference	
Short-term intermittent	0.74	0.29-1.91
Medium-term intermittent	0.50	0.14-1.74
Medium & long-term continuous combined	1.58	0.69-3.63

Phentermine and anaesthesia

Plastic or orthopaedic surgery is often required by patients taking phentermine and anaesthetists generally recommend that phentermine be stopped 2-4 weeks prior to surgery, largely due to concerns about hypotension during induction. However, due to the 20-hour half-life of phentermine, the plasma levels of phentermine are < 5% four days after discontinuation, therefore it is recommended that phentermine be stopped four days prior to surgery.[13]

Phentermine in the adolescent population

The addition of phentermine to standard of care in a small population of obese adolescent patients (mean age 16 years) resulted in significantly greater changes in BMI at 1 month, 3 and 6 months, compared to standard of care alone (**Figure 2**).[14]

At 6 months, the BMI change was 4% between the two groups and 40% of patients taking phentermine achieved a ≥5% reduction in bodyweight, compared to 8% in the control group. There were no increases in systolic or diastolic blood pressure, although there was an elevation in heart rate in patients taking phentermine.

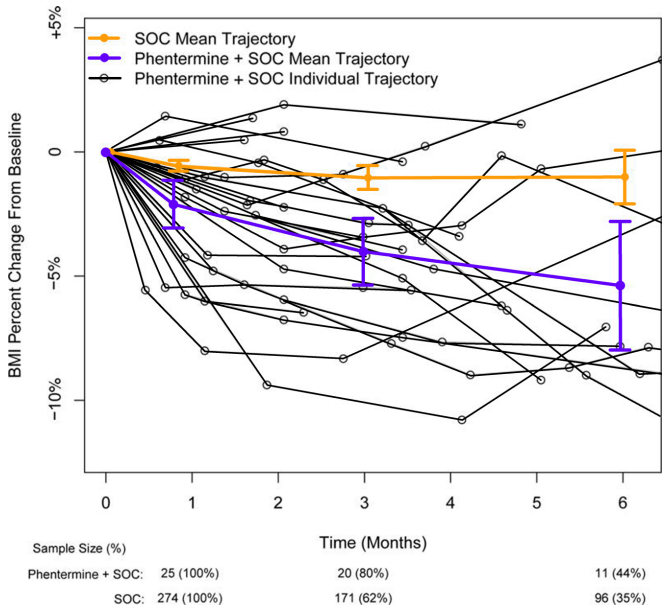

Figure 2: Body mass index (BMI) change from baseline for adolescent obese patients for phentermine + standard of care (SOC) versus SOC at 1 month, 3 months and 6 months, adapted from Ryder *et al* (2017)[14]

Gender and phentermine

A review of the influence of gender on the pharmacology of newer anti-obesity medicines found no pharmacokinetic differences associated with phentermine in animal models and no significant differences between genders in studies of phentermine in humans.[15] No adjustments in phentermine dosing on the basis of gender are therefore recommended.

Bias and phentermine prescribing

Dr Bade Horn discussed the Veterans Health Administration (VHA) MOVE! Behavioural weight management program that included 153,939 patients. Within this cohort, 1,719 patients (1.1%) received an anti-obesity medicine.[16] Of those receiving an anti-obesity medicine, 1,210 (70.4%) were prescribed orlistat and 93 (5.4%) were prescribed phentermine. Dr Bade Horn noted that phentermine is prescribed at much higher rates than this in practice and the low rates of phentermine use were striking despite the medicine being free or available at low cost. The difference between real-world prescribing and study data may because pharmacies in the VHA study were unable to dispense more than 3 months of phentermine.

Does education matter?

Obesity management surveys suggest that primary care providers under-value the potential benefits of anti-obesity medicines.[17] However, after training their perceived comfort in prescribing these medicines and their perceived effectiveness of them improved.

There is evidence that medical students may not be receiving sufficient training to manage obesity. A survey of 40 Medical Schools in the United States found that one-third did not have an obesity management programme and had no plans to develop one.[18]

A study of resident and fellow physicians attending an education summit assessed knowledge, competence and confidence in managing outpatient obesity.[19] Prior to the training, 8% of respondents rated themselves as having high confidence and competence in prescribing anti-obesity pharmacotherapy. Following the training, 70% of respondents were confident and comfortable with anti-obesity medicines.

Clinical decisions

When selecting an anti-obesity medicine, Dr Bade Horn recommends the 5Cs:

- Coverage – are there barriers to access such as cost? In New Zealand, this may involve a discussion about willingness to pay as anti-obesity medicines are not funded and costs range from $79 to $500 per month, although phentermine is on the lower scale at $79 (15 mg) and $90 (30 mg)
- Contraindications – confirm the patient can safely take the medicine
- Co-morbidities – confirm the medicine is compatible with any underlying health conditions
- Choose – ask the patient about the characteristics of their hunger such as timing or triggers, and tailor treatment appropriately
- Combinations – what other weight-loss interventions can be combined with treatment?

Dr Bade Horn noted that in the future, phentermine may be combined with other anti-obesity medicines.

Recently, studies have shown that phentermine can be an effective adjunct to bariatric surgery. For example, in a small group of patients (BMI ≥ 50 kg/m^2) who took phentermine before a laparoscopic sleeve gastrectomy and for two years following surgery, there was a -11.2% greater weight loss compared to historical control patients who had undergone surgery alone.[20] This finding may avoid the need for additional surgeries in surgical patients who are prescribed anti-obesity medicines. There is also evidence that phentermine may be more effective in patients who have undergone a Roux-en-Y gastric bypass than in those who have undergone a sleeve gastrectomy.[21,22]

Phentermine has been used successfully in combination with meal replacement programmes. In a 12-week, randomised placebo-controlled trial of 77 obese adults, the daily use of 37.5 mg of phentermine in combination with a meal replacement programme resulted in greater weight loss and greater reductions in fat and sweet cravings, compared to placebo with meal replacements.[23]

TAKE-HOME MESSAGES

- Phentermine is a safe and effective anti-obesity medicine when used within the correct patient population
- Phentermine treatment may be continued beyond 12 weeks if the patient has lost ≥ 5% body weight and they continue to be monitored, ideally in a dedicated clinical setting
- Patients who respond to phentermine and continue treatment for at least one year can expect an approximate -11% sustained reduction in body weight
- Phentermine use has not been associated with an increased risk of CV events and weight loss following phentermine use is likely to decrease CV risk, when used in the indicated population
- There is no data to support concerns that phentermine is associated with addiction or tolerance
- Health professionals often have a bias against prescribing anti-obesity medicines that can be overcome with training and experience

THE NEW ZEALAND EXPERIENCE WITH PHENTERMINE

– remarks from Auckland endocrinologist Dr Ole Schmiedel

Obesity, especially morbid obesity, is a chronic, relapsing, neuro-behavioural disease with metabolic, biomechanical, and psychosocial health consequences. In practical clinical terms, it can be described as a disease of eating behaviour, where appetite, which is centrally regulated like thirst, is one of the divers of weight gain. Our patients know this well, it is not a lack of willpower but powerful drivers to eat that lead to weight regain after successful diet attempts. This observation is supported by several clinical studies showing an average sustainable weight loss of 3-4% with lifestyle interventions. Medication or bariatric surgery are often required to achieve lasting success. Therefore, clinicians must be trained in the safe use of weight management medications.

The oldest of the available weight loss medications, Duromine® has benefits and risks. This article, reviewing the presentation by Dr Debra Horn, provides a brilliant summary of available evidence for the longer-term use of Duromine®. Prescribers must be aware of contraindications, potential complications, side effects and medication interactions when prescribing Duromine®. It is equally vital that any weight loss medication is an add on to a lifestyle programme and that prescribing Duromine® beyond three months requires regular monitoring and the correct clinical set-up, as detailed in the Medsafe datasheet.

Ole Schmiedel MRCP; MD; FRACP

Ole is an endocrinologist at ADHB and the Service Clinical Director of the Auckland Diabetes Centre. His clinical and research interests include the management of diabetes, obesity and obesity related complications.

How do I use Duromine®? I always start low, either 15mg daily or even 15mg on alternative days and increase the dose stepwise. It is vital to monitor side effects and benefits, looking for changes in hunger and increased satiety. I want to make you aware of an old study from Edinburgh that found no relationship between weight loss and phentermine dose or phentermine plasma concentration; however a strong correlation between weight loss and change in appetite. Hence, monitoring changes in hunger is a good clinical marker to predict success.

I would caution against prescribing weight loss for adolescents, except in exceptional circumstances, and I like to remind the prescriber that all weight loss medications are contraindicated in pregnancy. A multidisciplinary primary care obesity clinic is the best place to prescribe Duromine®, allowing regular monitoring of patients, using a lower dose for a more extended period, which will achieve the best results for long term outcome and safety.

REFERENCES:

1. iNova Pharmaceuticals (New Zealand) Limited. New Zealand data sheet: DUROMINE®. Published online 2018. https://www.medsafe.govt.nz/profs/datasheet/d/durominecap.pdf
2. Hendricks EJ, et al. Int J Obes. 2014;38(2):292-298.
3. Hendricks EJ, Greenway FL. Am J Ther. 2011;18(4):292-299.
4. Willson C. . Toxicol Rep. 2019;6:26-33.
5. Domecq JP, et al. J Clin Endocrinol Metab. Published online July 31, 2019:jc.2019-01269.
6. Lewis KH, et al. Obesity. 2019;27(4):591-602.
7. Garvey WT. Am J Clin Nutr. 2012;95(2):297-308.
8. Hendricks EJ, Greenway FL, Westman EC, Gupta AK. Obesity. 2011;19(12):2351-2360. doi:10.1038/oby.2011.94
9. Montan PD, et al. Ann Transl Med. 2019;7(16):393.
10. Ritchey ME, Harding A, Hunter S, et al. J Clin Endocrinol Metab. 2019;104(2):513-522. doi:10.1210/jc.2018-01010
11. Andrew CA, et al. Expert Opin Pharmacother. 2019;20(5):585-593.
12. Khera R, et al. Gastroenterology. 2018;154(5):1309-1319.e7. doi:10.1053/j.gastro.2017.12.024
13. Lim S, et al. Ann Plast Surg. 2018;81(4):503-507.
14. Ryder JR. Int J Obes. 2017;41(1):90-93.
15. Cataldi M, et al. Obes Rev. 2019;20(3):375-384.
16. Thomas DD, et al. Obesity. 2019;27(7):1168-1176.
17. Iwamoto S, et al. Obesity. 2018;26(10):1532-1538.
18. Butsch WS, et al. BMC Med Educ. 2020;20(1):23.
19. Velazquez A, et al. Clin Obes. 2019;9(5):e12315.
20. Ard JD, et al. Surg Obes Relat Dis. 2019;15(7):1039-1043.
21. Nor Hanipah Z, et al. Surg Obes Relat Dis. 2018;14(1):93-98.
22. Elhag W, et al W. Ann Med Surg. 2019;45:75-81.
23. Moldovan CP, et al. Obesity. 2016;24(11):2344-2350.

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