

Medicines Adverse Reactions Committee

Meeting date	9/09/2021	Agenda item	3.2.1
Title	Phentermine risk benefit review		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	Product name	Sponsor	
Phentermine	Duromine 15mg, 30mg modified release capsules	iNova Pharmaceuticals (New Zealand) Limited	
PHARMAC funding	Not PHARMAC funded.		
<i>Prescriber Update</i>	Valvular Abnormalities with Dexfenfluramine and Fenfluramine (June 1999) Update on Valvular Abnormalities with Dexfenfluramine and Fenfluramine (July 2000)		
International action	EMA : Qsiva (phentermine with topiramate) Assessment Report (2013).		
Classification	Phentermine is a Prescription Medicine (Class C5 Controlled Drug).		
Advice sought	<p>The Committee is asked to advise on:</p> <ul style="list-style-type: none"> • The evidence for efficacy and safety. • Whether the benefits of treatment with phentermine outweigh the risks of harm? • Whether further actions need to be taken, which could include for example a statutory benefit-risk review, updates to the data sheet to manage identified risks? • Further communication is required other than in MARC's Remarks? 		

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1 PURPOSE

In December 2020, the Centre for Adverse Reactions Monitoring (CARM) received a report of stroke where phentermine was listed as the suspect medicine (CARM ID 139240). This case was reviewed by the Medsafe pharmacovigilance team. Medsafe was concerned about the safety of phentermine relative to the clinical benefits as cerebrovascular and cardiovascular events have been reported to CARM in the past. It was decided a risk-benefit review should be undertaken and that this review be presented to the Medicine Adverse Reactions Committee (MARC) for advice.

In addition, a review of the New Zealand data sheet for Duromine (the approved product for phentermine) contains a statement in the therapeutic indications that treatment with phentermine may be continued beyond 12 weeks, however longer-term use has not been approved in other countries. Medsafe would like to seek the advice of the MARC as to whether this statement should be revised, subject to the Committee's overall view on the benefit risk for this medicine.

2 BACKGROUND

2.1 Obesity in New Zealand

According to the 2019/2020 New Zealand Health Survey [1]:

- Around 1 in 3 adults (aged 15 years and older) were obese (30.9%).
- The prevalence of obesity among adults differed by ethnicity: 63.4% of Pacific, 47.8% of Māori, 29.3% of European/others and 15.9% of Asians adults were obese.
- Adults living in the most socio-economically deprived areas were 1.8 times as likely to be obese compared to adults living in the least deprived areas.

2.2 Clinical Guidelines for Weight Management in New Zealand Adults [2]

The Ministry of Health released clinical guidelines on weight management in adults in 2017 (the Guidelines). The purpose of this document was to provide healthcare practitioners with the most up-to-date tool to monitor, assess, and support overweight and obese adults to attain and maintain a healthy weight.

Excess weight gain can have serious health consequences. Obesity in adults is associated with a number of health conditions, including type 2 diabetes, ischaemic heart disease, stroke, several common cancers, osteoarthritis, sleep apnoea and reproductive abnormalities.

The Guidelines outline a four-step continuous process for weight management:



Steps 3 and 4 outline pharmacological considerations:

Manage:

The use of weight-loss drugs is mentioned in this step:

“Weight loss medications may be useful in producing initial weight loss and preventing weight regain in longer-term management. The only medicines approved for weight loss in New Zealand are unsubsidised. Only recommend weight-loss drugs to an overweight or obese person if:

- *Lifestyle changes have not produced significant benefit after at least six months, and*
- *the person has a BMI ≥ 30 kg/m².*

People should always use weight loss drugs in conjunction with lifestyle changes”.

The Guidelines recommend evaluating the efficacy of the weight-loss drug after the first three months of treatment and regularly throughout the period of use, including careful monitoring for side effects (monthly for the first three months, then quarterly).

If a person on a particular weight-loss drug achieves a weight loss of < 5 percent of initial body weight within a period of 12 weeks, then the practitioner should discontinue the treatment. Only orlistat is approved for long-term use in New Zealand.

While other medicines are licensed elsewhere, the two drugs approved for use for weight loss in New Zealand are orlistat and phentermine. The use of low-dose topiramate in combination with low-dose phentermine for weight loss is an off-label use of topiramate in New Zealand (topiramate is approved for the treatment of epilepsy and the prophylaxis of migraine).

Comments:

It is interesting to note that the NZ Guidelines do not list liraglutide as a pharmacological option even though approved for this indication. Naltrexone with bupropion was recently approved by Medsafe in 2020 and this could explain why this is not yet included in the NZ Guidelines.

Duromine is the only approved phentermine product in New Zealand. Failure to achieve a weight reduction of 5% within a period of 12 weeks is an indication for discontinuation of treatment.

Although there have been no studies as yet to confirm an effect on mortality or morbidity, a weight reduction, a weight loss 5% or greater is considered clinically significant as relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight [3].

Maintain:

After the patient has achieved weight loss they aimed for, ongoing monitoring and support is required. Prescribed weight-loss medications require follow-up care. If the patient is using weight-loss drugs, consider continuing them for weight-loss maintenance only if the patient has lost at least 5 percent of their initial body weight in the first three months of starting the drug, and side effects are manageable.

2.3 Bpac^{nz} – Weight loss: the options and the evidence [4]

In 2019, Bpac^{nz} published an article on weight management. The article outlines the evidence of various pharmacological and non-pharmacological options for weight loss. The advice given reflects the Clinical Guidelines for Weight Management in New Zealand Adults. The following points are made regarding pharmacological options for weight loss:

- Pharmacological interventions for weight loss generally have limited long-term effectiveness, however, short-term use may be considered for people who are obese as an adjunct to lifestyle interventions, after the potential harms and benefits of treatment have been reviewed.
- The clinical benefits of weight loss begin once an overweight person loses as little as 5% of their body weight and benefits increases as the ideal weight range is approached.
- Phentermine is a dopaminergic agonist that acts as an appetite suppressant. It is indicated for short-term, ie, 12 weeks or less, adjunctive treatment for weight loss in patients with a BMI greater 30 kg/m².

- Phentermine is contraindicated in a number of patients, especially those with cardiac abnormalities and hypertension.
- Phentermine, like amphetamine, is a sympathomimetic drug and there are some concerns that it has addictive potential.
- A four-week trial of phentermine is recommended and treatment beyond 12 weeks may be considered for patients who are continuing to lose weight. However, prescribers should be alert to signs of dependence eg, requesting more than the usual maximum approved dose or lost prescriptions.
- A small number of randomised controlled trials have reported a beneficial effect of phentermine on weight loss.

Comments:

Bpac^{nz} mentions considering ongoing weight-loss if the patient continues to lose weight. The data sheet for phentermine states that therapy can continue beyond 12 weeks if there is continual weight loss and appropriate follow-up.

2.4 UK's National Institute for Health and Care Excellence (NICE) Guidelines [5]

Pharmacological treatment is recommended only after dietary, exercise and behavioural approaches have been started and evaluated. It can be considered for patients who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes.

Pharmacological treatments may be used to maintain weight loss, rather than to continue to lose weight.

- Orlistat: consider only if BMI ≥ 28 kg/m² with associated risk factors or BMI ≥ 30 kg/m² or more. Therapy for longer than three months should only be considered if the person has lost at least 5% of their body weight since starting drug treatment.
- Liraglutide – a glucagon-like peptide-1 (GLP-1) receptor agonist.
- Naltrexone with bupropion.

Comments:

Phentermine is not marketed in the UK and therefore not reflected in the NICE guidelines.

2.5 Profiles of different pharmacological treatments for weight-loss approved in New Zealand

Table 1 compares the efficacy and safety of the various weight-loss medicines approved in New Zealand. Unlike phentermine that is indicated for short-term use, other weight-loss medicines may be used for longer.

Orlistat has slightly less efficacy compared to other long-term weight-loss medicines. Orlistat reduces the digestion and absorption of fat which is excreted in the stool meaning the adverse effects can be significant (ie, faecal urgency, flatulence, cramps, and impaired absorption of fat-soluble vitamins). Less than 10% of patients will continue on orlistat for longer than a year [4]. Orlistat is a pharmacist-only medicine making it more accessible compared to the other options.

Liraglutide appears to have the best weight loss potential at 1 year compared to other products. It acts centrally to regulate appetite as well as having delayed gastric emptying effects. It has the added benefit of improving glucose homeostasis by reducing fasting and post-prandial glucose by increasing glucose-dependent insulin secretion and decreasing glucose-dependent glucagon secretion. Liraglutide has the disadvantage that it is the only weight-loss medicine that requires to be administered subcutaneously and be kept between 2-8 degrees Celsius. The common side effects are gastrointestinal in nature but can be mitigated by gradual dose escalation. Liraglutide has been associated with an increased incidence of symptomatic gallstones and, more rarely, pancreatitis. Liraglutide is one of the more expensive options [6].

Naltrexone with bupropion is a newly approved anti-obesity agent. It combines 8 mg of naltrexone with 90 mg of bupropion. As naltrexone is an opioid antagonist and bupropion has effects on the central nervous system, the use may be contraindicated for a large group of people. Naltrexone with bupropion has been associated with elevated blood pressure or heart rate during treatment [7].

Weight-loss medicines are not funded by PHARMAC.

Table 1: Approved weight-loss medicines in New Zealand

Medicine	Weight loss (% or kg)	Adverse effects	Contraindications (from their respective data sheets)
Phentermine	3.6 kg to 4.5 kg at six months [8]	Dry mouth, insomnia, agitation, constipation, and tachycardia [8]	Pulmonary artery hypertension, existing heart valve abnormalities, or heart murmurs, moderate to severe arterial hypertension, cerebrovascular disease, severe cardiac disease including arrhythmias, advanced atherosclerosis, hyperthyroidism, agitated states, history of psychiatric illness including anorexia nervosa and depression, glaucoma, drug/alcohol abuse/dependence. Hypersensitivity.
Orlistat	2.9% to 3.4% at one year [8]	Steatorrhea, oily spotting, flatulence with discharge, faecal incontinence, fat-soluble vitamin malabsorption [8]	Chronic malabsorption syndrome, cholestasis, during pregnancy or breastfeeding, hypersensitivity.
Liraglutide	5.4% at one year [8]	Nausea, vomiting, diarrhoea, constipation. Rare: pancreatitis and cholecystitis [8]	Hypersensitivity.
Naltrexone with bupropion	4.8% at one year [9]	Palpitations, nausea, constipation, vomiting, dizziness, hot flush	Uncontrolled hypertension, seizure, CNS tumour, during alcohol or benzodiazepine withdrawal, bipolar disorder, anorexia nervosa, bulimia, dependence on chronic opioids or opiate agonists, in acute opiate withdrawal, on monoamine oxidase inhibitors, pregnancy, severe hepatic impairment, and end stage renal failure.

2.6 Phentermine mechanisms of action and concerns

Phentermine is a sympathomimetic amine that is chemically related to amphetamine with significant anorectic activity in animal models [10]. Its appetite suppressant effect is generally considered to be mediated by the central actions of releasing catecholamines (ie, noradrenaline and dopamine) in the hypothalamus involving beta adrenergic and dopamine receptors. This results in the activation of the sympathetic nervous system. A secondary effect of increasing heart rate (HR) and blood pressure can be expected. Phentermine has not been associated with central or peripheral effects on serotonin [3].

Due to phentermine having structural similarities to amphetamine there is concern of its addiction potential. Compared to the mechanism of action of amphetamine (which is a non-selective stimulator of noradrenaline, dopamine and serotonin release), phentermine does not release dopamine at a clinically significant quantity [11]. Therefore, it is suggested that there is a low chance of substance abuse or misuse [12]. Hendricks (2014) argues evidence supporting addiction potential in humans is missing in the medical literature and that the theoretical idea of phentermine having addiction potential stems from early animal studies and its negative association to amphetamine [13].

2.7 History of anorectic medicines with an amphetamine analogue

Phentermine was first approved by the US Food and Drug Administration (FDA) in 1959. In New Zealand, phentermine is a grandfathered product and therefore no review of its initial efficacy and safety was required for marketing approval. [14]. Phentermine became popular during the 1980s with its use in combination with fenfluramine due to the outcome of a clinical trial by Weintraub showing this combination achieved greater weight loss compared to its individual components alone. This combination was also known as 'fen-phen' which was considered 'off-label' by the FDA as it had never been approved for use together [15, 16].

By 1997 there were increasing reports of valvular abnormalities on echocardiography in patients on fen-phen. The Mayo Clinic reported 24 cases of heart valve disease linked to fen-phen. There were also reports presented to the FDA from patients that had only taken fenfluramine or dexfenfluramine [15]. As a result, fenfluramine and dexfenfluramine were voluntarily withdrawn from the market due to the major concern of developing endocarditis in the damaged heart valves. This was thought to be due to the effects of these medicines releasing serotonin, and inhibiting its reuptake [8]. Phentermine itself was not withdrawn as it did not have central or peripheral effects on serotonin [3].

Dexfenfluramine and fenfluramines were also associated with primary pulmonary hypertension (PPH) due to effects on potassium channels, and the effects of serotonin on the vasoconstriction of the pulmonary artery and proliferation of smooth muscle cells [17].

Although the association of valve abnormalities and PPH stems from dexfenfluramine and fenfluramine, the possibility of an association between these adverse events and the use of phentermine alone could not be ruled out entirely. There have been rare cases of PPH and valvopathy in subjects who reportedly have taken phentermine alone (although these events were assessed to be unrelated to phentermine) [3].

2.8 New Zealand data sheet [10]

Table 2: Duromine data sheet sections 4.1 to 4.8

Section of the data sheet	Wording
4.1 – Indications	<p>As a short-term adjunct in a medically monitored comprehensive regimen of weight reduction based on exercise, diet (caloric restriction) and behaviour modification in obese patients with a body mass index (BMI) of 30kg/m² or greater who have not achieved an adequate clinical response to an appropriate weight-reducing regimen alone.</p> <p>Phentermine may appropriately be initiated in overweight patients with a lower BMI when risk of morbidity from other medical conditions is increased. Patients with the following co-morbidities are particular candidates for medical assistance with weight reduction, and may be considered for treatment even if their BMI does not exceed 30 kg/m²:</p> <ul style="list-style-type: none"> • sleep apnoea • insulin-resistant diabetes mellitus • pre-diabetes or impaired glucose tolerance in association with obesity • high cardiovascular risk status as a consequence of obesity. <p>Failure to achieve a weight reduction of 5% within a period of 12 weeks is an indication for discontinuation of treatment. Treatment may continue beyond this point provided continued monitoring of the patient occurs (for weight loss and medical conditions) and for as long as weight loss is maintained.</p> <p>Secondary organic causes of obesity should be excluded by diagnosis before prescribing this agent.</p>
4.2 – Dose and method of administration	<p>Adults and children aged over 12 years: one capsule daily at breakfast, swallowed whole. Evening dose should be avoided as this agent may induce insomnia.</p> <p>The usual starting point of therapy is 30 mg daily. For lighter framed individuals or when side effects are evident, the 15 mg strength is the recommended alternative. Maintenance therapy, either continuous or intermittent, can be effectively managed with a dose between 15 mg and 30 mg daily. The recommended dose of DUROMINE should not be exceeded and DUROMINE should not be combined with other appetite suppressants in an attempt to increase the effect. Patients require medical review after a defined course of treatment which ideally should not exceed 3 months.</p>

	<p>Children: DUROMINE is not recommended for children under the age of twelve.</p> <p>Elderly: DUROMINE is not recommended for the elderly.</p>
4.3 – Contraindications	<p>Pulmonary artery hypertension, existing heart valve abnormalities or heart murmurs, moderate to severe arterial hypertension, cerebrovascular disease, severe cardiac disease including arrhythmias, advanced arteriosclerosis, known hypersensitivity to sympathomimetic drugs, hyperthyroidism, agitated states or a history of psychiatric illness including anorexia nervosa and depression, glaucoma, history of drug/alcohol abuse or dependence. Concomitant treatment with monoamine oxidase (MAO) inhibitors or within 14 days following their administration.</p>
4.4 – Special warnings and precautions for use	<p>DUROMINE capsules are indicated only as short-term monotherapy for the management of exogenous obesity. The safety and efficacy of combination therapy with phentermine and any other drug products for weight loss have not been established. Therefore, co-administration of drug products for weight loss is not recommended.</p> <p><u>Valvular heart disease</u></p> <p>Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The aetiology of these valvulopathies has not been established and their course in individuals after the drugs are stopped is not known. There have been no reported cases to date of this valvular condition occurring with the use of phentermine alone.</p> <p>Since the selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline, fluvoxamine, paroxetine), ergot derived drugs and clomipramine affect serotonin metabolism there remains a theoretical risk that combination of these agents with phentermine may also be associated with cardiac valvular disease, although there is no direct scientific evidence to confirm this theory.</p> <p><u>Primary pulmonary hypertension</u></p> <p>Cases of severe, sometimes fatal, primary pulmonary hypertension (PPH) have been reported in patients who have received anorectics. PPH has also been reported in patients receiving phentermine combined with fenfluramine/dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out. There have been very rare cases of PPH in patients who reportedly have taken phentermine alone.</p> <p>The initial symptom of PPH is usually dyspnoea. Other early symptoms include angina pectoris, syncope, lower extremity oedema or the unexplained onset or aggravation of diminished exercise tolerance. Under these circumstances, treatment should be immediately discontinued and the patient referred to a specialist unit for investigation.</p> <p><u>Use with caution in the following circumstances</u></p> <p>DUROMINE should be used with caution in patients with mild hypertension. In the first days of treatment determine that there is no loss of blood pressure control.</p> <p>In patients receiving DUROMINE, response to insulin and oral hypoglycaemic agents may vary due to alterations in dietary regimens. This should be kept in mind if DUROMINE is used in diabetic patients.</p> <p>DUROMINE is not recommended in patients with pre-existing valvular heart disease.</p> <p>Rarely, cases of cardiac and cerebrovascular accidents have been reported, often following rapid weight loss. Special care should be taken to ensure gradual and controlled weight loss in obese patients, who have an increased risk of vascular disease.</p> <p>DUROMINE should be used with caution in patients under treatment with anti-hypertensive agents, since it may cause some loss of blood pressure control, and in patients receiving psychotropic drugs, including sedatives and sympathomimetic agents. DUROMINE should be used with caution in epileptic patients.</p> <p>Inappropriate use of DUROMINE and similar medicines has been reported and the possibility of this occurrence should be considered and patients managed accordingly. As a result patients should be reviewed regularly in the process of their treatment and informed of other measures to effect weight loss.</p> <p>DUROMINE should not be used in men or women for loss of weight for cosmetic reasons. Those who have failed to respond to medical treatment for weight loss in the past should only be treated after review by a medical practitioner specialising in the treatment of weight loss. The ability of the patient to maintain effective lifestyle interventions of exercise and diet, and adhere to a medical regimen should be assessed before treatment is commenced.</p>
4.8 – Undesirable effects	<p><u>Cardiac disorders:</u></p>

	<p>The most commonly reported reactions are tachycardia, palpitations, hypertension and precordial pain. Rarely, cases of cardiovascular or cerebrovascular accidents have been described in patients treated with anorectic agents. In particular stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.</p> <p><u>Nervous system disorders:</u></p> <p>Overstimulation, restlessness, nervousness, insomnia, tremor, dizziness and headache. Rarely euphoria may occur and this may be followed by fatigue and depression. Psychotic episodes and hallucinations are rare side-effects.</p> <p><u>Gastrointestinal disorders:</u></p> <p>Nausea, vomiting, dry mouth, abdominal cramps, unpleasant taste, diarrhoea, constipation.</p> <p><u>Renal and urinary disorders:</u></p> <p>Micturition disturbances</p> <p><u>Reproductive system and breast disorders:</u></p> <p>Impotence, changes in libido</p> <p><u>Skin and subcutaneous tissue disorders:</u></p> <p>Rash, facial oedema</p>
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2.9 New Zealand data sheet – phentermine may be used beyond 12-weeks?

Although the New Zealand Duromine data sheet is indicated as a “short-term adjunct” in obesity, section 4.1 (therapeutic indications) contains a statement suggesting it may be used longer than this –

“Treatment may continue beyond this point provided continued monitoring of the patient occurs (for weight loss and medical conditions) and for as long as weight loss is maintained”.

The above statement is not in the Australian product information [18], or the FDA’s product labelling [19].

During 2010-2012 the European Medicines Agency (EMA) considered the approval of Qsiva (a fixed, low-dose phentermine/topiramate combination product). Qsiva is approved for long-term ≥ 12 months use by the FDA. A concern the EMA raised with the sponsor was that phentermine has historically only been approved for short-term use (less than three months) yet Qsiva could be used for longer [3].

In response to the EMA, the sponsor stated that the historical origin for phentermine having a three month indication were for a variety of reasons, and were not as a result of a safety signal:

- the observations of tolerance developing within the first three months of treatment
- concern regarding potential abuse liability
- the limited or non-existent longer-term data available at the time of approval 53 years ago, based on the regulatory requirements in effect at the time and
- the lack of any incentive to support long-term clinical trials of a generic, non-proprietary drug.

The sponsor further commented that the three month limitation has not been lifted simply because no entity has been willing to fund and conduct the required clinical trials for a generic, non-proprietary drug. The sponsor notes that in ‘everyday medical practice’, US physicians who treat large numbers of patients for obesity routinely use phentermine on a chronic basis, well exceeding the labelled treatment duration of three months [3].

Overall, the EMA refused authorisation of Qsiva for use in the European Union. Please refer to Section 4.1 of this report as to why the EMA refused authorisation [3].

Comments:

There has been a shift in the approach to treating obesity. Weight loss approaches are evolving to favour long-term therapy emphasising that obesity is a chronic disease requiring sustained treatment [20, 21].

Lewis (2019) argues that limiting phentermine use to less than three months does not align with this current concept [20].

2.10 Usage

As phentermine is not a PHARMAC funded medicine there is no usage data.

3 SCIENTIFIC INFORMATION

A literature search was conducted for information on the safety and efficacy of phentermine. Most of the safety and efficacy studies for phentermine were published prior to 2000, with a limited number of studies published between 2000 to 2021. The lack of published studies in the past two decades may be due to the fact that phentermine is now considered an 'older' drug.

The literature search on the safety and efficacy of phentermine found studies to be relatively short in duration (around 12-weeks) and involved small cohorts. Recently there have been studies on the safety and efficacy of phentermine when used long-term (Hendricks 2011 and 2014, and Lewis 2019).

Table 3 below summarises the studies reviewed in this report. Full articles for Weintraub 1984, Kang 2010 and Lewis 2019 are provided as Annex 1-3. Other publications reviewed in this report are publicly accessible.

Table 3: Summary table of studies looking at phentermine safety and/or efficacy

Author (country, year) [RefNo.]	Study design	Population	Study medicine and duration of follow-up	Outcome measure	Efficacy	Safety
Weintraub (US, 1984) [22]	Double-blinded, parallel-group design	81 participants between age 18 to 55 years. Phentermine (n=20, endpoint=14), Placebo (n=20, endpoint=10).	Phentermine 30mg daily vs fenfluramine 20mg three times daily, vs phentermine 15mg+fenfluramine 30mg vs placebo. Duration: 16 weeks, followed by 4-week tapering off. Diet instructed.	Weight loss (kg) at week 20 (16-weeks of drug treatment with diet followed by 4-weeks tapering off).	16-weeks of therapy (endpoint analysis): Phentermine 30mg daily: weight difference from baseline 11.3kg ± 1.4 (SEM) vs placebo 6.2 kg ± 2.1 (SEM), p<0.01. % weight loss from baseline was 11.0% in phentermine treated group	Phentermine, and fenfluramine group had statistically significantly more complaints from all adverse effects, as well as cardiovascular and central nervous system (CNS) effects compared to placebo (p<0.05). Phentermine with fenfluramine reported no difference in all complaints or cardiovascular and CNS adverse effects compared to placebo.
Haddock (US, 2002) [21]	Pooled meta-analysis of published randomised controlled trial's primary efficacy analysis. Years of publication from 1969 to 1992.	Six studies included 386 participants in pooled analysis.	Dosage of phentermine ranged from 15 mg to 30 mg per day. Mean follow-up of 13.2 weeks	Mean difference in weight loss at six months	Mean difference in weight loss at six months = 3.6 kg (CI, 0.6 to 6) compared to placebo. (ie, phentermine users lost 3.6 kg more weight than placebo).	-
Kang (Korea, 2010) [23]	Randomised, double-blinded, placebo controlled	Phentermine 30mg daily for 12-weeks, n=37 (completed=30) Non-treated, n=35 (completed=27). All participants on lifestyle interventions.		Primary endpoint ITT: weight change from baseline. Secondary endpoints ITT: changes in waist circumference, blood parameters, % participants achieving 5% and 10% or more weight loss.	At week 12: <ul style="list-style-type: none"> Phentermine treated group had a loss of 8.1±3.9 kg (p<0.001), and control group loss of 1.7±2.9 kg (p<0.05). Phentermine treated had significantly greater reduction in waist circumferences compared to placebo: 7.2±0.5 cm (p < 0.05) vs 2.1±0.6 cm respectively (p < 0.001). Phentermine: 96.7% lost 5% or more of their body weight and 53.3% lost 10% or more versus 22.2 and 3.7%, respectively, of the placebo group (p < 0.001). 	Heart rate in the phentermine group (2.7±11.4 bpm) had significantly increased outside the normal ranges compared with placebo group (-4.3±12.5 bmp) (p=0.02). Dry mouth and insomnia were the events that occurred significantly more frequently in the phentermine group but were considered mild.

					<ul style="list-style-type: none"> Statistically significant reduction in TG and LDL-C in phentermine compared to placebo ($p < 0.001$). 	
Kim (Korea, 2006) [24]	Randomised, double-blinded, placebo-controlled study.	68 participants of which 35 were randomised to receive phentermine, and 33 to placebo.	A 2-week placebo run-in period followed by either 12-weeks of phentermine 37.5 mg/day or placebo. All participants advised on diet and lifestyle guidelines.	Change in weight, waist circumference, lipid profile, and blood pressure at 14-weeks from baseline. % of participants having ≥ 5 % weight reduction from baseline.	<ul style="list-style-type: none"> 36 participants (68.6% in phentermine group and 36.4% in the placebo group) completed the 14-week trial. Phentermine 37.5 mg was associated with significant weight reduction (-7.1 [SD 2.4] kg for completers and -6.7 [SD 2.5] kg for ITT $p < 0.001$) Shortening of waist circumference (-6.9 [SD 3.3] cm for completers and -6.2 [SD 3.5] cm for ITT $p < 0.001$). No significant differences in systolic and diastolic blood pressure in ITT phentermine group and placebo. Weight reduction of 5% or greater from the baseline (ITT 85.7% vs 16.7% $p < 0.001$, completers 87.5% vs 33.3% $p = 0.002$) and 10% or more from baseline (ITT 50% vs 8.3% $p = 0.001$, completers 58.3% vs 16.7% $p = 0.018$). <p>Only non-HDL cholesterol and total cholesterol had a statistically significant decrease.</p>	Phentermine group had more participants reporting adverse events than placebo. Among all reported adverse events, dry mouth and insomnia events occurred significantly more frequently in phentermine group.
Kim (Korea, 2013) [12]	Post-marketing surveillance study	n=711 for efficacy analysis n=735 for safety analysis	Phentermine 37.5 mg daily or placebo for 12-weeks.	Patients were examined to ascertain adverse effects and efficacy (changes in mean weight, BMI, and blood pressure) for the study duration. Treatment was considered effective if ≥ 5 % loss in body weight.	<ul style="list-style-type: none"> Weight reduction of ≥ 5% from baseline was achieved in 324 patients (45.6%). Compared to baseline $p < 0.001$): mean weight reduction was 3.8 ± 4.0 kg ($5.2\% \pm 5.0\%$ SD) mean BMI reduction was 1.5 ± 1.5 kg/m² ($5.4\% \pm 5.2\%$ SD) mean reduction in blood pressure was 2.6 ± 8.1 mm Hg ($1.9\% \pm 6.3\%$ SD) for systolic pressure and 1.5 ± 6.7 mm Hg ($1.4\% \pm 8.1\%$ SD) for diastolic pressure. 	Adverse events were common (30.6%) – 266 adverse events reported by 218 patients, but none were serious. Of the 735 patients, most common adverse effects were insomnia (11.4%), dry mouth (5.9%) mouth and dizziness (2.7%). 64 patients (9%) discontinued phentermine in this study as a result of their adverse effects.

Ritchey (US, 2019) [25]	Retrospective cohort study	Patients aged > 18 years with ≥6 months of continuous enrolment in the health claim database before taking phentermine and/or topiramate or after stopping these medications.	Phentermine and topiramate, taken separately and together (including fixed dose). 165,737 current use periods contributed to the risk period for 'current' users of phentermine with the average treatment duration of 1.7 months. 472,630 unexposed phentermine periods, averaging 7.9 months.	Crude incidence rates (per 1000 person-years) of MACE, AMI, stroke, and CV-related death among current use periods Adjusted incident rate ratio (IRR) and incident rate difference (IRD) for MACE for current phentermine use period vs unexposed periods.	-	Current use of phentermine was associated with lower rates of MACE compared with the unexposed periods (0.91 events per 1,000 person-years, 95% CI 0.57 to 1.38 vs 2.00 events per 1,000 person-years, 95%CI 1.85 to 2.17). Adjusted IRR and IRD for MACE among current phentermine users remained lower than the unexposed periods (aIRR=0.56, 95%CI 0.34 to 0.91, with an aIRD= -0.62, 95%CI -1.02 to -0.22).
Hendricks (US, 2011) [26]	Retrospective study	US bariatric medicine practice that has employed the use of long-term phentermine for weight management. The duration of phentermine treatment ranged 12-weeks to 12 years (<1 year hiatus was considered continuous treatment)	Phentermine monotherapy with starting dose ranging 15 to 37.5 mg/day – doses adjusted based on response (n=269) vs no pharmacotherapy (n=31). Mean follow-up period 92-weeks, longest follow-up was 416 weeks. All participants were instructed in a very low-carbohydrate ketogenic diet.	The short-term and long-term changes in weight, blood pressure and HR from baseline. As phentermine doses could be adjusted accordingly to response, dose-effect was also examined.	<u>Phentermine treated:</u> Greatest % mean weight loss was at week 26 (n=215) =18.9% (SD 6.5, p<0.0001), and by week 52 =17.6% (SD 7.8, p<0.0001) from baseline. % mean weight loss at week 416 (n=5) was 14.1% (SD 12.5, p>0.05). Systolic blood pressure/diastolic blood pressure (SBP/DBP) declined from baseline at all data points (SBP/DBP =6.9/-5.0 mmHg at week 26, -7.3/-5.4 at week 52, and -5.8/-5.8 at week 104 (p<0.0001)). <u>Untreated:</u> gained similar benefits to phentermine-treated patients over the first year of treatment, but the benefits for this group of patients began to vanish as weight was regained.	HR changes in treated/untreated subjects at weeks 26 (-0.9/-3.5) and 52 (+1.2/-3.6) were not significant. No significant differences in SBP, DBP, or HR comparing patient cohorts at the five dose levels 0 to 75 mg phentermine/day, except for a significant drop in DBP in those on phentermine 18.75 mg group vs no phentermine (P < 0.05).
Hendricks (US, 2014) [13]	Clinical intervention trial with interruption of patients on long-term phentermine. Patients were asked to fill out various addiction	Long-term (minimum 1 year) phentermine users were recruited from an obesity medicine practice. Must not have history of drug dependence other than with nicotine.	n=117 long-term phentermine (minimum 1 year, dose 18.75 to 112.5 mg/day) and	To determine the addiction potential of phentermine	-	Long-term phentermine up to 21.5 years and at doses up to 112.5 mg per day did not induce abuse or psychological dependence (addiction), or drug craving. Abrupt treatment cessation did not induce amphetamine-like withdrawal.

	medicine metric questionnaires.		n=152 short-term phentermine users (4 to 22 days, dose 15 to 93.75 mg/day).			
Munro (US, 1968) [27]	Double-blind, placebo-controlled study	Women aged 21 to 60 years of age. Clinically obese but no evidence of endocrine or cardiovascular disease. Women who were physiologically unstable or experienced troublesome side-effects to amphetamine were excluded.	108 obese women were assigned to receive 1 of 3 treatments: continuous phentermine administration of 30 mg/day, intermittent phentermine administration (4 weeks phentermine, then 4 weeks off), or placebo for 36-weeks in duration. All participants on low calorie diet.	Change in weight (kg) by week 36	By week 36 weight loss was significantly greater (p<0.001) in patients treated with continuous phentermine (12.2 kg) or intermittent phentermine (13.0 kg) than with placebo (4.8 kg). In the last four months of treatment, there was no statistically significant difference between the mean weight in each group (ie, no additional weight loss was seen)	Adverse effects were considered minor: 6 in intermittent phentermine, 4 in continuous phentermine and 2 in placebo group experienced CNS stimulation adverse effects. 8% of drug-treated patients and 3% in the placebo group leaving the study because of perceived stimulant adverse effects.
Lewis (US, 2019) [20]	Retrospective cohort study using US electronic health records.	18 to 64 years of age with a 'first' phentermine dispensing (dose ≤ 37.5 mg per day), BMI ≥ 27 kg/m ² within three months prior to their first phentermine dispensing, no diagnosis of CV outcomes of interest (stroke, MI, angina etc)	Continuous phentermine users (long, medium-term), intermittent user (short, medium-term users) vs short-term one-off users (<112 days)	Efficacy and safety: % change in weight, change in SBP, DBP, HR at 6, 12 and 24 months. Hazard ratio: CV events or death up to 3 years from initiating phentermine	At 24 months the long-term continuous group: <ul style="list-style-type: none"> - Loss 7.36%, n=96 (95%CI, 5.76% to 8.96%) <i>additional</i> weight - HR increased by 2.64, n=96 (95%CI, 0.15 to 5.14) - SBP reduced by 3.31, n=99 (95%CI, 0.76 to 5.85) - DBP no difference Compared to short-term one-off users	No statistically significant difference between short-term one-off users vs other groups were seen in incidence of myocardial infarction, stroke, CVD related interventions, or death.

3.1 Efficacy and/or safety studies with a duration of around 12 weeks

3.1.1 Weintraub et al (1984) – A double-blind clinical trial in weight control: use of fenfluramine and phentermine alone and in combination [22]

Aim: to investigate whether low-dose combination of phentermine and fenfluramine maintained efficacy but with fewer side effects (ie, from higher doses of each therapy), and therefore improving the long-term acceptance of treatment.

Methods: double-blinded, parallel-group design comparing phentermine resin (delayed release) 30 mg daily in the morning, fenfluramine 20 mg three times daily, and phentermine resin 15 mg in the morning with fenfluramine 30mg at night. There was also a placebo group. The regimen for all four groups comprised of a 3-week run-in period of diet only, then 16-weeks of drug treatment plus diet, then 4-weeks tapering off the medicine, and then finally a 4-week follow up without medication.

Scheffe's test for multiple comparison was performed. Data handling for participants who left the study before its completion were: (1) to including dropouts: continuing the last value obtained from a participant as if they had stayed at that weight for the remainder of the study or (2) end-point analysis: including data from each participants only up to the point when the patient left the study.

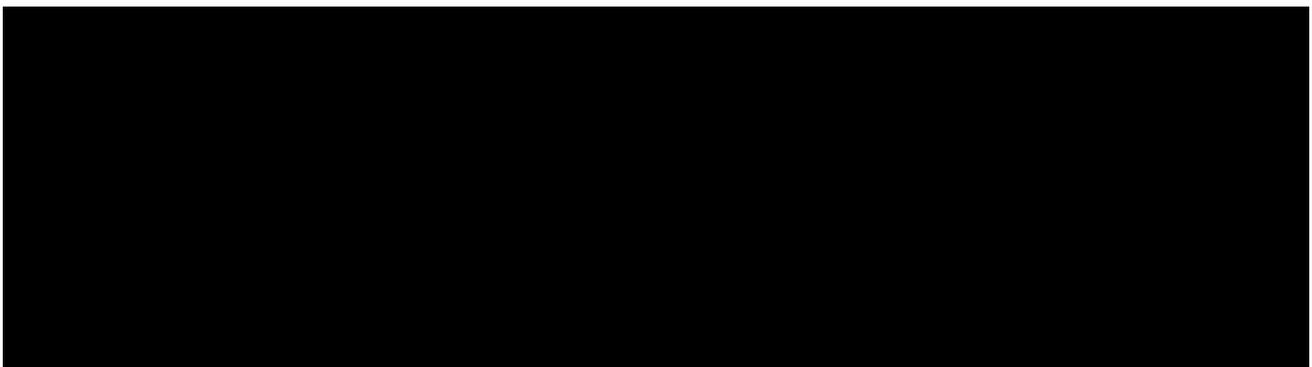
Adverse effects were assessed through open-ended questions and the use of a pre-determined checklist.

Results: 250 potential participants responded to the announcement of the study that was posted in several locations. After initial discussions and assessment, 81 participants were accepted. These participants were between the ages 18 to 55 years of age, and between 130% to 180% of their ideal body weight. They were on no other medications, and did not have diabetes, hypertension or hyperlipidaemia.

Efficacy:

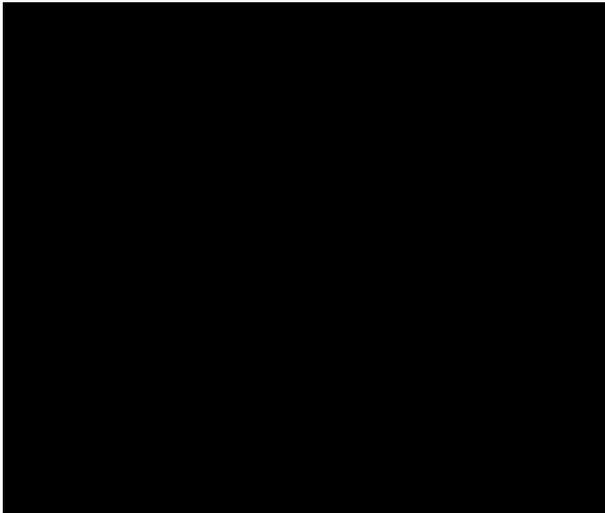
Table 4 below presents the data using the two conventions outline above – dropouts included and end-point analysis. Regardless of how the data was handled, at all time points from week 6, participants receiving phentermine treatment lost significantly more weight than placebo ($p < 0.01$). The weight loss as a percent of baseline weight was 11.0% in the phentermine treated group.

Table 4: Weight loss with time across the four groups.



Week 4 represents just before beginning medication, week 20 represents beginning of medication tapering

Figure 1: Feinsein Reduction Index (FRI) versus time in weeks. Higher levels indicate greater weight loss.

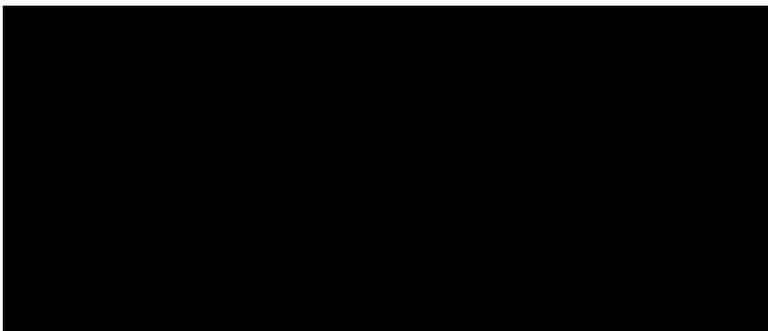


Absolute weight loss on a given hypocaloric diet is proportional to the initial weight. To take this into account, the authors corrected weight loss for initial weight by use of Feinsein Reduction Index (FRI). A higher FRI score indicates a greater weight loss. Figure 1 above shows that participants receiving phentermine had higher FRI scores compared to placebo. There is a sharp increase in the FRI score from week 4 to 12, before the rate of increase slowed after this period.

Safety:

Table 5 below shows the number of adverse effects up to the week in which the study period was completed or the participant left the study. Patients taking phentermine had statistically significantly more complaints from all adverse effects, as well as cardiovascular and central nervous system (CNS) effects compared to placebo ($p < 0.05$).

Table 5: Adverse effects reported (during the 20-week period)



Authors' conclusions: the findings showed that 30 mg phentermine was efficacious in weight reduction when taken for 16-weeks. However, there were statistically significantly more adverse effects for all complaints and cardiovascular and CNS effects compared to placebo in this study.

The limitation of this study was the high dropout rate – almost half of the participants dropped out (this was related to either the participants not losing weight, not wanting to continue, or side effects). Despite the dropout rate, the differences between phentermine and placebo remained statistically significant in both analysis at all time points from week 6. Further to this, the group with the highest dropout rate was the placebo which suggests that proportionally more placebo successes were included in the end-point analysis, making the potential true effect stronger.

Comments:

This study looked at whether half dose combination of phentermine and fenfluramine were synergistically beneficial in weight loss and safe compared to full doses of either medicine or placebo. Fenfluramine has since been withdrawn worldwide so only results related to the phentermine arm are discussed here. The study was published in 1984, so the results may not be generalisable to current time.

The number of participants in each group was small (n=20 for phentermine), and even smaller for those completing the trial.

After the 16-week trial, there was a period of 4 weeks when the medication was tapered off, and participants were then followed for a further 4 weeks without medication. During this period, weight or adverse reactions data was not collected. It would have been useful to see if participants maintained weight and/or had withdrawal effects.

3.1.2 Haddock et al (2002) – Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomised clinical trials [21]

Aim: to provide a comprehensive meta-analysis of anti-obesity medicines and to evaluate their clinical efficacy. Methodological factors (eg, length of treatment, year of publication) were also evaluated to see if they were related to the treatment outcome (ie, weight loss).

Methods: the authors included studies in this meta-analysis for drugs that were FDA approved for obesity at the time. Studies were analysed and group together as 'post-test' (if they occurred at the end of the intact treatment package, where the only outcome provided by the authors, or were designated as a post-test by the study authors).

Several studies continued to monitor the weight of patients past the initial study or post-test. Only the studies that maintained the basic structure of their research design and allowed for 'clean' examination of long-term treatment effects were included in the second part of this meta-analysis.

The effect size (d) is the standardised mean difference based on change scores (reduction in weight).

Results: nine phentermine studies met the study's inclusion criteria. The years of publication ranged from 1969 to 1992. Six studies for phentermine were included in 'post-test', and two studies were included in the follow-up analysis.

Post test

Table 6 presents design characteristics of studies with drug-placebo comparisons. Six studies represent the data for phentermine. The pooled data consisted of 386 participants with a mean follow-up of 13.2 weeks, reported a significantly greater weight loss for phentermine than the placebo (effect size <0.60). There was a mean weight loss of 2.8 kg for the placebo group and 6.3 kg for the group treated with phentermine. The overall placebo-subtracted weight loss averaged 3.6 kg over the study period.

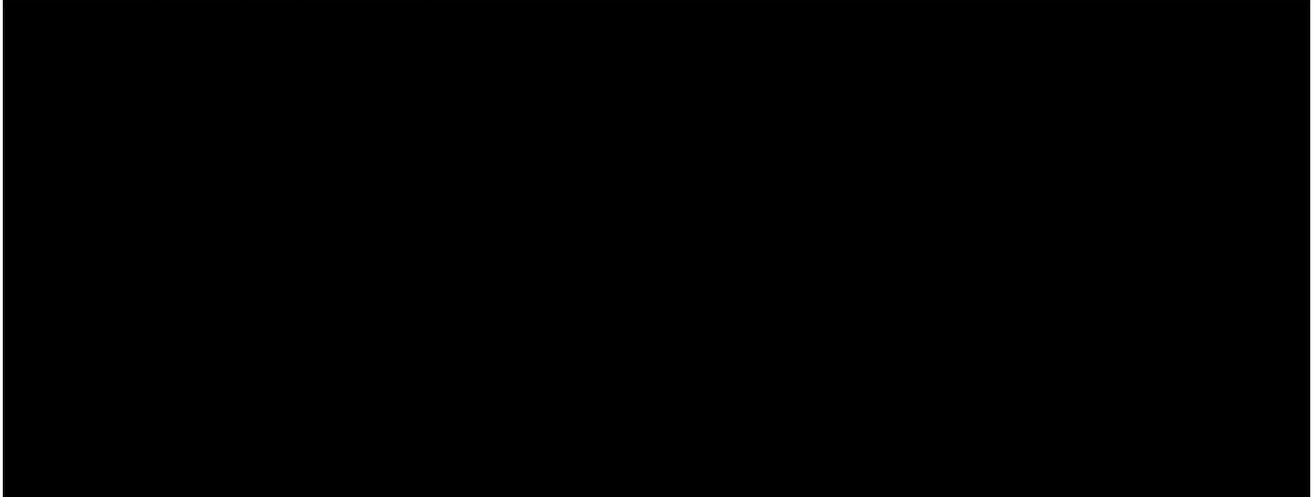
Table 6: Single drug vs placebo – post-treatment outcomesA large black rectangular redaction box covers the content of Table 6.

Figure 2 below shows the effect size and 95% confidence interval (CI) for drug-placebo comparisons. A magnitude $d > 0.80$ was considered a 'large' effect size. When the treatment effect size for phentermine was compared to that obtained for other drugs in the study, the effect size was second only to sibutramine and higher than either orlistat or diethylpropion. However, all confidence intervals overlapped, indicating that the differences in effect size among many drugs were not statistically significant.

Figure 2: Effective sizes and 95% CI of drug-placebo comparisons. High/low lines were not constructed for amphetamine and benzocaine due to insufficient studies (less than 3 studies). Horizontal line at an effect size of 0 represents no treatment effects

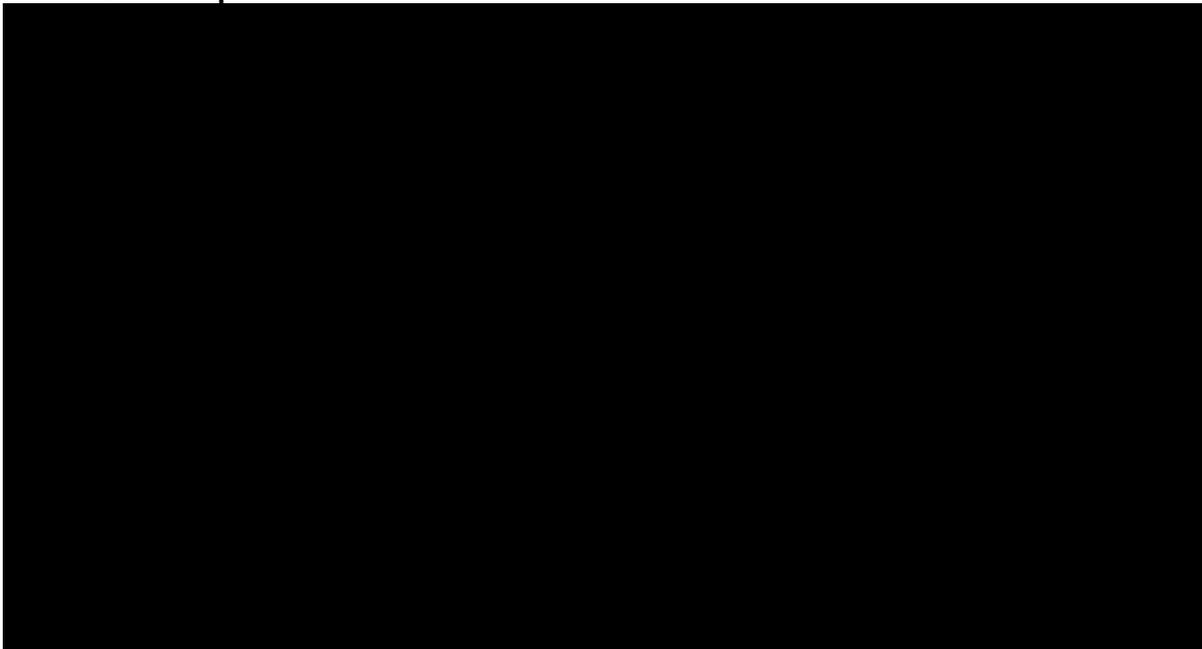


Table 7 shows the relationship between the effect size and the (1) length of treatment and (2) year of publication. The authors decided that a correlation coefficient, r , of 0.30 would be a potentially important indicator of association. A negative correlation meant that participants experienced less weight loss with increasing treatment time or less weight loss in earlier studies.

There were no significant associations between effect size and treatment length for any of the seven drugs examined ($p > 0.05$), although the magnitude of the correlation for phentermine was large (0.685), suggesting that treatment length may influence phentermine's effect size.

Table 7 also presents correlations between the amount of weight (kg) lost in the treatment group and placebo group for the seven drugs. Longer treatment length was associated with greater weight loss, which was true for both drug and placebo groups and the relationships were roughly equivalent (ie $r=0.430$ and 0.395 , respectively, $p<0.001$). In the phentermine group, the treatment length and the amount of weight loss (kg) had a positive correlation meaning this group experienced more weight loss with increasing time, however, this was not statistically significant ($r=0.035$, $p=0.956$).

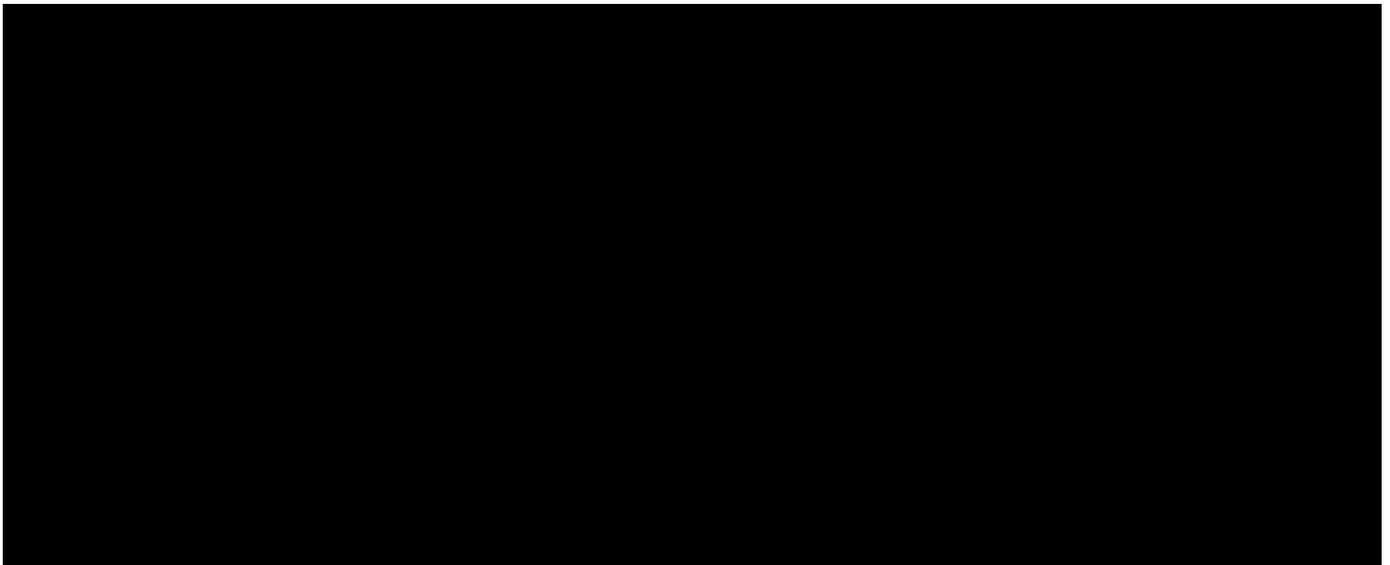
Table 7: Relationship among treatment length and year of publication on post-treatment single drug vs placebo outcomes

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Follow-up

There were two phentermine studies where the research designed remained intact after the formal study was completed (Table 8), though only one study recorded weight loss for individual groups. Phentermine maintained a fairly large placebo-subtracted weight loss of 2.43 kg, with a large effect size, $d=0.810$, even though pharmacotherapy had been discontinued.

Table 8: Single drug vs placebo: follow-up outcomes

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Authors' conclusions: The overall meta-analysis of all drugs showed that the length of drug treatment did not lead to more weight loss, therefore, longer treatments appear to promote weight maintenance, but further weight loss beyond the typical plateau at 6 months is unlikely. The absolute placebo-subtracted weight losses associated with studies of single drugs included in this meta-analysis never exceeded 4.0 kg. Thus, the incremental benefit of obesity drug treatments, in addition to lifestyle interventions, appears to be modest.

Although based on one study, phentermine continued to provide weight loss maintenance during drug-free follow up.

Comments:

Overall, the number of studies and the pooled number of participants were small for phentermine in this meta-analysis which explains the large confidence interval.

It is worth noting that this meta-analysis showed phentermine was less effective than sibutramine. Sibutramine was revoked in 2010 due to the unfavourable balance of the risks and benefits. Please refer to the following link for more information of this revocation:

<https://www.medsafe.govt.nz/hot/media/2010/SibutramineOct2010.asp>

3.1.3 Kang et al (2010) – Randomised controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity [23]

Background: this was a 12-week randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of a newly developed phentermine formulation in obese Korean patients.

Methods: eligible participants were adults 19 years and older, with obesity defined as BMI ≥ 30 kg/m² or participants with a BMI 27-30 kg/m² with co-morbidities (overweight and treated for dyslipidaemia, hypertension or type 2 diabetes). Participants were excluded if they had uncontrolled hypertension ($> 140/90$ mmHg), clinically significant cardiovascular or endocrine disease. Participants with a history of psychological disease or drug abuse were also excluded.

All participants were instructed on lifestyle modifications and were randomised to receive either phentermine 30mg daily or placebo for 12-weeks. Follow up occurred monthly where weight, waist circumference, blood pressure and compliance were assessed. Patients were asked to report any side effects. Blood tests were collected before treatment and at three months of medication.

The primary endpoint was weight change from baseline to the end of the study in the intention-to-treat (ITT) population. Secondary efficacy parameters included change in waist circumference, levels of total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, glucose levels, systolic and diastolic blood pressure and subjects achieving 5% or more and 10% or more weight loss.

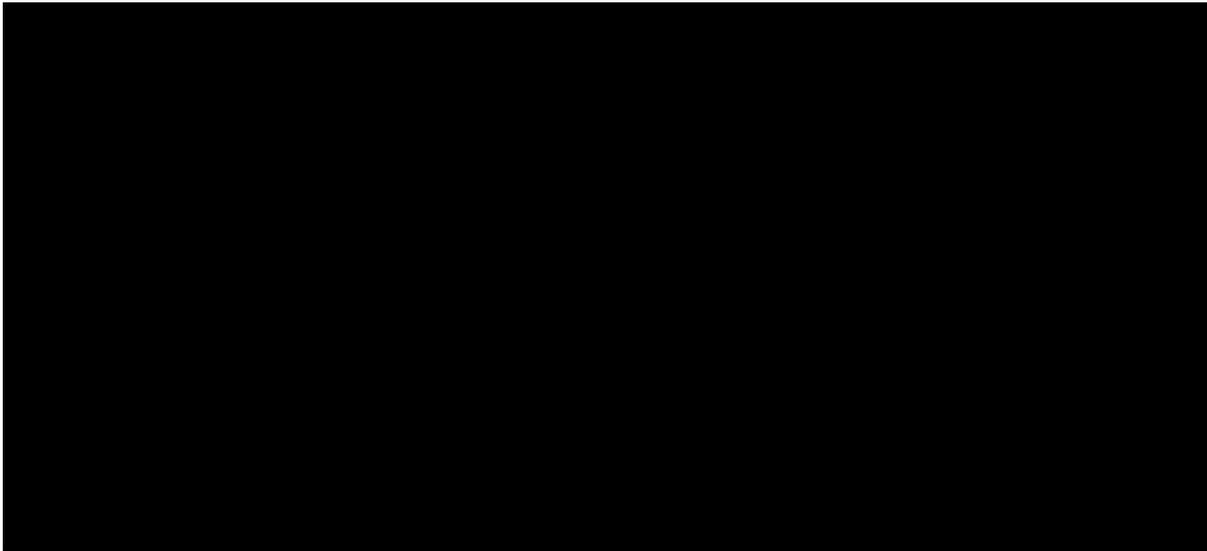
A sample size was estimated to provide 95% power to detect treatment differences of 4 kg with an α -level of 0.05 and assuming a dropout rate of 30%.

Results: at baseline, 37 participants were randomised to receive phentermine (completed=30), and 35 to placebo (completed=27).

Efficacy:

In the ITT population, the mean change in body weight from baseline at week 12 for phentermine treated group was a loss of 8.1 ± 3.9 kg ($p < 0.001$), and a loss of 1.7 ± 2.9 kg in control group ($p < 0.05$). Patients receiving phentermine also had significantly greater reductions in waist circumferences compared with the baseline level (7.2 ± 0.5 cm) ($p < 0.05$) and the placebo group (2.1 ± 0.6 cm) ($p < 0.001$). Figure 3 shows changes in weight and waist circumference with time.

Of the completers receiving phentermine, 96.7% lost 5% or more of their body weight and 53.3% lost 10% or more versus 22.2 and 3.7%, respectively, of the placebo group ($p < 0.001$).

Figure 3: Body weight (A) and waist circumference (B) changes in subjects during the 12-week trial

Data are mean (SE) values for the full intention-to-treat population with the last observation carried forward method. * $p < 0.001$ vs baseline and placebo; † $p < 0.05$ vs baseline; ‡ $p < 0.001$ vs baseline.

Safety:

Metabolic changes in ITT population: the only statistical significant decrease shown between phentermine treated versus placebo at week 12 was TC and LDL-C ($p < 0.001$).

There were no differences in systolic and diastolic blood pressure among the two groups. Heart rate in the phentermine group (2.7 ± 11.4 bpm) had significantly increased outside the normal ranges compared with placebo group (-4.3 ± 12.5 bpm) ($p = 0.02$).

There were 41 adverse events reported during the study period in 25 participants (67.57%) in the phentermine group and 30 adverse events reported in 17 participants (48.57%) in the placebo group. Of the reported adverse events, dry mouth and insomnia were the events that occurred significantly more frequently in the phentermine group but were considered mild.

Authors' conclusions: significant proportion of phentermine treated participants achieved a weight loss of 5% or more compared to lifestyle interventions alone. This shows the initial goal of obesity treatment can be achieved with short-term therapy of phentermine. The authors states that further studies are required, with the need for a larger sample size, diversity in obese population, and to evaluate its long-term safety and efficacy.

3.1.4 Kim et al (2006) – Effects on weight reduction and safety of short-term phentermine administration in Korean obese people [24]

Background: a randomised, double-blinded, placebo-controlled study was performed between February and July 2005 in obese adults in Korea.

Inclusion/exclusion criteria: study was conducted in both sexes, aged 20 years and older with a BMI ≥ 25 kg/m², and without documented health problems except hypertension (if their blood pressure was controlled on anti-hypertensives with a blood pressure $< 140/90$ mmHg) or dyslipidaemia (but not taking lipid-lowering therapy). Participants whose weight changed more than 5% of baseline body weight several months prior to recruitment were excluded. Participants with a history of significant cardiovascular disease, liver, or renal disease were also excluded.

Methods: participants had an initial screening period where baseline bloods (lipid profile and fasting glucose) and anthropometric measurements were taken. Participants were counselled on behavioural modification, diet and how to increase their overall exercise. The study was for 14-weeks, with an initial 2-week single-blind

placebo run-in period. After the 2-week run-in period, participants were randomised to receive either phentermine 37.5 mg once daily or placebo for 12-weeks. They were required to report to hospital every 4-weeks to measure body weight, waist circumference, and blood pressure. Compliance with guidelines and adverse events from treatment were also assessed during visits. Bloods were taken again at the end of the study period.

The data was analysed as intention-to-treat (ITT) and completers.

The differences in the occurrence rate of adverse events between the two groups were only included in the analysis if it were reported in $\geq 5\%$ of subjects in any group.

Results: 68 participants met the inclusion criteria. 35 participants were randomised to receive phentermine, and 33 to placebo. Only 36 participants (68.6% in phentermine group and 36.4% in the placebo group) completed the 14-week trial.

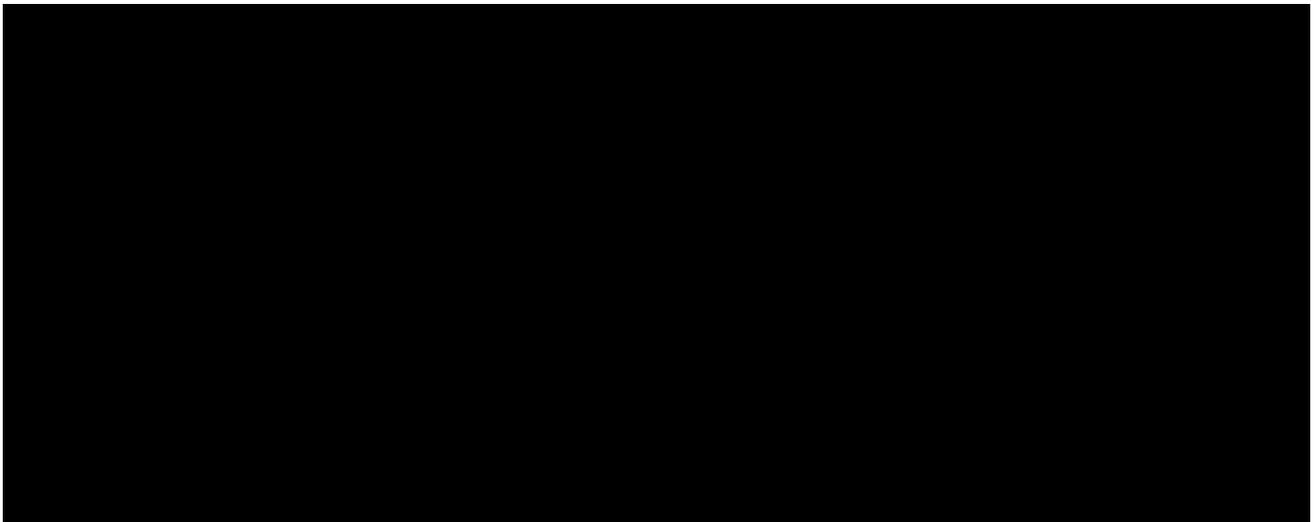
Efficacy:

There was a statistically significantly greater mean reduction in both body weight and waist circumference in phentermine-treated patients compared to placebo ($p < 0.001$). In the ITT population, the mean decrease in body weight from baseline in the phentermine treated group was -7.2 kg (SD 2.7) compared to placebo -1.9 kg (SD 2.7) and waist circumference in phentermine-treated group had a mean reduction of -7.2 cm (SD 3.1) compared to placebo -2.0 (SD 4.0) ($p < 0.001$). (See Figure 4)

The analysis among completers also showed statistically significant decrease in weight and waist change.

With the run-in period subtracted analysis, participants treated with phentermine 37.5 mg was associated with significant weight reduction (-7.1 [SD 2.4] kg for completers and -6.7 [SD 2.5] kg for ITT $p < 0.001$) and shortening of waist circumference (-6.9 [SD 3.3] cm for completers and -6.2 [SD 3.5] cm for ITT $p < 0.001$).

Figure 4: Changes from baseline in (A) body weight, and (B) waist circumference in the ITT population with the last observation carried forward ($p < 0.001$ for phentermine vs placebo)



There were no significant differences in systolic and diastolic blood pressure in ITT phentermine group and placebo ($p = 0.081$ for systolic BP; $p = 0.296$ for diastolic BP), or among the completers ($p = 0.122$ for systolic BP, and $p = 0.219$ for diastolic BP).

A significant number of subjects in phentermine group accomplished weight reduction of $\geq 5\%$ from baseline compared to placebo (ITT 85.7% vs 16.7% $p < 0.001$, completers 87.5% vs 33.3% $p = 0.002$) and 10% or more from baseline compared to placebo (ITT 50% vs 8.3% $p = 0.001$, completers 58.3% vs 16.7% $p = 0.018$).

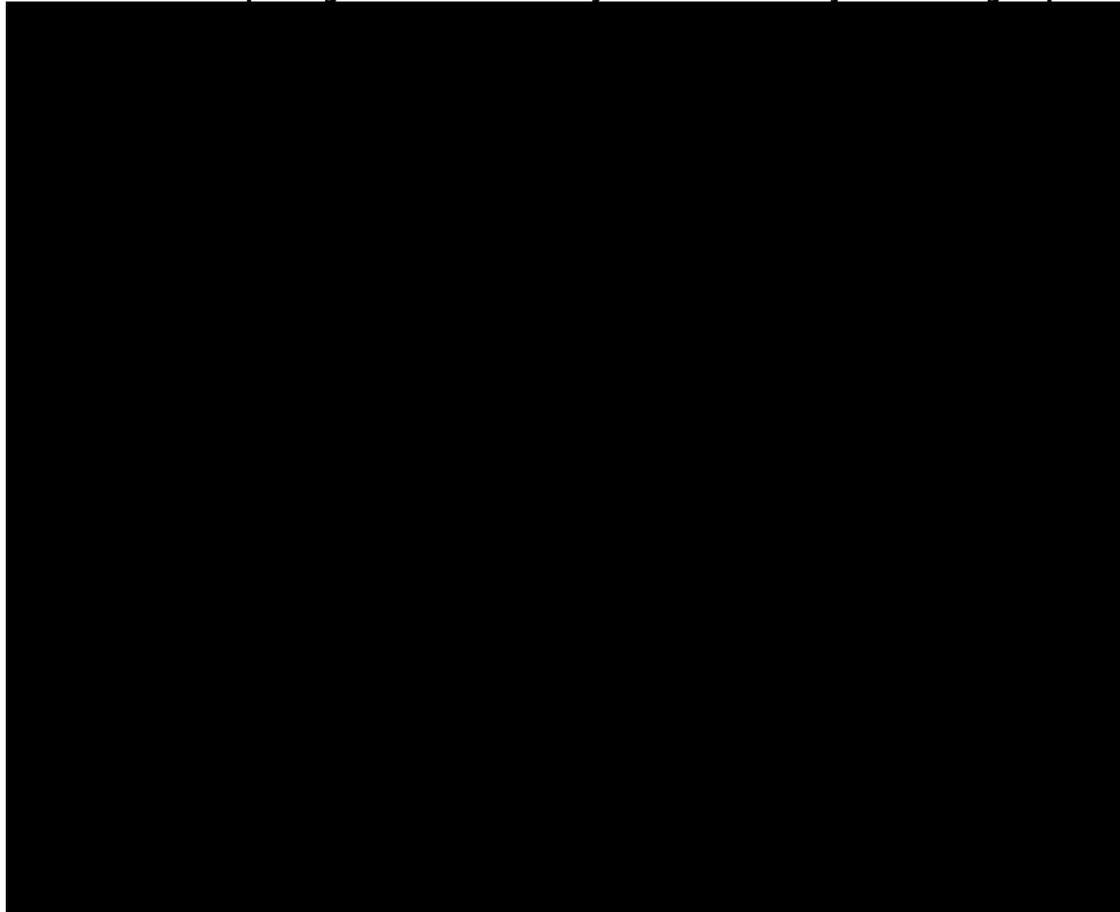
Among the participants that completed the study, the only statistically significant differences in their blood parameters were a decrease in total cholesterol and non-HDL cholesterol compared to placebo.

Safety:

The number of subjects who had reported any adverse events in the phentermine group was significantly larger than that in placebo group (Table 9). Among all reported adverse events, dry mouth and insomnia were the events which occurred significantly more frequently in phentermine group. The occurrence rates of the other adverse events were not significantly different between the groups. For the most part, these events were mild to moderate in intensity, and only a few cases needed to reduce their dose.

Six of 29 participants in the phentermine group complained of palpitation but the number was not significantly different to placebo.

Table 9: Patients reporting adverse events. Only events $\geq 5\%$ in any treatment group is shown



The discontinuation rate was significantly higher in placebo group ($p=0.008$). There was a significant difference in the mean duration of study participation between two groups – 11.0 (SD 4.9) weeks for phentermine group vs. 8.2 (SD 5.3) weeks for placebo group ($p=0.030$).

In phentermine group, 11 of 35 (31.4%) withdrew after run-in period. Seven of the study participants discontinued without any clear reason, and two participants discontinued because of adverse events. One participant withdrew due to no weight losing effect of the drug. One participant discontinued due to the difficulty in following the behavioural guideline.

Authors' conclusions: administration of phentermine 37.5 mg once daily for 12-weeks induced clinically significant weight reduction, shortening of waist circumference, and reduction of total cholesterol and non-HDL cholesterol level compared to placebo. This result would reduce the risk of cardiovascular disease in the ultimate. Moreover, over 80% of subjects of phentermine group lost 5% or more of initial weight and more than half subjects lost 10% or more. This demonstrates most obese patients can obtain the conventional goal of obesity treatment by short-term use of phentermine. Administration of phentermine did not induce any

serious cardiovascular effect at least for the patients whose risk of cardiovascular disease was not high in this study.

Comments:

This study had a dropout rate of 31.4% among the phentermine group which would affect the efficacy. In addition, the study did not perform a power calculation.

Heart palpitations were reported in the phentermine treated group however this was not statistically different between the two groups due the small numbers. Measuring heart rate at baseline and during subsequent visits would have been beneficial to rule out differences between the two groups. It is worth noting that study only included participants with low cardiovascular risk and are therefore less prone to cardiovascular events occurring during the study period.

This study's eligibility criteria included people with a BMI >25 kg/m² (which is the cut-off for obesity for the authors' region). The mean baseline BMI in this study was 29.29 kg/m². Given the cut-off for obesity is 30 kg/m² or greater in NZ, the relevance of this results to obesity management in NZ must be applied with caution.

3.1.5 Kim et al (2013) – Post marketing surveillance study of the efficacy and safety of phentermine in patients with obesity [12]

Background: A post marketing surveillance study on the safety and efficacy of phentermine in obese patients.

Methods: A post-market surveillance database was used to collect data on 795 obese patients who visited 30 primary care physicians in Korea from September 2006 to November 2007.

Patients with a BMI ≥ 25 kg/m² (which is used as the cut-off value for obesity for their region) and had not been administered phentermine were included in this study. Patients who had uncontrolled hypertension (blood pressure $\geq 140/90$ mmHg on antihypertensive medication), diagnosed with glaucoma, or were previously treated for psychological disorders were excluded. Patients who were receiving drugs that would affect body weight (eg, topiramate or selective serotonin reuptake inhibitor) or monoamine oxidase inhibitors were excluded.

Eligible patients were registered at the coordinating centre within a week after their first prescription for phentermine (at a dose of 37.5 mg once daily). Patients were examined to ascertain safety and efficacy at 4, 8 and 12-week follow-up.

The efficacy assessment was performed using data collected from patients who visited the clinic at least once with body weight checked during the study period. Whenever the patients visited the hospitals, they were checked for weight, waist circumference, blood pressure, and medication compliance with a case report form. The criteria for efficacy was defined as a weight loss $\geq 5\%$ of body weight.

The case report form also collected the number of adverse events (AEs), and the reasons for the discontinuation of medication for each patient.

Results: 795 case report forms were collected and used to analyse data from 735 patients for safety and 711 patients for efficacy. Most patients were women and the mean age for the whole group was 35.6 ± 11.1 years, the mean body weight was 94.2 ± 18.3 kg for men and 67.8 ± 11.6 kg for women, and the mean BMI was 31.5 ± 6.0 kg/m² for men and 26.8 ± 4.2 kg/m² for women.

Efficacy:

Of the 711 patients included in the efficacy analysis, 441 patients (62%) completed the 12-week treatment protocol, and 270 patients (38%) discontinued phentermine.

Weight reduction of 5% or greater from baseline was achieved in 324 patients (45.6%).

Figure 5 shows the changes in various parameters after 12-weeks of treatment. Weight, waist and hip circumference, systolic and diastolic blood pressure had statistically significant changes from baseline ($p < 0.001$). The mean weight reduction was 3.8 ± 4.0 kg (or $5.2\% \pm 5.0\%$ SD), mean BMI reduction was 1.5 ± 1.5 kg/m² (or $5.4\% \pm 5.2\%$ SD), mean waist circumference change was -4.1 ± 4.1 cm (or $-4.5\% \pm 4.2$), and the mean change in blood pressure was 2.6 ± 8.1 mm Hg (or $1.9\% \pm 6.3\%$ SD) for systolic pressure and 1.5 ± 6.7 mm Hg (or $1.4\% \pm 8.1\%$ SD) for diastolic pressure.

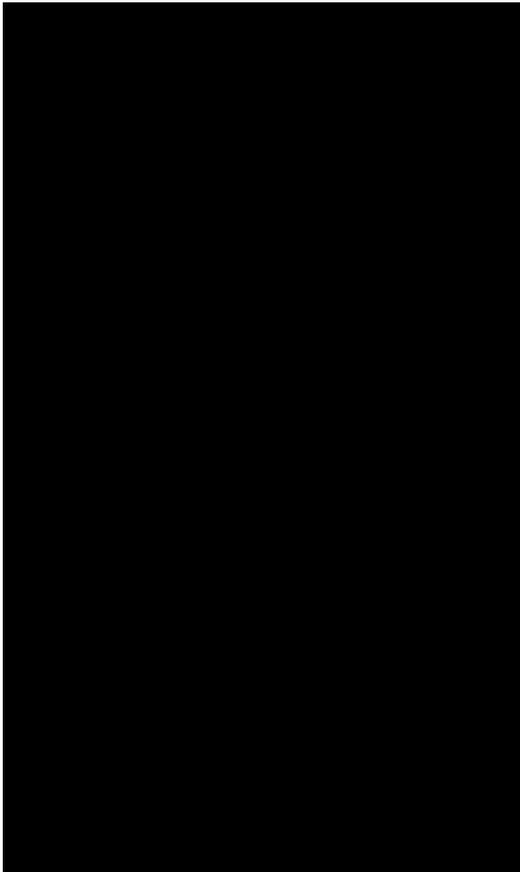
Figure 5: Mean changes (%) of anthropometry variables and blood pressure after 12 weeks of phentermine treatment, * $p < 0.001$ for paired t-test**



The authors expected a rise in blood pressure following the administration of this medicine, but no significant difference in blood pressure was noted. This could be explained by the fact that any increase in blood pressure may have been offset by the loss of weight.

Safety:

735 patients were included in the safety analysis, of which 218 patients (30.8%) reported side effects (266 adverse events) although none were considered serious. Table 10 outlines the adverse events reported. 64 patients (9%) discontinued phentermine in this study as direct result of their adverse event, but no serious adverse events were reported.

Table 10: Adverse events reported by the 735 patients administered phentermine

Authors' conclusions: phentermine is significantly effective for weight loss from baseline at 12-weeks. There were statistically significant reductions in BMI, waist and circumference, and blood pressure. Although patients complained of insomnia and dry mouth, they demonstrated relatively good tolerance to the medication during this period. In order to conquer obesity, which is a chronic disease, obesity medications should be evaluated in terms of their safety and efficacy over the long-term. The authors noted a limitation to the study was that patient information was only collected for three months and therefore the efficacy of phentermine may be overestimated. The authors could not exclude the possibility of underestimating the incidence of mild adverse events due to how this was collected from patients.

Comments:

The proportion of patients achieving a weight reduction of 5% or greater was low compared to other studies.

There were several limitations identified in this study:

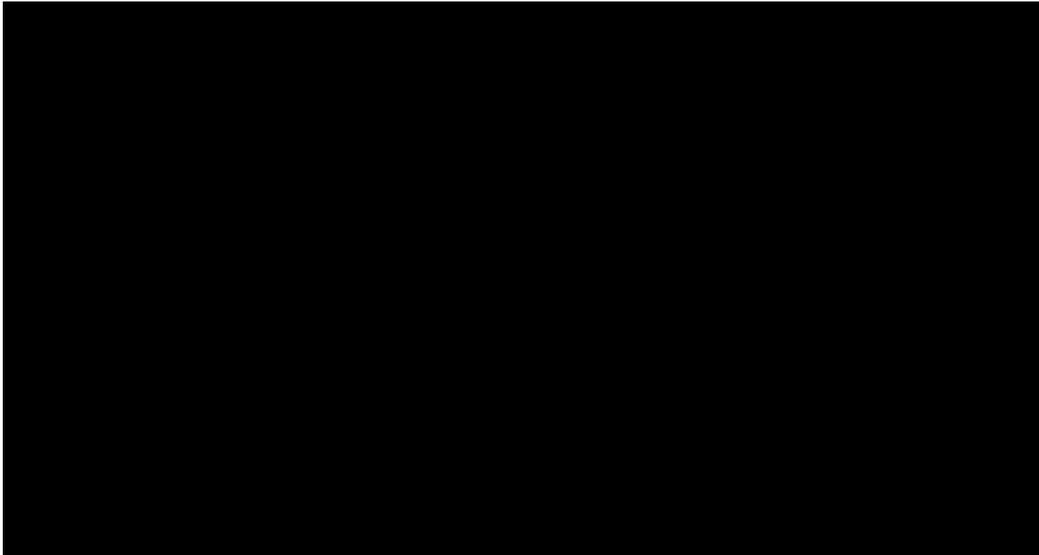
- The study did not have a control/placebo group and demonstrates a low efficacy assessment due to some failure in tracing the enrolled patient.
- Only 62% of patients completed the 12-week phentermine treatment. Nine percent of participants discontinued phentermine because of their adverse event. The authors did not state other reasons for discontinuation such as the lack of efficacy.

The results of this study must be applied with caution in the New Zealand context. The mean BMI among women in the study was 26.8 kg/m² which is considered 'overweight' in New Zealand. Further, the study found a mean systolic blood pressure reduction of 2.6 ± 8.1 mm Hg (or 1.9% ± 6.3% SD), however it is unclear whether this would be clinically significant in reducing cardiovascular and cerebrovascular complications.

3.1.6 Ritchey et al (2019) – Cardiovascular safety during and after use of phentermine and topiramate [25]

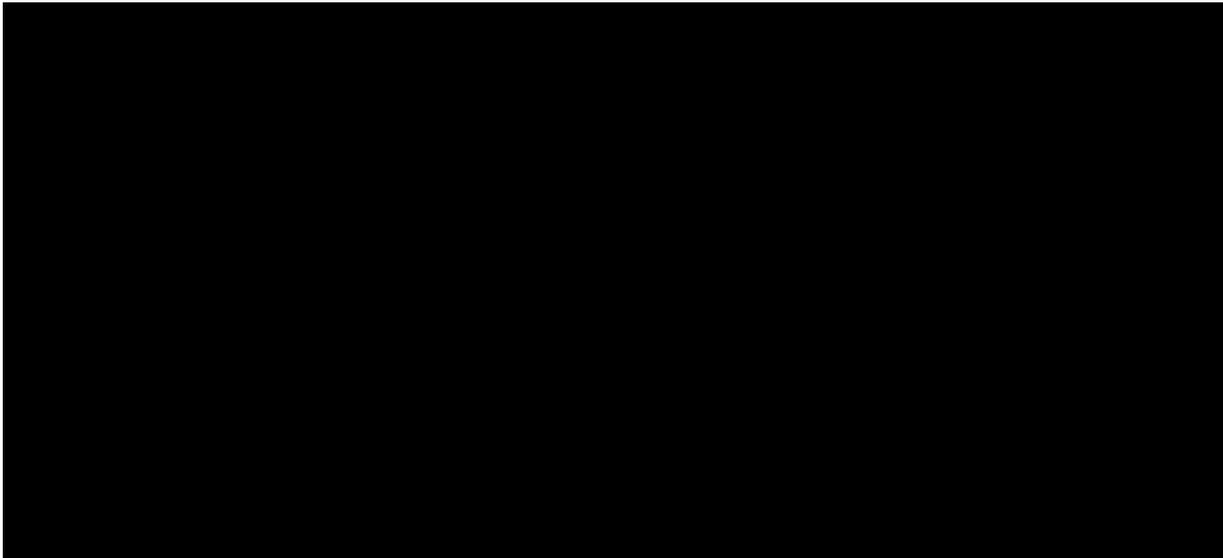
Objective: the aim of this retrospective cohort study was to determine the risk of major adverse cardiovascular events (MACE) during 'current use' period of phentermine, topiramate, phentermine-topiramate (as the two drugs separately and in a fixed-dose combination), versus 'unexposed periods' among former users of phentermine, topiramate or both (see Figure 6 for the schematic of cohorts, and the primary and secondary objectives).

Figure 6: Schematic of cohorts with comparisons



Methods: data was collected from a health claims database in the US. The data span period was between 1 July 2012 to 30 September 2015.

Patients were included in the study if they were aged 18 years and older and had enrolled in the health claims database for 6 months or longer. Patients also had to meet the inclusion criteria as a 'current' or 'former' user of phentermine, topiramate, phentermine/topiramate and/or fixed-dose combination of the two (see Figure 7 below). Depending on the participants medication use, patients could simultaneously contribute time to more than one of these variously defined current-use medication cohorts. For example, patients prescribed fixed-phentermine (PHEN)/topiramate (TPM) contributed to the current-use fixed-PHEN/TPM, PHEN, TPM, and PHEN/TPM medication cohorts simultaneously.

Figure 7: Schematic of risk period

The rates during the 'exposed' periods were compared with the rates among the unexposed periods among former users of the study medications. Because these cohorts are dynamic, with patients moving in and out of them, a given patient could contribute to both current use of medicine and, when no longer taking the medicine, to the unexposed time at risk.

The authors noted the rationale for including the unexposed periods among former users rather than non-users as the referent group was that the cardiovascular (CV) risk is expected to be greater in an obese population than in a non-obese population. However, it was not practical to identify an untreated obese population in the database because of inconsistent coding of obesity. By restricting the comparison rates to periods after the use of PHEN, TPM, or PHEN/TPM, the authors identified a population that was not currently exposed to the medicines of interest (PHEN, TPM) but was expected to have similar CV risk to the obese population currently using these medications.

The crude incidence rates, crude and adjusted incidence rate ratios (IRRs), and crude and adjusted incidence rate differences (IRDs) for each study outcome were calculated separately for current-use periods of each medication and for the unexposed periods.

Propensity score methods were used to control for confounding, and sensitivity and bias analyses were used to see if the results differed.

Propensity score models assessed the effects of each potential covariate on the composite MACE outcomes. The covariates included age at index date, sex, hospitalisation for CV disease, length of hospitalisation, duration of look-back time, comorbidities defined by diagnosis, and history of medication use.

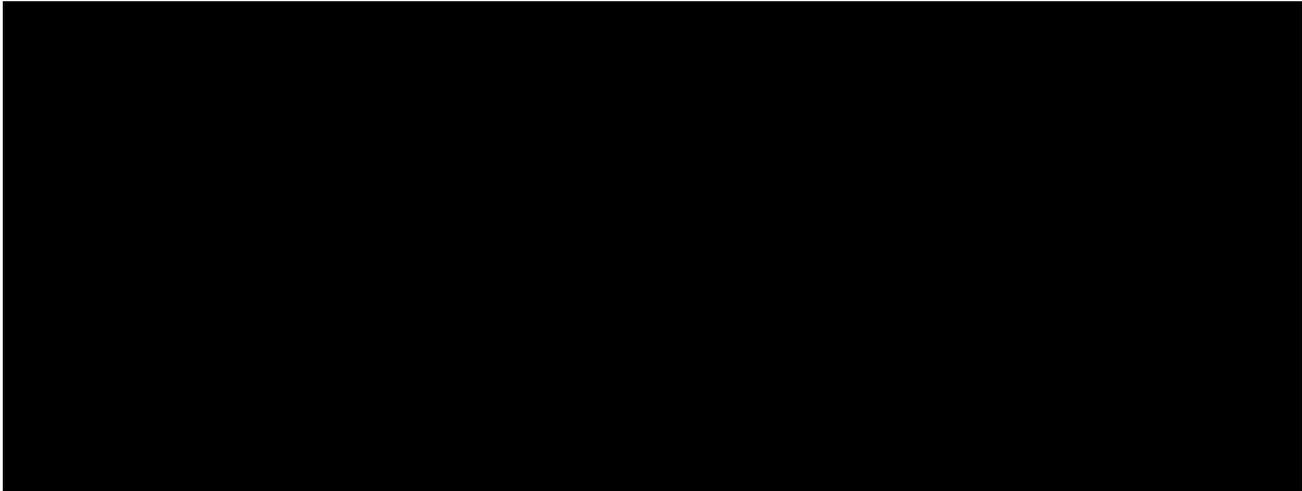
Outcomes: MACE and its components (hospitalisation for acute myocardial infarction or stroke or in-hospital cardiovascular related death).

Results: for phentermine – 165,737 current use periods contributed to the risk period for 'current' users with the average treatment duration of 1.7 months, and 472,630 unexposed periods, averaging 7.9 months.

Crude/unadjusted incidence rates (per 1000 person-years):

Current use of phentermine had lower rates of MACE compared with the unexposed periods (0.91 per 1,000 person-year, 95% CI 0.57 to 1.38 vs 2.00 per 1,000 person-years, 95%CI 1.85 to 2.17) (see Table 11). The rates of acute myocardial infarction (AMI), stroke and CV-related death for current phentermine user were also lower than the unexposed periods. However, it is important to note the number of events were small, producing considerable statistical variability (as evidenced by wide 95% CI).

Table 11: Crude incidence rates per 1,000 person-years and 95% CI for MACE and components of this outcome

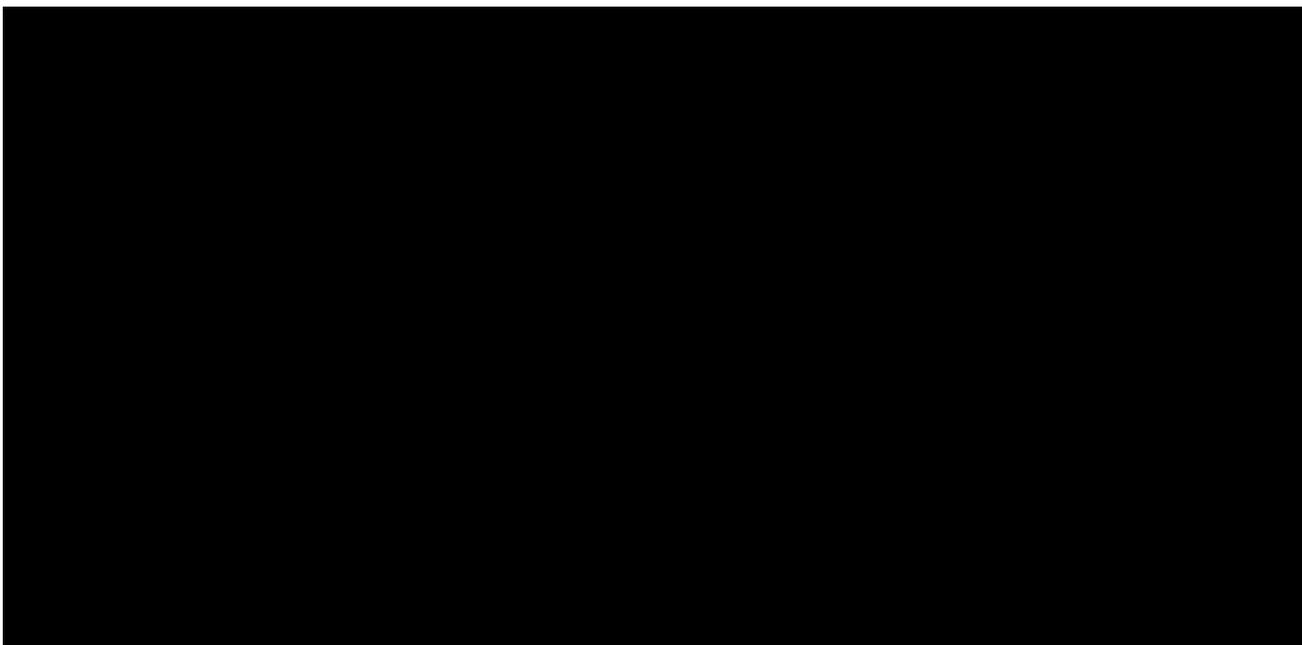
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Adjusted analyses of MACE and individual components:

The number of events and person-years of follow-up after propensity score adjustment and trimming give the adjusted IRRs, IRDs, and 95% CIs for all outcomes outlined in Table 12 below. No substantial differences were found in the adjusted and unadjusted IRRs and IRDs indicating that the net amount of confounding was modest.

The rate of MACE among current phentermine users remained lower than the unexposed periods (adjusted IRRs (aIRR)=0.56, 95%CI 0.34 to 0.91, with an adjusted IRD (aIRD)= -0.62, 95%CI -1.02 to -0.22). Current users of phentermine also had lower rate of AMI compared to unexposed periods (aIRR 0.51, 95%CI, 0.26 to 1.00 with an aIRD=-0.39, 95%CI, -0.68 to -0.10) and stroke (aIRR=0.58, 95%CI, 0.27 to 1.24, with an aIRD=-0.23, 95%CI, -0.49 to 0.03). In contrast, the rate of CV death was similar for current users and the unexposed periods (aIRR=1.03, 95% CI, 0.12 to 8.67, aIRD=0.00, 95%CI, -0.09 to 0.09).

Table 12: Adjusted IRRs and IRDs for MACE and components of this outcome

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Authors' conclusions: This study found lower rates of MACE, AMI and stroke in current phentermine use periods compared to unexposed periods. The rate of CV-related death was similar among the two periods. These findings suggest the absence of large risks of CV outcomes caused by phentermine.

It is worth noting that because CV outcomes are rare, and the duration of medication use was brief, few events occurred which may explain 95% CIs that ranged from strong negative associations to small positive associations.

Comments:

The adjusted IRR for AMI and stroke for current phentermine use periods versus unexposed periods were not statistically significant as exposure was low and for short periods, however the 95% CI leaning towards <1 gives some reassurance that people using phentermine have the same or lower rate of AMI or stroke compared to unexposed periods.

3.2 Efficacy and/or safety studies with a duration > 12 weeks

3.2.1 Hendricks et al (2011) – Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity [26]

Background and objectives: little clinical data has been published on blood pressure and heart rate (HR) changes with phentermine use. The purpose of this retrospective study was to examine patients records in a US bariatric medicine practice that has employed the use of long-term phentermine for weight management. The short-term and long-term effects on blood pressure and HR were measured and analysed.

Methods: patients were selected from the *continuing* patient population of a private medical bariatric practice. Patients were selected if they had existing records of (i) enrolment in a prescribed rigorous weight management protocol, (ii) attendance at a return visit a minimum of six times within 12 weeks of the initial exam, (iii) existing complete vital sign data at seven clinic observation visits that recorded weight, blood pressure, and HR measurements at 0 time, and at 1, 2, 3, 4, 8, and 12 weeks, and (iv) used either phentermine monotherapy or no pharmacotherapy with any obesity drug. All participants were instructed in a very low-carbohydrate ketogenic diet. Patients who were pregnant, had a recent myocardial infarction or uncontrolled hypertension were excluded from the study.

Many patients who met the inclusion criteria had a duration of therapy that ranged from 12 weeks to 12 years. Treatment holidays may have occurred in those taking phentermine long-term, however were included in the analysis if treatment interruption did not exceed one year.

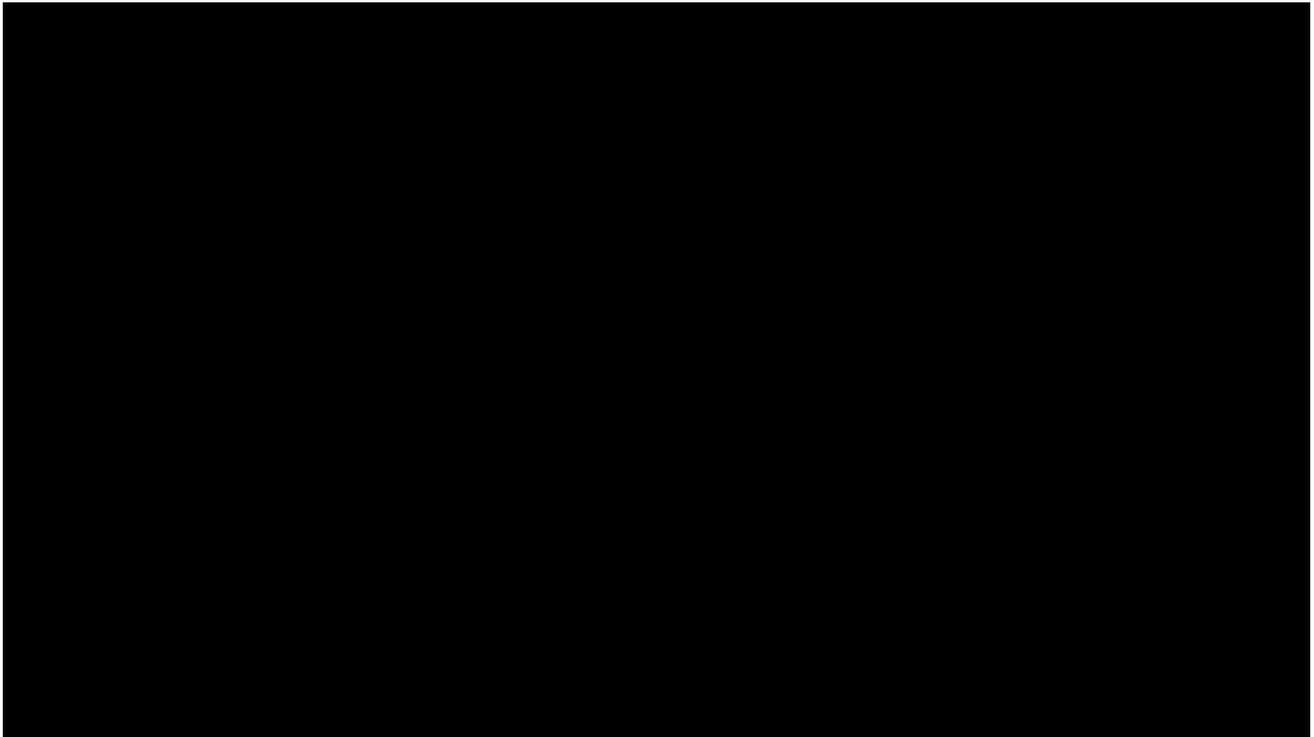
Patients on phentermine were routinely asked about adverse effects at every encounter.

Results: 300 subjects were selected who met the inclusion criteria. 269 subjects met the criteria for pharmacotherapy and elected to include phentermine in their treatment protocol (PT group). 31 subjects were included in the no pharmacotherapy (P0) group. The mean time in therapy was 92 weeks. As time progressed, the drop-out rate increased, particularly after week 12. The author noted this was especially the case in those whose weight loss was less than average.

Patient retention at 26, 52, and 104 weeks for PT patients was 81, 65, and 37%. Patient retention for P0 patients was significantly lower for the same periods at 61, 48, and 16%.

Table 13 and Figure 8 shows the weight loss, blood pressure and heart rate changes in the no pharmacotherapy group (P0) with time.

Table 13: Weight loss, blood pressure, and heart rate changes from baseline in untreated patients P0

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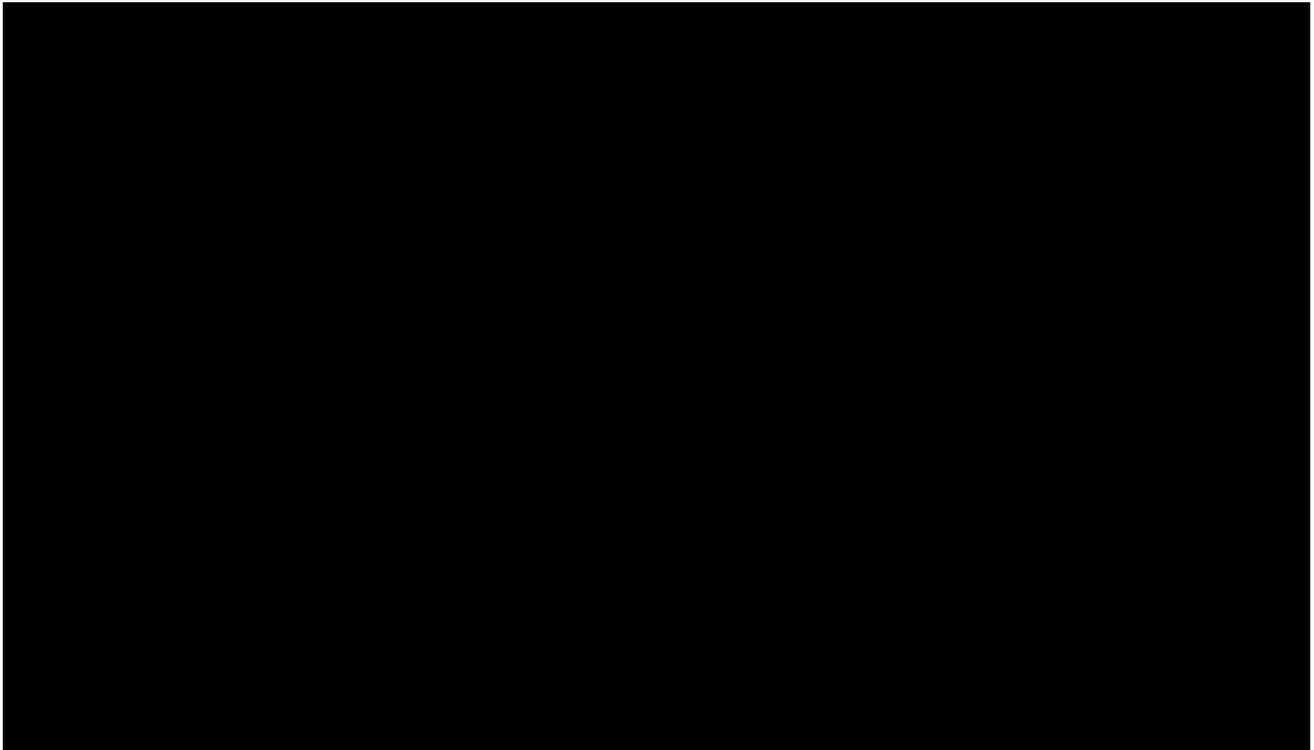
Weight week 52 $P < 0.0001$, week 104 $P > 0.05$, SBP week 52 $P < 0.04$, week 104 $P > 0.05$, DBP week 52 $P < 0.04$, week 104 $P > 0.05$, HR ($P > 0.05$).

Figure 8: %Weight loss, and changes in SBP, DBP and heart rate with time in untreated patients (P0)



Table 14 and Figure 9 below show the weight loss, blood pressure and heart rate changes for phentermine-treated patients (PT) with time.

Table 14: Weight loss, blood pressure, and heart rate changes from baseline for phentermine-treated patients (PT)

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Weight $P < 0.0001$, SBP week 26, 52, 104 $P \leq 0.0001$, and week 156–312 $P > 0.05$, DBP week 26, –156 $P > 0.04$, and week 260–312 $P > 0.05$, HR $P > 0.05$.

Figure 9: %Weight loss, and changes in SBP, DBP and heart rate with time in phentermine-treated patients (PT)



Weight loss and maintenance: Percentage weight loss examined as treatment effect by week over 2 years in the entire data set was significantly greater in the PT cohort ($p=0.0144$). Some patients in the PT cohort continued to maintain a $>10\%$ weight loss for as long as 8 years.

Among the 175 PT patients with data for 1 year, 97% lost 5% or more of their initial weight. In the same group 83% lost 10% or more, 62% lost 15% or more, 32% lost 20% or more, 17% lost 25% or more, 9% lost 30% or more, and 3% lost 30% or more. Among the 15 P0 patients with data for 1 year 80% lost at least 5%, 73% lost 10%, 47% lost 15%, 33 lost 20%, 20% lost 25%, 13% lost 30%, and 7% lost 35%.

Blood pressure changes: The mean SBP and DBP fell in both the P0 group and PT group as patients lost weight. In the PT group, SBP and DBP fell rapidly during the initial 4 weeks of weight loss during which time the average weight loss was 7.6%. Although the average PT subject regained some weight by year 3, the mean weight loss of PT subjects remained at about 10% from year 3 through year 7 and SBP in these patients remained significantly below base line at week 26 ($p < 0.0001$), week 52 ($p < 0.0001$), week 104 ($p = 0.0001$), and week 208 ($p = 0.0186$), below baseline but not significantly at week 156 ($p = 0.1126$) or weeks 260–364 ($p = 0.1037$ – 0.6207) whereas DBP in these patients remained significantly below baseline at weeks 26 ($p < 0.0001$), 52 ($p < 0.0001$), 104 ($p < 0.0001$), 156 ($p < 0.0088$), and 208 ($p < 0.0314$), below baseline but not significantly at weeks 260–364 ($p = 0.5622$ – 0.9576).

In the P0 group, SBP and DBP continued to fall until maximum weight loss occurred at 40 weeks. Although the mean decrease in SBP and DBP was greater in the P0 group than the PT group, the SBP decrease from baseline did not persist as the patients regained their weight reaching baseline values at 104 weeks, even though average weight loss was still 8.4%.

Heart rate changes: The mean HR in the PT group did not change or only slightly increased but this was not statistically significant from baseline. In the P0 group, the mean HR decreased slightly but not significantly as patients lost weight.

Measuring the effect of higher phentermine dose-effect on SBP, DBP and HR with time: The starting dose of phentermine ranged from 15 to 37.5 mg/day in this study. The phentermine dose could be increased or decreased according to response. Phentermine-treated (PT) patients were questioned regarding their appetite side effects at each examination. Phentermine dose was adjusted when side effects were not tolerated or when the dose the participant was on no longer helped suppress appetite. To examine for the possibility that higher doses of phentermine might adversely affect blood pressure or HR, the data for all PT subjects grouped by phentermine dose levels was examined at 52, 104, and 156 weeks. There were no significant differences in SBP, DBP, or HR comparing patient cohorts at the five dose levels 0, 18.75, 30–37.5, 48.75–56.25, and 60–75 mg phentermine/day, except for a significant drop in DBP in the phentermine 18.75 mg group compared to no phentermine ($p < 0.05$).

Side effects:

Patients on phentermine were routinely asked about adverse effects at every encounter. The most common adverse effects were dry mouth and insomnia. The authors noted no other adverse effects were observed in the study group.

The authors identified only one patient who was initially prehypertensive and developed hypertension after taking phentermine continuously for 1 year. Phentermine was continued and blood pressure was controlled with an antihypertensive.

Authors' conclusions: data from this retrospective study suggests that the addition of phentermine pharmacotherapy for patients in a comprehensive weight management programme did not adversely affect HR or systolic/diastolic blood pressure. This study suggests that phentermine can be especially beneficial for the obese hypertensive and prehypertensive patients since persistent weight loss assisted with such therapy may lower blood pressure long-term and retard the progression of prehypertension to hypertension. Some of these patients maintained a weight loss of 10% or greater for as long as 8 years suggesting long-term phentermine pharmacotherapy may be a useful treatment for long-term weight maintenance. The authors acknowledged that as this study was taken place in a well-established clinic comprising of many long-term patients, there may have been bias in subject selection even though criteria were set in place to avoid this bias.

Comments:

This study showed people treated with phentermine had a decline in their systolic and diastolic blood pressure from baseline and these changes remained statistically significant with time until week 104 and week 208 respectively. Heart rate changes were not statistically significant from baseline with phentermine

use at any time during treatment. Weight loss was significantly greater in the phentermine cohort for week 1 through to week 104 ($p=0.0144$).

The P0 patients who adhered to diet alone without phentermine treatment garnered similar benefits to PT patients over the first year of treatment, but the benefits for the P0 patients began to vanish as they regained weight whereas PT patients' benefits persisted. PT patients also had slightly better initial weight loss.

The small number of participants, particularly after week 156 ($n=59$) among the PT group was a limitation.

3.2.2 Hendricks et al (2014) – Addiction potential of phentermine prescribed during long-term treatment of obesity [13]

Background and objectives: phentermine-induced addiction and adverse cardiovascular reactions are two fears that have profound negative impact on phentermine prescribing. The aim of this study was to examine if psychological dependence, abuse, craving and withdrawal occur in obese patients receiving long-term treatment with phentermine. The authors state to date, there have been no published reports that phentermine treatment for obesity has been associated with abuse or physiological dependence as defined by the DSM-IV TR.

Methods: patients were recruited from a private fee-for-service obesity medicine specialty practice. This practice usually prescribes anti-obesity drugs over a long-term period. Patients were recruited for the long-term phentermine-treated (LTP) cohort if they had been treated with phentermine for a minimum of 1 year, while patients for the acute-term phentermine (ATP) cohort were recruited after they had been on phentermine for 7–14 days. Patients with dependence on drugs other than nicotine were excluded.

To determine the addiction potential of phentermine, several validated addiction medicine metrics were used. Some of these metrics were designed to assess other drugs of dependence but we modified in this study to assess phentermine:

- The Mini International Neuropsychiatric Interview (MINI): a structured interview guide for making a DSM-IV-TR diagnosis such as substance dependence and abuse
- The Severity of Dependence Scale (SDS) to assess the severity of substance dependence
- The Phentermine Craving Questionnaire NOW (PCQ-NOW) which was modified from the Cocaine Craving Questionnaire NOW to assess phentermine drug craving
- The Phentermine Withdrawal Questionnaire (PWQ) which was modified from the Amphetamine Withdrawal Questionnaire to measure the severity of phentermine withdrawal in addicted subjects based on ten major symptoms (eg, dysphoria, anxiety, motor retardation, agitation, fatigue, hyperphagia, hypersomnia) found to occur in amphetamine-addicted subjects after abrupt withdrawal.

ATP patients were tested once in the clinic with SDS, PCQ-NOW upon recruitment.

LTP patients were tested in the clinic with MINI-SUD, SDS, PCQ-NOW and PWQ. PWQ was tested three times – patients were instructed to continue to take their usual dose of phentermine until 1 day prior to their next office visit when they were to skip their phentermine, and self-examine with the PWQ (D1) at ~24 h after their last phentermine dose at home. They were instructed to skip their phentermine again the following day, the day of their scheduled office visit. Upon arrival at the clinic they were again tested with the PWQ (D2) at ~48 h after their last dose of phentermine, after which they resumed phentermine treatment.

Results: there were 152 participants in the ATP cohort and 117 participants in the LTP cohort. Duration of treatment among the ATP cohort varied slightly with a median value of 8.0 days. More striking were the variations in duration of treatment in the LTP cohort ranging from 1.1 years to 21.1 years with a median value of 7.2 years.

- The Mini International Neuropsychiatric Interview (MINI): 100% of the LTP MINI-SUD examinations were negative for either phentermine abuse or psychological dependence

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- The Severity of Dependence Scale (SDS) to assess the severity of substance dependence (a higher score means higher severity): the mean scores from the LTP cohort were slightly higher than the ATP cohort's mean score, but this was not statistically significant. Majority of SDS total scores in both ATP and LTP were 0 or 1, corresponding to answering 'never' or 'sometimes' respectively. This indicated that LTP and ATP patients were not psychologically dependent on phentermine.
- The Phentermine Craving Questionnaire NOW (PCQ-NOW): was low for all LTP and ATP patients, indicating neither short-term or long-term phentermine treatment had induced phentermine craving
- The Phentermine Withdrawal Questionnaire (PWQ) which was modified from the Amphetamine Withdrawal Questionnaire to assess the severity of phentermine withdrawal in addicted subjects based on ten symptoms. Hyperphagia was the only withdrawal symptom significantly noted, however, this represents a loss of phentermine therapeutic effect rather than an amphetamine-like withdrawal symptom. If hyperphagia was not taken into account, the nine-item PWQ total scores obtained from the three time points when the questionnaire was administered were not significantly different.

Authors' conclusions: the findings suggests that long-term phentermine pharmacotherapy for obesity for up to 21.5 years and at doses up to 112.5 mg per day does not induce abuse or psychological dependence (addiction), that long-term phentermine pharmacotherapy does not induce phentermine drug craving, and that abrupt treatment cessation does not induce amphetamine-like withdrawal.

Comments:

While this study provides some evidence that phentermine can be used safely in patients without prior addiction or dependency issues, it would need to be replicated in large patient cohorts and in patients with history of dependency to gauge the addiction potential of phentermine in this group. Addiction clinicians in NZ note that phentermine is sought disproportionately by patients with addiction difficulties, frequently for reasons that do not reflect a management weight control programme [28]. Therefore, the applicability of these results must be applied with caution within the New Zealand context.

3.2.3 Munro et al (1968) – Comparison of continuous and intermittent anorectic therapy in obesity [27]

Background: this study examines the long-term (36-weeks) use of phentermine in terms of safety and efficacy through a double-blind, placebo-controlled study.

Methods: 108 obese women who were assigned to receive one of three treatments: continuous phentermine administration of 30 mg once daily, intermittent phentermine administration (4 weeks phentermine, then 4 weeks off), or placebo for 36-weeks in duration. All participants were on a low carbohydrate diet of approximately 1,000 calories per day. Participants were asked to attend the clinic every four weeks where weight was measured and adverse effects questioned. If participants did not report within a week of their appointment, they were excluded from the trial and therefore the analysis.

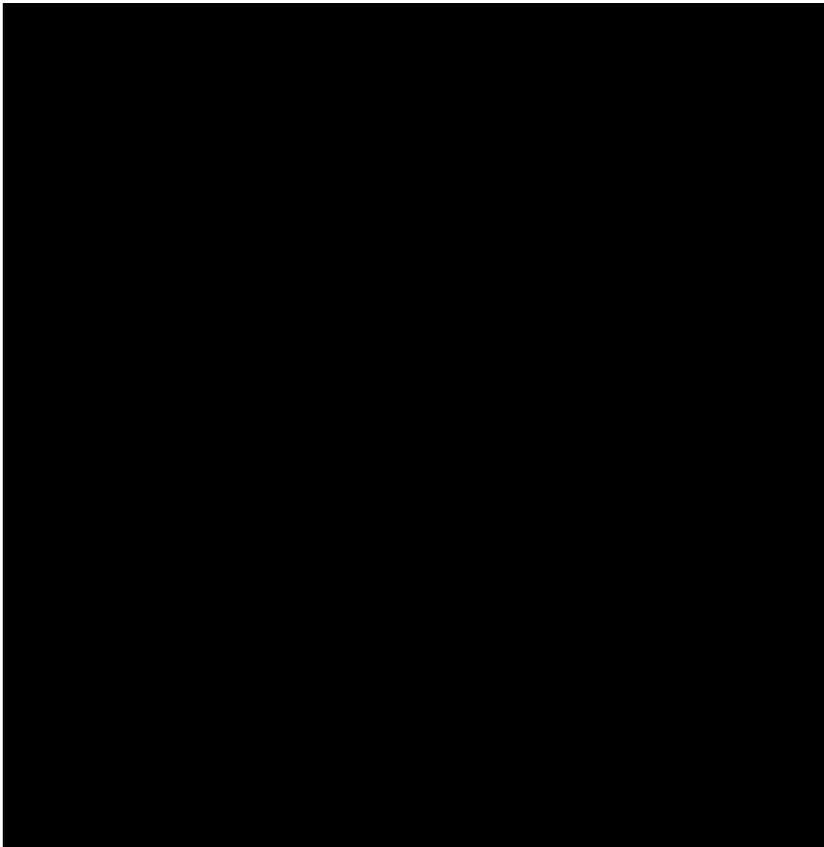
Results: only 64 of the 108 participants completed the full trial (59%). There were 25 participants that completed the placebo, 17 participants that completed the continuous phentermine regimen, and 22 participants that completed the intermittent phentermine regimen. The efficacy and safety analysis shown only includes data from those who completed the study.

Weight loss was significantly greater ($p < 0.001$) in patients treated with continuous phentermine (12.2 kg) or intermittent phentermine (13.0 kg) than with placebo (4.8 kg). In the last four months (from week 20) of treatment, there was no statistically significant difference between the mean weight change in all three groups of patients (ie, no further weight loss was seen).

Figure 10 shows the weight loss in pounds with time of the three groups, and the reported subjective effects during the study period. Adverse effects were considered minor. Six patients in the intermittent group, four in the continuous group, and two in the placebo group experienced CNS stimulation side effects (agitation, anxiety, tension or insomnia). This represents 24% receiving continuous vs. 27% receiving intermittent

phentermine therapy, compared with 8% in placebo. 8% of drug-treated patients and 3% in the placebo group left the study because of perceived stimulant adverse effects.

Figure 10: Among the completers: weight loss (in pounds) with time among the three groups. The table below shows the subjected adverse effects reported



Authors' conclusions: individual response to weight loss varied but irrespective of the method employed, further weight loss diminished with duration of treatment. There seems to be no advantage to taking phentermine continuously or intermittently. Since intermittent therapy was as effective and possibly safer, the authors concluded that further clinical trials are required to find out how anorectic medicines can best be used.

Comments:

The authors recruited women who were 'clinically obese and overweight' by 'at least 20% of their standard'. Individual BMI of participants was not recorded at baseline. Only % over standard weight was recorded. It would have been helpful to know the mean BMI or the percentage of participants who were obese or overweight to see if this study was predominately treating people obese or overweight.

This study restricted women to approximately 1,000 calories/day, which may be considered extreme.

The data presented is for completers only, which is likely to overstate efficacy. In addition, it is likely those who respond and lose weight early in the study are more likely to stay on and continue the full trial and be included in the study's efficacy analysis.

3.2.4 Lewis et al (2019) – Safety and effectiveness of long-term phentermine use: clinical outcomes from an electronic health record cohort [20]

Background and objectives: most studies examining phentermine monotherapy have been limited to a treatment duration of 12 weeks. The aim of this retrospective cohort study using US electronic health records

from data across several integrated health insurance and care-delivery system was to study whether adults prescribed phentermine for longer than 12 weeks experienced differential weight loss, change in blood pressure (BP) or heart rate (HR), or increased risk of incident CVD (cardiovascular disease) or death compared with adults prescribed phentermine in an on-label short-term episode.

Methods:

Inclusion/exclusion criteria: the study included patients 18 to 64 years of age with a 'first' phentermine dispensing (dose \leq 37.5 mg per day) between 1 January 2010 and 30 September 2015. Patients were required to have a BMI \geq 27 kg/m² within three months prior to their first phentermine dispensing. Patients were excluded if they had a history of bariatric surgery, cancer diagnosis, pregnancy at baseline year, use of other weight-loss medicines, or had diagnosis or procedure codes for any cardiovascular outcomes of interest (myocardial infarction, stroke, angina, coronary artery bypass grafting, carotid artery intervention).

Classification of treatment groups:

The referent group was defined as short-term single users of phentermine (individuals with one phentermine treatment episode lasting \leq 112 days and no subsequent use during follow-up). This was compared with:

- Continuous users = medium-term continuous users, and long-term continuous users.

Intermittent phentermine treatment

As individuals may take phentermine intermittently over time, to capture these individuals and allow for follow-up beyond the first treatment episode, two additional groups were created:

- "short-term intermittent" users and
- "medium-term intermittent" users.

The duration of phentermine use for each user group can be found in the footnote of Table 15.

The authors treated phentermine use as a *time-varying exposure*. A patient's inclusion in a particular exposure category was dependent on their exposure pattern up to the time point of interest, meaning that patients could change exposure categories over time. For example, at the 6-month mark, the authors could not yet classify anyone as being in the long-term continuous group because less than a year of phentermine exposure had elapsed. Therefore, these individuals were included in their medium-term continuous group for 6-month analyses, only separating out as a distinct group after 12 months of continuous exposure to phentermine.

Outcome measures

Drug effectiveness was calculated as percent change in weight from baseline, measured at 6, 12, and 24 months after initial phentermine dispensing.

Systolic and diastolic blood pressure, and heart rate changes were extracted from outpatient reports, selecting the nearest measure per window at the 6, 12 and 24 months follow-up.

Cardiovascular risks were incidents of myocardial infarction, stroke, angina, coronary artery bypass grafting, carotid artery intervention, or death and this was looked at up to three years from initiating phentermine.

Results:

Weight change:

Figure 11 below shows the estimated % mean weight change (loss) at 6, 12 and 24 months after phentermine initiation. The mean weight loss for short-term single users by 6 months after drug initiation (or 3 months after discontinuing phentermine) was 2.7% (95%CI, 2.1% to 3.3%) total weight loss. By 12 months, weight loss was 1.4% (95%CI, 0.7% to 2.1%), and by 24 months, the weight change in this group was not different from zero.

Overall, at 6, 12 and 24 months after phentermine initiation, weight loss was greater among all medium/long-term groups and short/medium-term intermittent users than the referent group (short-term single use phentermine).

At 24 months after phentermine initiation, long-term continuous users (>12 months use) had a mean weight loss of 7.5% from baseline (or 7.36% (95%CI, 5.76% to 8.96% *additional* weight was loss compared to short-term single phentermine users).

Figure 11: Estimated percent weight loss at 6, 12 and 24 months after phentermine initiation

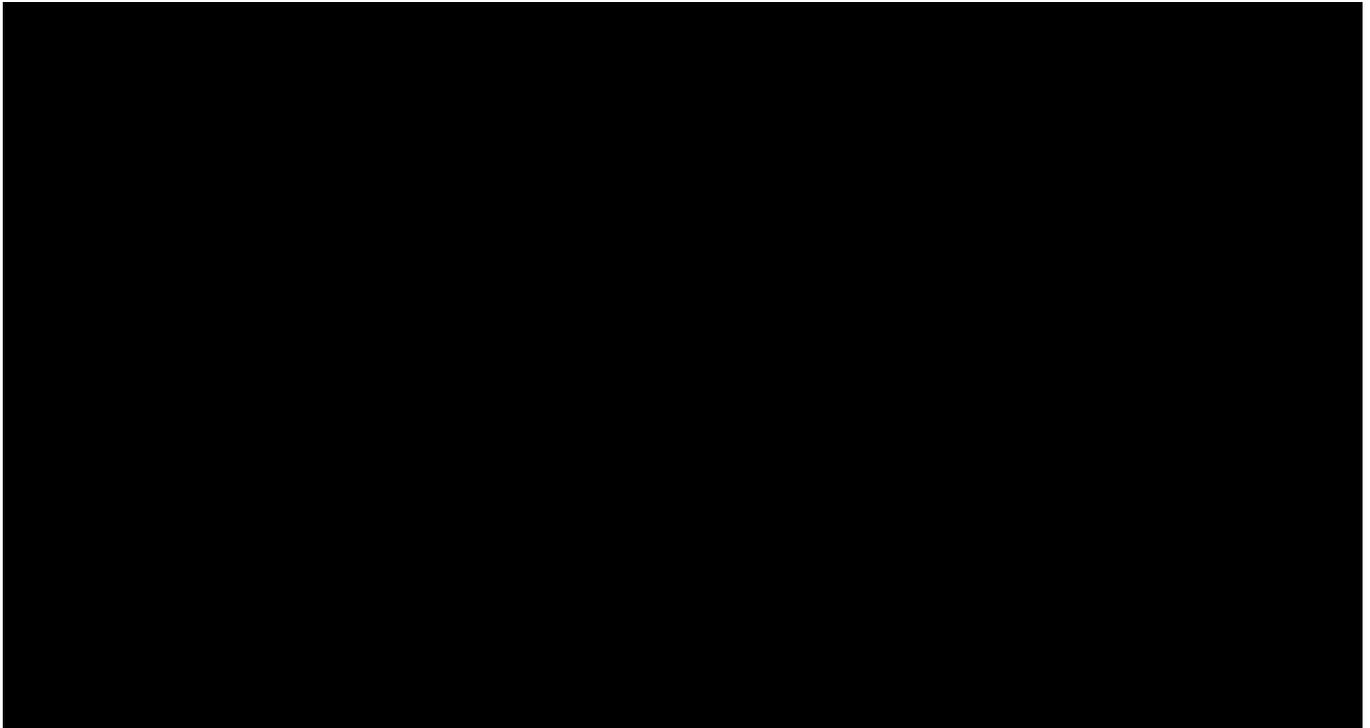
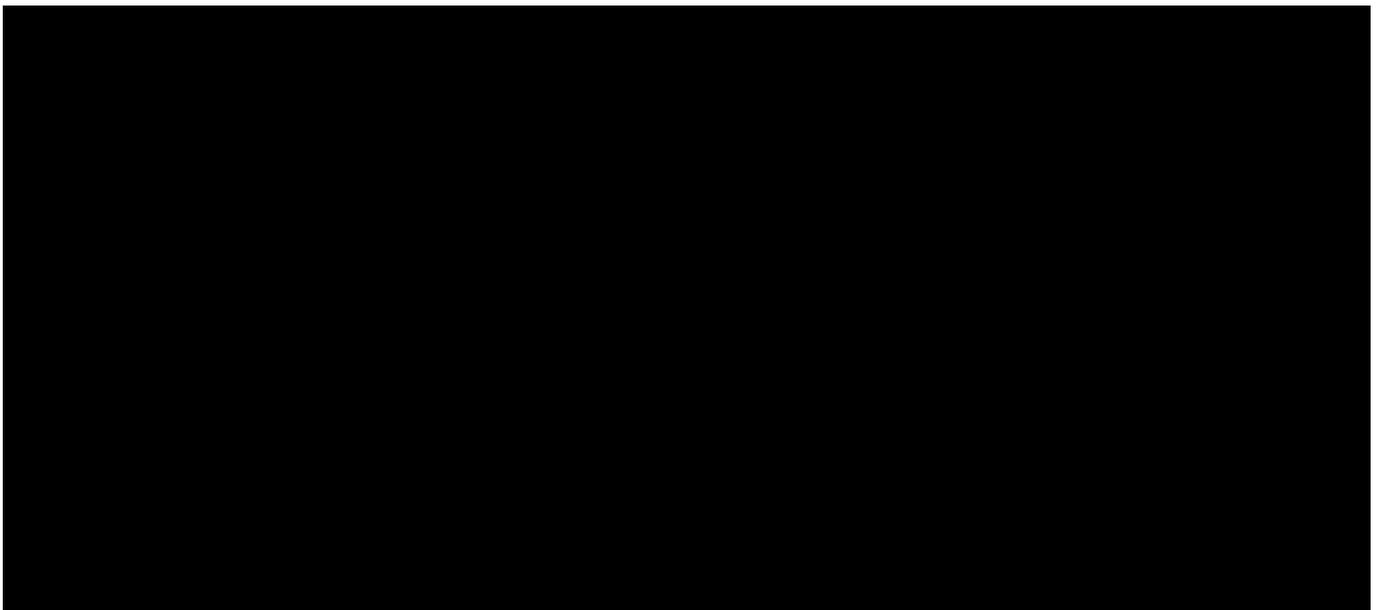


Table 15 below shows the additional weight loss change compared to short-term single phentermine users (intercept parameter).

Table 15: *Additional* weight loss change compared to short-term single phentermine users



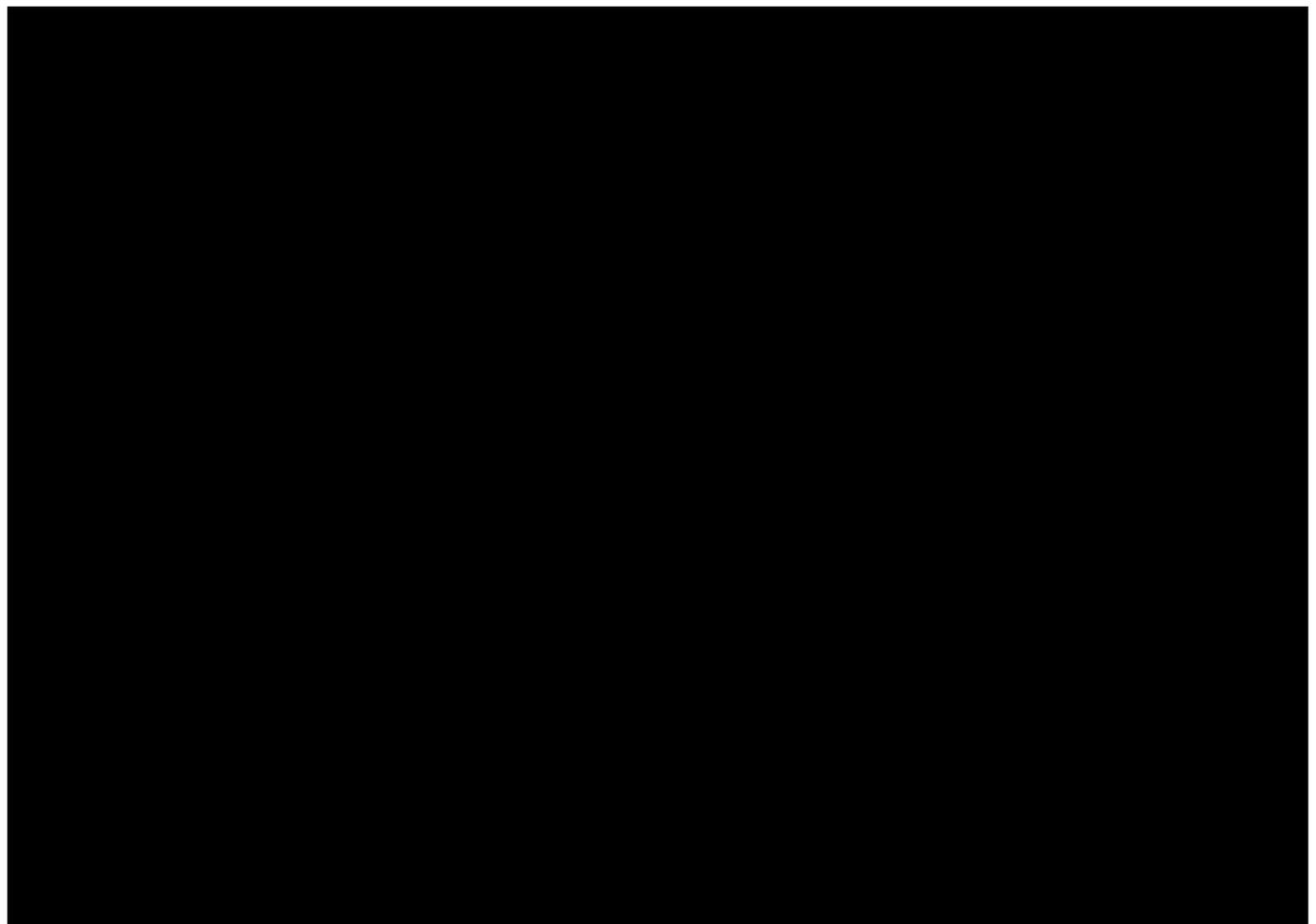
Blood pressure and heart rate changes:

Table 16 outlines the changes in heart rate, and blood pressure with time among the different groups.

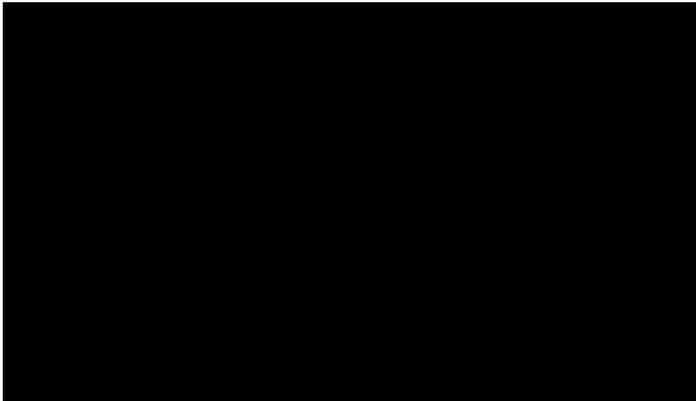
Patients in the short-term single phentermine group had no significant changes in HR at 6, 12 or 24 months. The greatest relative HR increase in the 6 month follow-up was in medium-term continuous users where mean HR was 1.61 (95% CI, 0.99 to 2.24) bpm higher than the referent group; at 12 month follow-up it was the medium-term continuous users with mean HR 1.16 (95%CI, 0.28 to 1.92) bpm higher than the referent group; and in the 24 month follow-up period, long-term continuous users had a mean HR that was 2.64 (95%CI, 0.15 to 5.14) higher than the referent group.

SBP in the referent group was stable at 6 and 12 months, but at 24 months, it had increased by 1.83 (0.48 to 3.19) mmHg, relative to baseline. There was no between-group difference in SBP change at 6 months; however, the comparison groups on the whole had slightly lower BP than the referent group at 12 and 24 months, again with variability in magnitude of difference by group.

DBP in the referent (short-term) group was stable relative to baseline at 6, 12, and 24 months, and there were no significant between-group differences in DBP over follow-up.

Table 16: Changes in heart rate, blood pressure at 6, 12 and 24 months follow up period*Three-year cardiovascular risk:*

Up to 3 years after initiating phentermine, the incidence of composite adverse outcomes was low. Forty-one people out of 13,972 (0.3%) experienced an event. Multivariable Cox regression models treating phentermine use as a time-varying covariate found no significant difference in risk of incident CVD or death between groups ($p=0.30$) (Table 17).

Table 17: Results from multivariable Cox models^a: hazard ratio for composite outcome of incident myocardial infarction, stroke, CVD intervention, or death up to three years after phentermine initiation

Authors' conclusions: In this large cohort study, a longer duration of phentermine use was associated with clinically significant greater weight loss up to 2 years after initiating medication, with no observed increase in risk for incident cardiovascular events or death over 3 years of follow-up. Discontinuation of phentermine consistently resulted in weight regain. The authors observed a slight increase in average HR among phentermine users that normalised after discontinuation. The decrease in SBP associated with longer-term phentermine use, despite phentermine being a sympathomimetic may be attributed to greater weight loss, resulting in a net-lowering effect.

Limitations outlined by the authors:

- The authors note that their referent group likely includes patients who discontinued phentermine because of ineffectiveness, and their comparison groups contained people who remained on medication, conversely because it was effective for them. The authors conducted a sensitivity analysis on this and this confirmed their suspicion.
- This study looked at dispensing data and may not fully indicate compliance.
- Study did not look at other medications the patient was on that could attribute to weight loss/gain and changes in BP or HR (ie, topiramate, metoprolol). Only FDA approved weight loss medicines were censored
- Cardiovascular events and death are rare outcomes and require long-term follow up. This study excluded patients with existing cardiovascular disease.

Comments:

The results showed long-term phentermine had sustained weight loss, with SBP reduction. There was a small increase in heart rate compared to short-term referent users. The authors did not discuss whether this small increase in heart rate would be clinically significant in increasing cardiovascular harm.

4 International regulatory review and action

4.1 European Medicines Agency (EMA) [3]

Prior to 1995, phentermine was authorised nationally in the EU for treating obesity. However following a class review of various anorectic agents, concerns in relation to the use of these agents were raised specifically regarding the lack of therapeutic efficacy when assessed on the basis of accumulated scientific knowledge acquired over the years. There were further concerns of the safety profile of phentermine containing products and the potential risk of cardiac valve disorders with phentermine monotherapy, risk of primary pulmonary hypertension, and other serious cardiovascular and CNS adverse reactions such as dependence. Following the

review, the use of phentermine was significantly reduced. Phentermine does not have approval in most member states of the EU to this day.

Between 2010 to 2012, the EMA considered the application Qsiva (a fixed, low-dose phentermine/topiramate combination product) for approval. The addition of low-dose topiramate is thought to cause weight loss from increased energy expenditure, decreased energy efficacy, and decreased caloric intake.

In 2012, the Committee for Medicinal Products for Human Use (CHMP) considered the application and decided not to approve Qsiva. The benefit-risk balance was considered negative based on the:

- Lack of long-term cardiovascular safety of Qsiva had not been established, and the current cardiovascular outcome data for Qsiva is considered inconclusive
- Concerns with phentermine’s mechanism of action as it has sympathomimetic properties including cardiac stimulation and increased heart rate.
- Phentermine has only been approved for short-term period of treatment (less than three months) and its long-term cardiac toxicity is unknown.
- Concerns around long-term topiramate use and psychiatric and cognitive effects, and their consequences are unknown.
- The teratogenic risks of Qsiva when used in less controlled, real-life setting.

4.2 International Information

[Redacted text block containing international information]

Table 18: New Zealand reports of cardiovascular, cerebrovascular or psychiatric events where phentermine was the suspect or co-suspect medicine

Reaction class of interest	CARM ID	Age in years	Sex	Reaction(s)
Cardiovascular events	001988	30	M	Hypertension aggravated
	019970	27	M	Heart block
	036394	UNK	UNK	Atrial fibrillation
	130689	49	F	Tachycardia and hypotension
	130766	40	F	Chest pain
	135732	41	F	Cardiomyopathy and cardiac failure
	136731	20	F	Chest pain and tachycardia
Cerebrovascular events	017090*	41	F	Cerebrovascular disorder
	074943	UNK	M	Cerebral infarction
	139240	46	F	Stroke
Psychiatric events	087280	39	F	Psychosis
	115389*	44	F	Psychosis and schizophrenic reaction
	120442	20	F	Psychosis and violent thoughts
	120677	20	F	Psychosis
Cases where there was more than one event of interest reported	006067	49	F	Thinking abnormal and tachycardia
	117859	38	M	Cardiomyopathy, thrombosis cerebral vascular arterial, ejection fraction abnormal, and atrial fibrillation.
	123511	26	F	Tachycardia and paranoid reaction.
	131022	24	F	Depression, agoraphobia, and palpitation.

*phentermine was listed as a co-suspect medicine. UNK = unknown.

6 DISCUSSION AND CONCLUSIONS

Overview

Phentermine is indicated as a short-term adjunct in weight loss with exercise, diet and behavioural modification in obese patients. It may also be considered in overweight patients with certain co-morbidities.

Phentermine has been on the market for over 50 years and therefore there have been limited safety and efficacy studies published in recent decades. With the recent interest in newer anti-obesity agents becoming available and phentermine now a generic medicine, it is unlikely that any industry-sponsored trials will be conducted in the future.

The evidence for the safety and efficacy of phentermine when used short-term relies on a limited number of clinical trials that date prior to 2000. These studies were small in cohort sizes.

Only one clinical trial examining the long-term safety and efficacy of phentermine monotherapy has been identified.

Efficacy

Within its current approved treatment duration (12-week use), the clinical trials identified indicated that phentermine can produce a modest weight loss. Studies have shown that patients can lose around 3.6 to 4.8 kg of additional weight compared to lifestyle interventions. More recently, the concept of losing 5% or more in body weight has been considered clinically significant as relevant decreases in certain risk factors associated with obesity have been seen with loss at this threshold. Studies by Kang 2010, Kim 2006 and 2013 have shown a higher proportion of patients achieving this whilst on phentermine for a 12-week period. However, it should be noted that all of these clinical studies included very small numbers of subjects and in a comparator trial phentermine was less effective than sibutramine.

Safety

As phentermine is a sympathomimetic amine, there have been concerns with its effect on blood pressure and heart rate. Concerns have also been raised with its potential to increase the risk of cardiovascular and cerebrovascular events. In addition, because of its structural similarity to amphetamine it is thought there may be potential for abuse.

Contrary to the idea that phentermine can increase blood pressure, studies by Kim 2006 and 2013, Hendricks 2011, and Lewis 2019 have demonstrated a decrease in blood pressure with phentermine use. This may be attributed to the fact that as patients lose weight, their cardiovascular profile improves.

Ritchey 2019 found lower rates of MACE, AMI and stroke among current phentermine users compared to unexposed periods. The rates of CV-related deaths were similar across both groups, however due to CV events being a rare outcome the confidence interval was wide.

A study by Kang 2010 found that heart rate in phentermine treated patients had significantly increased outside the normal ranges compared with placebo in their 12-week clinical trial.

Long-term efficacy

With the exception of Munro 1968 demonstrating that weight loss was maintained when phentermine was used over a 36-week period, no longer randomised controlled trials looking into the long-term safety and efficacy of phentermine have been identified. Observational studies by Hendricks 2011 and Lewis 2019 observed weight and systolic blood pressure and these continued to be significantly lower than baseline for up to two years, however the number of participants included in their follow-up at the two-year mark was small (n<100).

Hendricks 2011 observed people on a strict low-calorie diet had similar benefits to those treated with phentermine over the first year. However, the benefits began to vanish as they regained weight whereas the phentermine group benefits persisted.

Long-term safety

Lewis 2019 identified that long-term use (up to two years) was associated with a statistically significant increase in heart rate while Hendricks 2011 found a slight increase in heart rate, but this was not statistically significant compared to the untreated cohort.

Lewis 2019 found no observed increase in risk for incident cardiovascular disease or death over 3 years of follow-up however it was noted that these events are rare with the period this was follow up for.

Limited research was identified regarding the addiction potential of phentermine. Hendricks 2014 looked at the long-term addiction potential of phentermine but found no concerns of this. It is worth noting that participants in this study did not have prior substance abuse issues and therefore caution needs to be applied in the New Zealand setting where phentermine is sought disproportionately by patients with addiction

difficulties, frequently for reasons that do not reflect a management weight control programme. CARM has not received reports of abuse or misuse of phentermine to date.

There does not appear to be any information on rare side effects with either short or long-term use as all of the study information found included small number of subjects.

Individual risk benefit balance

The individual decision to initiate phentermine should be based on the discussion of the benefits of a modest weight reduction and the risks of potential adverse effects. The current data sheets adequately highlight contraindications and precautions the prescriber must consider before initiating a patient on phentermine to ensure a potential positive benefit-risk profile when used in the approved patient population. The data sheet states that phentermine is contraindicated in moderate to severe arterial hypertension, cerebrovascular disease, severe cardiac disease, advanced atherosclerosis and a history of psychiatric illness and drug/alcohol abuse or dependence. This mitigates the risk of individuals who may be at a high risk of cardiovascular, cerebrovascular or psychiatric events.

Population risk-benefit consideration

The benefits phentermine has of achieving a weight loss of 5% or more and therefore improving the cardiovascular profile must be weighed against the paucity of clinical trial evidence, the sympathomimetic effects, and other pharmacological and non-pharmacological interventions available for weight-loss.

7 ADVICE SOUGHT

The Committee is asked to advise on:

- The evidence for efficacy and safety.
- Whether the benefits of treatment with phentermine outweigh the risks of harm?
- Whether further actions need to be taken, which could include for example a statutory benefit-risk review, updates to the data sheet to manage identified risks?
- Further communication is required other than in MARC's Remarks?

8 ANNEXES

Annex 1 – Weintraub et al 1984

Annex 2 – Kang et al 2010

Annex 3 – Lewis et al 2019

Annex 4 – CARM data

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