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Review

Obesity pillars roundtable: Phentermine – Past, present, and future

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A B S T R A C T

Background: Phentermine is a sympathomimetic amine, approved for "short-term"treatment of patients with obesity. Among phentermine contraindications include use in patients with cardiovascular disease or patients with uncontrolled hypertension.
Methods: This roundtable discussion includes perspectives from 3 obesity specialists with experience in the clinical use of phentermine. The questions asked of the panelists were derived from publications regarding phentermine safety and efficacy.
Results: While the panelists generally agreed upon core principles of phentermine use, each obesity specialist had their own priorities and style regarding the administration of phentermine. Among the variances in perceptions (based upon their individual "real world" clinical experiences) included the degree of efficacy and degree of clinical benefit of phentermine, degree of concern regarding phentermine use in patients with cardiovascular disease risk factors, the advisability of a screening electrocardiogram, and the role of telehealth in prescribing phentermine and monitoring for the efficacy and safety of phentermine.
Conclusions: Providing universal guidance regarding phentermine treatment for obesity is challenging because of the lack of long-term, prospective, randomized, placebo-controlled, health outcomes data. Such data is unlikely forthcoming any time soon. Also challenging are the substantial variances in governmental restrictions on phentermine use. Therefore, clinicians are left to rely on the best available evidence, their individual practical clinical experience, as well as the collective clinical experiences of others – as reflected by this roundtable.

1. Introduction of the panelists

Dr. Bays: Hello. My name is Dr. Harold Bays. I am Editor-in-Chief of Obesity Pillars [official journal of the Obesity Medicine Association (OMA)], and Chief Science Officer of the OMA. Today, I am serving as moderator for this "Obesity Pillars Roundtable: Phentermine: Past, Present, and Future."

In today's roundtable discussion, we will be discussing the efficacy, safety, and practical tips regarding the use of phentermine for treatment of patients with obesity. With the possible exception of different perspectives regarding ketogenic diets [1–6], few therapies generate more varied opinions than the role of phentermine in management of obesity. As such, I will begin with a disclaimer that, irrespective of the OMA leadership position of the roundtable participants, the opinions expressed in this roundtable discussion do not reflect any official position of the OMA itself.

Today I am honored to have a discussion with 3 leading clinicians having experiences and perspectives regarding the treatment of obesity with phentermine. I would like to start by asking each of you to briefly describe your medical practice. Dr. Lazarus, please summarize your clinical background and clinical practice setting.

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Dr. Lazarus: Hello. I began my career as a family physician. In 2004, I assumed management of a large obesity medicine practice from a retiring physician. Having no prior training in obesity medicine, I shadowed him for a month and attended my first obesity-focused medical conference hosted by the American Society of Bariatric Physicians (ASBP), whose name was subsequently changed to the "Obesity Medicine Association" (OMA). Our practice offers individualized obesity treatment programs. Medical treatment is administered by a physician assistant and myself. Our behavioral modification is supervised by Registered Dietitian Nutritionists. Our teamwork approach has proven highly effective – and fun – for staff and patients alike.

I became certified by the American Board of Obesity Medicine the first time they offered their certification in 2012 and have since been involved in teaching obesity management review courses. I later joined the Board of Directors of the Obesity Medicine Association (OMA), where I also served in leadership as Secretary Treasurer, Vice President, and President-Elect. At the time of this publication, I serve as President of the OMA. In addition to these leadership positions, I was appointed by the OMA Board of Directors to represent the OMA in the house of delegates of the American Medical Association (AMA). I have worked with the AMA to reduce weight bias, improve obesity education, recognize obesity as a disease, and try to find strategies to curb the obesity epidemic.

Dr. Bays: Dr. Primack, please summarize your clinical background and clinical practice setting.

Dr. Primack: I am board certified in Internal Medicine and in Pediatrics and started my medical career in primary care. In response to the expressed desire of our local hospital, my business partner and I joined as medical providers of their medical weight loss program. I felt the local hospital was too apprehensive in administering anti-obesity medications or aggressively engaging in nutritional intervention. Therefore, we started our own program based on a comprehensive approach to obesity. We designed a program consistent with the 4 essential pillars of obesity medicine: **(1) Nutritional Guidance**, where we use multiple nutrition plans (i.e., most often medical meal replacements); **(2) Physical Activity** counselling; **(3) Behavior Modification** (i.e., delivered as a class series taught by psychologists and registered dietitians); and **(4) Anti-Obesity Medications**. Over time, my practice has evolved to 4 locations and 5 full-time medical providers in the greater Phoenix Arizona area. I have served on the board of the OMA for the past 11 years, and currently serve as the Immediate Past President of the OMA.

Dr. Bays: Thank you Dr. Primack. Dr. Fitch, please summarize your clinical background and clinical practice setting.

Dr. Fitch: I completed a residency in Internal Medicine and Pediatrics and served as Chief Resident of Internal Medicine at the University of Cincinnati. In 2002, I moved to Minnesota to begin my career as a primary care physician in a large hospital system that was passionate about quality and care innovation. We implemented a team approach towards advancing quality patient care and improving patient outcomes. Given my chemical engineering undergraduate training, and with regard to body systems, I was always intrigued by biologic metabolic functions. In the case of obesity, insulin resistance, and diabetes mellitus, I was equally intrigued by the biologic metabolic *dysfunctions* that contributed to these common diseases. As the result of my primary care experience in treating type 2 diabetes and metabolic syndrome, I decided to enhance my training in obesity medicine. I became certified in obesity medicine in 2012 with the sitting of the first exam. I subsequently transitioned to full time obesity medicine by leading a multidisciplinary program within an eating disorder institute. Complementary to treating eating disorders, I also established a medical/surgical weight center in Cincinnati Ohio.

I have since moved to Boston Massachusetts to lead the oldest and largest multidisciplinary weight center in the country. At the Massachusetts General Hospital Weight Center, we have 22,000 patient visits a year and we care for both pediatric and adult patients. We employ the spectrum of treatment options spanning lifestyle intervention, pharmacotherapy, endoscopic treatment, and surgery. Regarding the OMA, I have served as a member since 2010, and look forward to becoming President of the OMA later in 2022.

2. Phentermine history & weight reduction efficacy

Dr. Bays: Thank you for your introductions. It may be relevant that each of you are either a current, past, or future President of the OMA. Regarding me, at the time of this roundtable, I am an Officer of OMA. Additionally, I am a clinical trialist who has served as a Principal Investigator for over 500 clinical trials, and I have authored/coauthored over 300 peer review manuscripts. As an Endocrinologist, I have also worked in direct patient care (sometimes primary care) and have done so for over 30 years. In the past regarding anti-obesity medications, I mainly prescribed orlistat and sibutramine (with the latter being withdrawn; see discussion below). I then gravitated towards the use of phentermine/topiramate and naltrexone/buproprion combination agents. More recently, I have gained much (mainly research) experience with semaglutide, liraglutide, and tirzepatide. Outside of clinical trials, I have limited experience with phentermine as monotherapy. This may place me as an outlier compared to many other obesity medicine specialists. It is therefore fair to say my questions to the panelists will reflect my clinical research bias. My questions reflect someone emersed in the heavily regulated environment of pharmacologic research. My questions reflect someone who routinely responds to, or drafts reviewer comments pertaining to, the scientific evidence supporting peer-review publications.

As importantly, my questions reflect someone having life experiences during the "bad old days" of the 1990's, when the "off label" use of "phen-fen" was all the rage. "Phen-fen" was the combined use of phentermine (a sympathomimetic) and fenfluramine (a serotonergic agent) [7,8]. In this time prior to year 2000, clinicians who prescribed "phen-fen" often did so in a style of practice involving high volumes of "weight loss drugs,"

with dubious attention to safety and quality. We often referred to these prescribing clinicians and their "weight loss clinics" as "docs in a box." (This was not a compliment.)

Despite the impressive weight reduction efficacy of "phen-fen," the fenfluramine component of "phen-fen" was ultimately withdrawn from the market in 1997 (as was dexfenfluramine) due to findings of valvular heart disease (i.e., aortic and mitral valve damage with regurgitation). This was followed by subsequent widespread litigation [9]. Most evidence supported the fenfluramine component of "phen-fen" as the etiology of the (mainly) left sided valvulopathies, not the phentermine component [7]. However, despite being decades ago, it is interesting this experience with fenfluramine, and dexfenfluramine is still reflected in the prescribing information of some phentermine preparations (https://www.lomaira.com/Prescribing_Information.pdf).

The aftermath of the "phen-fen" debacle accentuated the already negative perception of "weight loss drugs,", which was an underlying perception created by withdrawal of previous anti-obesity agents due to safety findings [10]. Finally, this negativity was layered on the surrounding "noise" of inappropriate prescribing of "weight loss drugs" by some clinicians. In one illustrative case, a clinician is said to have been found guilty, imprisoned, fined, and surrendered his medical license due to the "sale of 500,000 units of phentermine, a Schedule IV diet pill, and 2,000,000 units of phendimetrazine, a Schedule III diet pill" (https://www.overdosefreepa.pitt.edu/wp-content/uploads/2018/10/Cases-Against-Doctors.pdf - accessed April 12, 2022).

Thus, until the advent of more recent anti-obesity medications having greater clinical trial evaluation, safety, and efficacy regarding both biomarker and health outcomes [10], an untold story regarding clinician past hesitancy in prescribing anti-obesity medications was the lasting influence of the withdrawal of "phen-fen." The past withdrawal of anti-obesity drugs due to their lack of safety and the inappropriate prescribing of "weight loss drugs" needlessly dampened the enthusiasm of clinicians for pharmacologic treatment of the obesity epidemic. It was telling that especially after the "phen-fen" debacle, many of my colleagues declined to prescribe any anti-obesity medication, for fear of being labeled a "weight loss doctor."

The good news is that with the recognition of obesity as a disease [11], emergence of organizations such as the Obesity Medicine Association and The Obesity Society, the establishment of the American Board of Obesity Medicine in 2011 (https://www.abom.org/), and especially with the advent of safer and more effective anti-obesity medications, my sense is we are in a much different place than we were in the 1990's.

Dr. Lazarus, we will discuss combination phentermine therapy later in this roundtable discussion. But regarding phentermine monotherapy, phentermine hydrochloride (HCl) is a sympathomimetic Drug Enforcement Agency (DEA) scheduled IV drug approved as an anti-obesity medication and marketed in the US since 1959 (See Table 1). The reported weight reduction efficacy of phentermine [10] derived from reported prospective controlled clinical trials is about 3–8% [12–15]. In a meta-analysis of phentermine monotherapy clinical trials, the placebo-corrected reduction in body weight with phentermine was less than 4 kg [16]. Conversely, from the perspective of retrospective medical chart reviews, the reported weight reduction efficacy of phentermine seems to range from 4% to 19%. Many patients in these chart reviews were treated with phentermine doses of 60 mg per day (and thus doses higher than approved by the FDA) [17,18], with reports that some clinicians prescribed phentermine doses as high as 112 mg per day [19].

With this background, Dr. Lazarus, what is your assessment specifically about the weight reduction efficacy of phentermine, and the clinical risks and benefits of prescribing phentermine beyond FDA-approved doses?

Dr. Lazarus:

Thank you, Dr. Bays, for this interesting and important question. When I first started in Obesity Medicine, I found many patients could effectively lose weight even *without* anti-obesity medications. Our registered dietitian nutritionists were, and continue to be, extremely effective at administering nutritional and behavioral interventions to help people with obesity reduce their body weight. Under our guidance and supervision, I found some of our patients with obesity lost as much as 50 or 100 pounds. However, while we often achieved success with weight reduction, keeping the weight off was a different animal. Virtually 100% of those who lost weight regained it quickly within the months to years afterwards. A common thread interwoven with this common experience of weight regain after initial weight loss was that patients blamed themselves.

We now have a better understanding that the human body typically resists weight reduction, both by reactive metabolic responses to weight loss (e.g., alterations in gut hormones affecting hunger) and by lowering body metabolism [20]. After weight loss, hunger is increased. This increased hunger, coupled with lower caloric intake to sustain a lower body weight, often leads to weight regain. The important point is that the subsequent neurometabolic maladaptations that promote weight regain after initial weight reduction is not due to a lack of willpower; it is due to reactive biology.

Your question was about phentermine efficacy. But how is "efficacy" best defined? A principle derived from the experiences with other metabolic diseases is that the longer the successful treatment of metabolic disease, the greater the health outcomes benefits (e.g., diabetes mellitus [21,22], hypertension [23], and dyslipidemia [24]). Obesity is no less a disease than other metabolic diseases [11]. We await the results of longer-term cardiovascular disease outcomes trials with anti-obesity medications [10]. However, my sense is that a sole focus on the initial short-term percent weight loss achieved from phentermine (or any anti-obesity medication) is short-sighted. The question we should be asking is whether phentermine safely helps a patient sustain weight loss for the long-term. At least regarding 1–2 year data derived from the phentermine and topiramate extended-release combination, the answer is "Yes." [25].

In my clinical experience, after implementing our weight reduction program, we find similar weight reduction - irrespective of whether we start patients on phentermine or other anti-obesity medications. However, when we look at 1- and 2-year data, a different picture is painted. Our typical patients on phentermine or other anti-obesity medications often maintain a weight reduction of more than 10% when pharmacologic treatment is continued. Conversely, patients not treated with anti-obesity pharmacotherapy often regain most, if not all the weight they lost. This weight regain can occur quickly, and certainly within 2 years. Except for perhaps semaglutide 2.4 mg weekly, I do not see a substantial

Table 1
Phentermine brief summary description, main side effects, illustrative drug interactions, and dosing [10].

Phentermine Description: Sympathomimetic amine approved as a weight management medication in 1959 and is a DEA Schedule IV stimulant agent approved for short-term use (12 weeks). Approved for age 17 years or older. Average weight reduction is about 3–8%.
Main side effects: Side effects include headache, high blood pressure, rapid or irregular heart rate, overstimulation, tremor, dry mouth, and insomnia. Contraindicated in patients with cardiovascular disease, stroke, uncontrolled hypertension, within 14 days of monoamine oxidase inhibitors, hyperthyroidism, glaucoma, agitated states, or with a history of drug abuse.
Illustrative Drug Interactions: May have interactions with other sympathomimetics, alcohol, adrenergic neuron blocking drugs, and possibly some anesthetic agents. Should not be taken during or within 14 days following monoamine oxidase (MAO) inhibitors.
Dosing:
• Phentermine HCl tablets = 37.5 mg per day or sometimes 18.75 mg (one half 37.5 mg tablet) once per morning or 18.75 mg twice a day • Phentermine HCl tablet (different formulation than above) = 8mg (or 4 mg if using one half 8 mg tablet) three times a day before meals • Phentermine HCl capsules or disintegrating tablets = 15 and 30 mg once per morning or 15 mg twice a day • In the US, phentermine is almost exclusively available in the HCl formulation. Phentermine resin outside of the US = 30 mg (or 15 mg) once per morning

Table 2
Estimated degree of mean weight reduction associated with anti-obesity medications, as well as the percent achievement of weight reduction ≥5, ≥10%, ≥15%, and ≥20%.

Anti-obesity medication	Mean percent and categorical percent weight reductions[a]	Notes	References
Phentermine 15 mg per day (oral)	Overall mean = 7% ≥5% = 46% ≥10% = 21% ≥15% = NA	The placebo group had a 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% weight reduction, respectively	[12,13]
Semaglutide 2.4 mg subcutaneously once weekly	Overall mean = 15% ≥5% = 86% ≥10% = 69% ≥15% = 51% ≥20% = 32%	The placebo group had a 2% mean weight reduction, with 32%, 12%, 5% and 2% achieving ≥5%, ≥10%, ≥15%, and ≥20% categorical weight reduction, respectively	[34]
Liraglutide 3.0 mg subcutaneously once daily	Overall mean = 8% ≥5% = 63% ≥10% = 33% ≥15% = 14%	The placebo group had a 3% mean weight reduction, with 27%, 11%, and 4% achieving ≥5%, ≥10%, and ≥15% categorical weight reduction, respectively	[35]
Phentermine HCl/Topiramate Extended Release (oral) (top dose = phentermine 15 mg/92 mg topiramate)	**EQUATE 28-week study:** [13] Overall mean = 9% ≥5% = 66% top dose ≥10% = 41% top dose ≥15% = NA **SEQUEL 56-week extension study:** [36] Overall mean = 10% ≥5% = 79% top dose ≥10% = 54% top dose ≥15% = 32% top dose ≥20% = 15% top dose	**EQUATE 28-week study:** [13] The placebo group had a 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% categorical weight reduction respectively **SEQUEL 56-week extension study:** [36] The placebo group had a 2% mean weight reduction, with 30%, 12%, 7%, and 2% achieving ≥5%, ≥10%, ≥15% and ≥20% categorical weight reduction respectively	[13,36]
Naltrexone sustained release (SR) 32 mg/day plus bupropion SR 360 mg/day (oral)	Overall mean = 7% ≥5% = 56% ≥10% = 27% ≥15% = 10%	The placebo group had a 2% mean weight reduction with 18%, 7%, and 2% achieving ≥5%, ≥10%, and ≥15% categorical weight reduction, respectively	[37]
Orlistat 120 mg three times per day (oral)	Overall mean = 9% ≥5% = 66% ≥10% = 39% ≥15% = NA	The placebo group had a 6% weight reduction with 44% and 25% achieving >5% and >10% categorical weight reduction, respectively	[38]
Non-systemic Oral Hydrogel, three 2.25-g capsules before lunch and dinner (oral)	Overall mean = 6% ≥5% = 59% ≥10% = 27% ≥15% = NA	The placebo group had a 4% mean weight reduction with 42% and 15% achieving ≥5% and ≥10% categorical weight reduction, respectively	[39]
Tirzepatide (subcutaneous once a week) Approved and indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, but investigational for treatment of obesity at the time of publication[b]	Overall mean = 21% (15 mg)[b] ≥5% = 91% 15mg ≥20% = 57% 15mg	The placebo group had a 3% mean weight reduction with 35% and 3% achieving ≥5% and ≥20% categorical weight reduction, respectively	[b]

NA = Not available (data was not found).

[a] The values in this chart are not intended to represent head-to-head comparisons. Data are derived from different studies. In most cases, the percent weight reductions were dose dependent. Therefore, the listed mean values may be less than the percent weight reduction with the highest doses of anti-obesity medications.

[b] Preliminary treatment-regimen estimand results from a News Release on April 28, 2022: https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-delivered-225-weight-loss-adults-obesity-or. Tirzepatide Prescribing information: https://pi.lilly.com/us/mounjaro-uspi.pdf?s=pi.

difference between percent sustained weight loss with phentermine and other available anti-obesity medications. That said, if a patient were to only lose 3–5% on the phentermine, then I would likely discontinue it and try a different anti-obesity medication having a greater potential for weight reduction.

Regarding prescribing phentermine at dosages higher than FDA-approved, I do not prescribe phentermine beyond the approved doses listed in the phentermine prescribing information.

3. Phentermine health outcomes efficacy

Dr. Bays: Thank you for that perspective on phentermine weight reduction efficacy. Dr. Primack, I now want to redirect the discussion from weight reduction efficacy to health outcomes efficacy. For disclosure, respective to the questions I posed to Dr. Lazarus, I did prescribe some "phen-fen" decades ago, not only because of the reported weight reduction efficacy of the combination, but also because of the improvement in metabolic parameters with fenfluramine [7]. Back in the day, I also prescribed sibutramine, which was a reuptake inhibitor of serotonin (5-hydroxytryptamine; 5-HT), noradrenaline (NA) and, to a lesser extent, dopamine, with some suggestion that sibutramine increased energy expenditure [26]. At that time, sibutramine and orlistat were the only 2 anti-obesity medications approved for long-term management of obesity [27]. My clinical impression was that sibutramine was relative effective and safe in promoting clinically meaningful weight reduction among my patients with obesity. Most of all, based upon my clinical experience with patients, I anticipated a favorable outcome would be found in the Sibutramine Cardiovascular Outcomes Trial (SCOUT). However, somewhat to my surprise, the SCOUT study did not have a favorable outcome. The SCOUT study evaluated 10,744 patients with overweight or obesity, 55 years of age or older, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both, with a mean follow-up of 3.4 years. This study demonstrated that while sibutramine maintained weight reduction of 1.7 kg and reduced blood pressure (but less so compared to placebo with a mean difference of 1.2/1.4 mm Hg), the risk of a primary cardiovascular outcome event was 11.4% in the sibutramine group compared with 10.0% in the placebo group (P = 0.02) [28]. After this study, sibutramine was removed from the market in 2010 (https://www.fda.gov/drugs

/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-against-continued-use-meridia-sibutramine). What was also surprising was that participants in the SCOUT trial experiencing the greatest intentional weight loss had the highest mortality, albeit potentially attributable to those dying of non-cardiovascular causes, especially cancer [29].

While this was a sentinel study from a pharmacologic data standpoint, it was equally important because it demonstrated how my subjective clinical impressions based upon my clinical experience proved to be at variance to what was ultimately proven when evaluated by a controlled clinical trial. If I had solely relied upon my clinical impression from the direct care of patients with obesity, then my subjective assessment of the risks and benefits of sibutramine would have been opposite from the objective clinical trial evidence. In the SCOUT study, not only did sibutramine fail to demonstrate health outcomes benefits over placebo, but the sibutramine group had worse CVD outcomes compared to placebo group. The clinical trial evidence from this SCOUT study was that patients with preexisting cardiovascular conditions who received long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke (but not cardiovascular death or death from any cause) [28].

Dr. Primack, with a focus on health outcome effectiveness (we will discuss safety later), and beyond the weight reduction efficacy described by Dr. Lazarus, what is the objective evidence that phentermine improves health outcomes? Given that obesity promotes cardiovascular disease [11], what is the objective evidence that phentermine reduces cardiovascular disease, the #1 killer of adult patients with obesity? [30] Beyond potential improvement in biomarkers found in blood testing, what is the objective evidence that phentermine monotherapy reduces the risk of, or otherwise improves other adverse obesity-relevant health outcomes, such as a reduction in the onset, or improvement in diabetes mellitus, hypertension, cancer, sleep apnea, osteoarthritis, or depression? To what degree should clinicians rely upon their personal clinical experiences when assessing phentermine's potential risks and benefits regarding long-term health outcomes in patients with obesity?

Dr. Primack:

First off Dr. Bays, I want to thank you for including me in this very important discussion. When I started in clinical obesity care, it was just after the phen-fen fiasco. After this unfortunate and challenging experience, many frowned upon the use of phentermine. As such, for obesity pharmacotherapy care, we mainly used the only other 2 other drugs on the market at the time: orlistat and sibutramine. Both were $140 per month cash priced because no insurance companies covered their use. Orlistat is known to have gastrointestinal side effects, such as oily rectal discharge. Based upon patient experiences of embarrassing gastrointestinal "accidents" with orlistat, I stopped prescribing it. As for Sibutramine, I found its efficacy was limited.

Regarding phentermine, since its approval by the FDA in 1959, no cardiovascular outcomes studies have been done. Therefore, prior to my use of phentermine, I learned that other obesity medicine specialists often performed a complete medical history, physical exam, with laboratory evaluation, as well as possible electrocardiogram. Luckily for patients, phentermine is an effective anti-obesity medication that cost significantly less money than the other approved anti-obesity medications.

As a style of practice, we typically start patients on half of a 37.5mg phentermine tablet first thing in the morning. Most patients lose a bit of sleep on this dose, but only for the first 2–3 nights. After that, if patients are experiencing clinically meaningful weight reduction, then I keep them on this dose for as long as the response lasts. For patients who fail to respond to this dose, then the phentermine dose may need to advance to 37.5mg per day. Several of my mentor physicians who have published journal articles on the clinical use of phentermine, have used higher doses of phentermine in selected patients. In the right patient who has tolerated 37.5mg of phentermine per day, I have sometimes added another half tablet "off label" as tolerated and as needed for clinical response. In more rare circumstances, I maximally use two 37.5mg tablets of phentermine in the proper patient.

Regarding health outcomes, limited long-term outcomes study data exists regarding phentermine. Observational analyses of clinical use are limited because the prescribing information limits phentermine treatment to 12 weeks. In short, we don't have great studies. Regarding the heart, as you mentioned in your prior question to Dr. Lazarus, most evidence supports the fenfluramine component of "phen-fen" as being responsible for the (mainly) left sided valvulopathies, not the phentermine component.

Overall, we now have over 60 years of clinical experience with phentermine use. As noted by Dr. Lazarus, at least regarding 1–2 year data derived from the phentermine and topiramate extended-release combination, such use does not appear to increase cardiovascular risk in the patient population studied [25].

4. Phentermine weight reduction efficacy relative to other anti-obesity medications

Dr. Bays:

Thank you Dr. Primack. We now turn to you Dr. Fitch. My sense is the reason most clinicians prescribe phentermine to patients with obesity is not because of robust objective data supporting improved long-term health outcomes. Instead, clinicians mainly prescribe phentermine to patients with obesity for the purpose of weight reduction. Moreover, because obesity is a chronic disease, many clinicians use phentermine beyond its approved "short-term" use (i.e., 12 weeks), as otherwise directed by the prescribing information.

The discussion thus far has mainly focused on phentermine monotherapy. However, as noted by both Drs. Lazarus and Primack, another approved anti-obesity medication is the combination of phentermine HCl with topiramate extended release. This combination agent has undergone rigorous clinical trial evaluation for efficacy, and safety [31], has demonstrated reasonably robust efficacy, and demonstrated improvement in multiple cardiometabolic parameters [32]. Specifically, regarding phentermine in fixed combination with topiramate, such a combination can contribute to clinically meaningful weight loss, as well as improvements in blood glucose, blood pressure, and blood lipids [31,32]. While pulse may increase with phentermine/topiramate, a retrospective cohort study from US insurance billing data suggested no increased risk of major adverse cardiac events among phentermine/topiramate users, although the 95% confidence intervals were large, suggesting wide range of possible values [33].

Dr. Fitch, given this clinical trial support of both efficacy and safety, and given you were one of the coauthors on the "OMA Clinical Practice Statement on Anti-Obesity Medications," [10] then what is your sense about the relative efficacy of anti-obesity medications, including mean and categorical values, as shown in Table 2. For clarity, this data is limited because it does not represent head-to-head comparisons; the data are derived from different studies. Nonetheless, what is your sense of the relative efficacy of (a) semaglutide (and potentially tirzepatide and other such agents in the future), (b) liraglutide and phentermine HCl/topiramate extended release, and (c) phentermine alone? Also, if ongoing research of anti-obesity medications ultimately result in multiple medications with mean weight reduction of 15% or more, and with proven cardiovascular outcomes benefits, what do you believe will be the role of phentermine in the future?

Dr. Fitch:

This is an excellent and important question. I have always been intrigued by the complexity and diversity in response to treatment of the disease of obesity. One of my early mentors was Dr Charles Billington at the University of Minnesota, who taught me about obesity "phenotypes." This is the concept that people with obesity represent a diverse patient population with different adverse health risk factors, different etiologies of their increased adiposity, and different clinical presentations (e.g., medical, mental, and functional as suggested by the Edmonton Obesity

Staging System) [40]. Differences in presentation is no different than what is found with other diseases. For example, there is not just one cancer genotype and phenotype.

It would be beneficial if we could identify which patient will respond best to which medication to achieve the best long-term outcome. If you look at the SEQUEL study [36] of phentermine and topiramate in Table 2, 32% of people were able to achieve 15% weight loss. If we could identify who might best respond to this treatment, and be one of those 32%, then perhaps this would be the best treatment for them. Additionally, cost continues to be a challenge for many of our patients. If we could identify patients who might substantially respond to a less expensive, or even generic anti-obesity medication, and achieve clinically meaningful benefits, then this may be beneficial towards adherence. Improved adherence may facilitate long-term efficacy, which is clinically relevant given the chronicity of treatment needed. Currently we use a "trial and error" approach to treatment which is more costly to the health care system and is more frustrating for clinicians and patients. However, in the future I do think we will have better tools to identify who might respond best to what treatment (i.e., clinical realization of "precision medicine" [41]). Some pragmatic clinical trial evidence already supports that selection of anti-obesity medications based upon biologic and behavioral phenotypes may enhance weight reduction [42].

Phentermine is a sympathomimetic drug that works differently than other medications (Table 1). The future of obesity pharmacotherapy will likely employ a complimentary approach. The use of phentermine as combination therapy may allow for even greater weight loss when added to other anti-obesity medications having different mechanisms of action [10,43]. This is analogous to combination treatment of diabetes, hypertension, and dyslipidemia, where use of drug treatments with complimentary mechanisms of action are commonly used to allow for lower doses of individual components, with overall enhanced safety, tolerability, and efficacy.

In our clinic, we already combine phentermine with incretin agents (i.e., glucagon like peptide-1 receptor agonists) "off label" to try to achieve further weight reduction, especially in our patients with a high burden of the disease of obesity. Regarding more recent medications that promote substantial weight reduction (i.e., semaglutide approved for obesity and type 2 diabetes mellitus and tirzepatide approved for type 2 diabetes mellitus), as well as anti-obesity medications in development [10], it is unknown if adding another agent that works differently (i.e., phentermine) produces greater weight reduction, or allows for greater health outcomes benefits. More robust research is needed to determine the right treatment for the right patient in the right combination for the most optimal outcome. This also includes how to combine endoscopic procedures and bariatric surgery with adjuvant pharmaceutical therapy [10,44], much like we do with cancer treatment today.

Table 3
Illustrative cardiovascular disease risk factors to consider when managing patients with obesity[a] [48].

Clinical Cardiovascular Disease
- History of acute coronary syndrome
- History of myocardial infarction (other than recent ACS event listed above)
- Stable or unstable angina
- Coronary or other arterial revascularization
- History of stroke or transient ischemic attack
- Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation
- Aortic aneurysm

High-Risk Conditions
- Previous CVD event (see above)
- Men ≥55 years or women age ≥65 y
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or percutaneous coronary intervention
- Diabetes mellitus
- Hypertension
- Persistently elevated low-density lipoprotein cholesterol
- Metabolic syndrome
- Chronic Kidney Disease
- Current smoking
- History of congestive heart failure
- Coronary artery calcium score ≥100

Risk-Enhancing Factors
- Family history of premature atherosclerotic cardiovascular disease (men, age <55 y; women, age <65 y)
- Primary hypercholesterolemia
- Metabolic syndrome
- Chronic kidney disease
- Chronic inflammatory conditions (e.g., psoriasis, rheumatoid arthritis, human immunodeficiency virus infection (HIV/AIDS)
- Premature menopause (before age 40 years)
- Pre-eclampsia
- High risk populations (i.e., South Asian ancestry)
- Persistently elevated triglyceride levels
- Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
- Elevated Lipoprotein(a) (Lp(a) ≥50 mg/dL or ≥125 nmol/L)
- Elevated apolipoprotein B ≥ 130 mg/dL
- Ankle brachial index <0.9

[a] Not an inclusive list (e.g., list does not include increased Lipoprotein(a)).

5. Phentermine safety

Dr. Bays: Now we will discuss phentermine safety. Cardiovascular disease is the major cause of death among adult patients with obesity [45,46]. (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Within the prescribing information, phentermine is contraindicated in patients with CVD or uncontrolled hypertension [10]. In an observational study of 13,972 patients *at low cardiovascular disease risk* (i.e., participants were excluded who had diagnosis and/or procedure codes for any cardiovascular outcomes), phentermine monotherapy for longer than 3 months was associated with greater weight loss, without an increase in incident cardiovascular disease or death. The conclusion was that: *"this study* supports *the effectiveness and safety of longer-term phentermine use for low (cardiovascular disease) risk individuals."* [18]

In a chart review analysis of 300 consequential patients comparing those treated with those not treated with phentermine (with measurements spanning 1 through 104 weeks), the phentermine treated group did have greater weight loss, but did not have increased systolic blood pressure, diastolic blood pressure, or heart rate. In fact, in this comparative analysis, the phentermine treated group had a decrease in categorical blood pressure [17].

In an evaluation of 269 patients treated with phentermine up to 21 years having current or past criteria for the diagnosis of overweight or obesity, no evidence suggested signs or symptoms of psychological dependence (addiction), nor amphetamine-like withdrawal symptoms [47]. Based upon data such as this, some authors believe phentermine has been "*maligned inappropriately*," with a conclusion that *"US physicians will likely continue to use any drug proven useful off-label for this illness (obesity) until such time as more effective drugs are approved."* [19]

The challenge is that like the disease of obesity, atherosclerotic CVD is a chronic disease that often begins in childhood. In many, if not most cases, a myocardial infarction or stroke is most likely a manifestation of decades of progressive atherosclerosis. We often speak of primary prevention (i.e., preventing new onset of myocardial infarction and stoke) and secondary prevention (i.e., preventing recurrent myocardial infarction and stroke). But if the underlying atherosclerosis was decades in the making, then for the patient, the difference between primary prevention and secondary prevention may be reflected as a "bad day" (i.e., the day of the myocardial infarction or stroke). In other words, just as with many cases of the disease of obesity, atherosclerosis is a lifelong disease process with acute complications being the endpoint clinical expression and manifestations of an underlying chronic disease process. Table 3 is listing of clinical CVD and factors that increase CVD risk.

Dr. Primack, given phentermine is contraindicated in patients with CVD, given the adiposopathic immunopathies and endocrinopathies of obesity contribute to major CVD risk factors (e.g., diabetes mellitus,

hypertension, dyslipidemia), given obesity is a CVD risk factor, given we often don't know the degree of atherosclerosis in our patients with obesity who have not yet had a myocardial infarction or stroke, and given CVD is the most common cause of mortality regarding patient with obesity, then what is your general sense about the CVD safety in prescribing phentermine to patients with obesity without CVD? What is your specific sense about prescribing phentermine to patients with any of the conditions listed in Table 3?

Dr. Primack:

My general sense about CVD safety comes from the plethora of studies I have read about anti-obesity medications. Clinically, I find most people benefit when phentermine is added to a reduced calorie diet and behavior modification. However, I find patients benefit from stopping rules (i.e., clinical criteria wherein the medication might best be discontinued). If a patient is not receiving sufficient clinical benefit, then the risks and cost of an anti-obesity medication may outweigh the benefits. Thus, if after a reasonable amount of time, a patient does not achieve clinically meaningful weight reduction, or other clinical benefits, then I either stop the medicine or add a second anti-obesity medicine to their regimen. Within the framework of a patient-centered approach, I treat my patients as individuals. In my practice, I am fortunate to see my patients about every 2 weeks for the first 20 weeks of their program, so I can assess their progress.

Patients with obesity are at high risk for CVD events. Therefore, although not required by the phentermine prescribing information, we screen all patients with an electrocardiogram. Patients with known CVD are not started on phentermine. Patients with advanced age or with CVD risk factors noted in Table 3 are not prescribed phentermine as first line. If after use of the armamentarium of other anti-obesity medications, patients at medium CVD risk are still struggling, then we may consider phentermine for selected patients – again using a patient centered approach.

6. Phentermine use for longer than 12 weeks

Dr. Bays:

According to the prescribing information, phentermine HCl is approved for short-term (12 week) treatment of obesity [10]. From a scientific perspective, the limitation of "short-term" indicated use of phentermine has often led to omission from published reviews and meta-analyses of efficacy and safety data [49]. In absence of prospective, randomized, long-term clinical trials, and omission from meta-analyses, clinicians may reasonably look towards the best available evidence. In the 2015 Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline, [50] these authors acknowledged the conundrum wherein phentermine is approved for the treatment of a chronic disease but does not have an FDA approved indication for long-term use. One suggested approach was to implement intermittent therapy. Regarding prescribing phentermine long-term, the authors advised:

> "Direction and guidance provided by State Medical Boards and local laws always take precedence. However, in the many locations where these sources have not provided clear advice, clinicians are left to make their own best professional judgments".

The authors also noted how phentermine was the most widely prescribed weight loss medication (at least partially because it was generic and low cost), and that likely much of this prescribing was *"off label."* In this Endocrine Society Clinical Practice Guideline, the authors acknowledged minimal evidence of any serious long-term side effects when phentermine monotherapy was used alone for weight loss. Their conclusion was that it was reasonable for clinicians to prescribe phentermine long term, provided the patient:

> "1) has no evidence of serious cardiovascular disease; 2) does not have serious psychiatric disease or a history of substance abuse; 3) has been informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not; 4) does not demonstrate a clinically significant increase in pulse or blood pressure when taking phentermine; and 5) demonstrates a significant weight loss while using the medication. These aspects of care should be documented in the patient's medical record, and the off-label nature of the prescribing should be documented at each visit. Medication should be started at 7.5 or 15 mg/d initially and only increased if the patient is not achieving clinically significant weight loss. Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose" [50].

Dr. Lazarus, please provide your guidance how a clinician can safety prescribe phentermine for longer than 12 weeks? How do clinicians best maintain compliance with local laws and regulations?

Dr. Lazarus:

Regarding the clinical use of phentermine, first and foremost, clinicians must know the rules of their state medical and pharmacy boards. Further, the rules are not always the same for all clinicians – sometimes Medical Doctors and Doctor of Osteopathic Medicine have different rules than Nurse Practitioners and Physician Assistants. So again, it is best to know the rules in your state! Assuming it is not a violation of state requirements, then I support the approach in the quotes you noted above.

With our weight management program, we perform a full history and physical exam before prescribing phentermine or prescribing any other medication for obesity treatment. Illustrative health measures include body weight, body mass index, blood pressure, pulse, and body composition [20]. We do a careful cardiovascular exam. Further, like Dr. Primack, we perform an electrocardiogram on all patients before implementing intensive weight loss programs or anti-obesity pharmacotherapy. These initial visits are done in-person.

When starting phentermine, we typically see patients weekly for behavioral assessment visits [51], and monthly for medical visits. At the medical visits, pulse and blood pressure are re-checked, and the patient is examined by the clinician. We document the efficacy, safety, and tolerability of the anti-obesity medication. We generally follow the Obesity Medicine Association Clinical Practice Statement on Anti-Obesity Medications [10].

> "If an anti-obesity medication is initiated, and if the anti-obesity medication does not have a prescribing information time limitation for use, then the decision to continue or discontinue anti-obesity medication treatment is best based upon the individual patient response and clinical judgment regarding the risks of further or recurrent weight gain. Local/state laws may impose restrictions of use of anti-obesity medications, irrespective of the potential benefit to the patient and irrespective of the clinical judgment of the clinician. Prescribing information guidance regarding longer-term anti-obesity medication therapy varies depending on the specific anti-obesity medication. For many anti-obesity medications, if no clinical improvement (e.g., at least 3–5% loss of baseline body weight) occurs after 12–16 weeks, then the prescribing information may recommend clinicians instruct patients to increase the dose or perhaps discontinue the anti-obesity medication. Conversely, other anti-obesity medications (e.g., semaglutide 2.4 mg weekly injection) do not have explicit stopping instructions based upon therapeutic response.
>
> For anti-obesity medications in general, if weight regain occurs where the patient and clinician determine the medication is no longer effective, then the anti-obesity medication should be discontinued. However, if the patient achieved clinically meaningful weight reduction with the anti-obesity medication, and if the patient and clinician determine the medication is helping to avoid weight regain, then a weight reduction plateau should not necessarily be interpreted as "tolerance" to the drug. Just as with medications for other metabolic diseases (e.g., drug treatments for diabetes mellitus,

hypertension, and dyslipidemia), medications for weight reduction are efficacious only if they are taken. Continued weight reduction maintenance may represent a manifestation of efficacy maintenance and should not automatically warrant the anti-obesity medication be discontinued."

In short, if the patient is not on-track to lose at least 5% of their body weight in the first 3 months, then we adjust the dose, or sometimes change the treatment plan (e.g., food plan, medication, frequency of visits, etc.)

We avoid prescribing phentermine (or any other medication) in patients where it is contraindicated. For example, we do not prescribe phentermine for patients with CVD or angle closure glaucoma. Further, we inform patients about all FDA-approved anti-obesity medication options. We have a handout in our new patient packet that reviews available anti-obesity treatments, and we review this with patients at the first visit. If we plan on using phentermine "off-label," (i.e., for longer than 12 weeks), then we document the patient was informed of this "off-label" use. We also document that the prescriber determined the benefits of phentermine treatment beyond 12 weeks outweighed the known risks. This documentation includes an informed consent process, as evidenced by the patient signing an informed-consent document. After the first 5 months, most of our patients have switched to a program where they come every other week for a behavioral visit, and every other month for a provider visit. Our longer-term patients typically come monthly for behavior visits and every 3rd month for medical visits.

7. Phentermine prescribing and telehealth

Dr. Bays: Thank you Dr. Lazarus for practical information in prescribing phentermine for longer than 12 weeks within the clinical setting. Dr. Fitch, you were first author of the "Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022." This document provides helpful guidance regarding obesity management via telehealth. Now that we are nearing the end of the coronavirus disease (COVID)-19 experience, I believe it fair to say most of us believe that going forward, the accelerated and more widespread use of telehealth prompted by COVID-19 is here to stay.

Special approaches are required regarding telehealth management of Drug Enforcement Agency (DEA) controlled substances. Phentermine is a DEA schedule IV medication approved in 1959 [10], and as noted before, at least as a few years ago, reported to be the most prescribed anti-obesity agent [50]. Historically, controlled substances could not be initiated in the US without an in-person encounter. During COVID-19, the DEA waived the need for an in-person visit prior to an initial prescription, provided that required two-way, real-time, audio-visual telehealth is used [52].

Table 4 provides some general principles in prescribing phentermine via telehealth. Within the context of shared decision-making, clinicians and patients often consider the potential risks and benefits of any obesity pharmacotherapy via telehealth. After this patient-centered approach, after an evaluation of cardiovascular risk factors as listed in Table 3, and after general considerations in prescribing phentermine via telehealth as listed in Table 4, the patient and clinician often decide a path forward that is in the best safety and medical interest of the patient. An illustrative example of a patient who may be appropriate for initial prescribing of phentermine via telehealth might be an established younger patient in the applicable medical practice, not at risk for pregnancy, without cardiovascular risk factors listed in Table 3, who meets the criteria in prescribing phentermine via telehealth as listed in Table 4, and who had taken phentermine in the past with demonstrable efficacy, safety, and tolerability.

Dr. Fitch, considerable variance exists in the telehealth prescribing of phentermine. Some clinicians feel obesity is such a major cardiovascular disease risk factor that phentermine should be prescribed only after a face-to-face clinical encounter and only after an electrocardiogram (i.e., although an electrocardiogram is not required according to the prescribing information). Some clinicians only prescribe phentermine for 12 weeks (at a time). Conversely, other clinicians have different approaches, and prescribe phentermine for longer than 12 weeks. Dr. Fitch, for clinicians who chose to prescribe phentermine for patients with obesity, what are your recommendations to regarding phentermine prescribing, specifically via telehealth?

Dr. Fitch:

Our experiences at the Massachusetts General Hospital Weight Center have proven to be very positive in judiciously prescribing phentermine via telehealth during the COVID 19 pandemic. Fortunately, we were already conducting telehealth visits prior to the pandemic, although we were not initiating phentermine treatment due to prior federal laws. I did my first telehealth visit back in 2005 in my primary care practice. It is challenging to make the case that the COVID 19 pandemic resulted in much that is positive for patients. However, my sense is while telehealth was always going to be more prominent in helping clinicians provide greater accessibility to care and greater quality of care, COVID 19 accelerated telehealth acceptance. Our clinic went 100% virtual on March 15, 2020. Even today we are still seeing patients 75% of the time virtually by patient preference.

As clinical scientists, we really need to take a hard look at our data during this telehealth experience to evaluate the "real world" safety and efficacy of treatments for obesity, including the initiation of phentermine without an in-person exam. As laws may variably return to pre-pandemic requirements, we will likely need to change our practice and determine which patients can be treated with phentermine via telehealth, and which might best be managed by treatment in-person.

Many of the patients we see come from our integrated health system. Within the interoperability of electronic medical records, we have the benefit of data from other treating clinicians who have seen the patient

Table 4
General considerations in prescribing phentermine via telehealth [50].

- Both clinician and patient should be aware of direction and guidance provided by State Medical Boards and local laws, current applicable medical guidelines, obesity medicine standards of practice, and the phentermine prescribing information; the dose and duration of phentermine treatment should follow a patient-centered approach, with shared decision making based upon documented informed consent
- Phentermine contraindications include:
  - History of cardiovascular disease (e.g., coronary artery disease, stroke, cardiac dysrhythmias, congestive heart failure, uncontrolled hypertension)
  - During or within 14 days following the administration of monoamine oxidase inhibitors
  - Hyperthyroidism
  - Glaucoma
  - Agitated states
  - History of drug abuse
  - Pregnancy and/or nursing
  - Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Clinician and patient should be aware of the prescribing information warnings for phentermine, with some warnings that include:
  - Co-administration with other drug products for weight loss
  - Primary pulmonary hypertension
  - Valvular heart disease
- Phentermine is not approved in patients <17 years of age
- Avoid phentermine in patients with restrictive eating disorders
- Discuss the potential benefits and risks of phentermine in a shared decision-making process with patients, especially regarding patients with cardiovascular disease risk factors
- Have monitoring plans in place to assess for potential increases in pulse or blood pressure upon prescribing phentermine
- Have a monitoring plan in place to ensure clinically meaningful weight loss is achieved while using phentermine, with agreed-upon metrics to discontinue phentermine in the event of lack of clinically meaningful benefit
- Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose.
- During interim encounters with the clinician, patients should be encouraged to routinely monitor their weight, blood pressure, and pulse by self-devices and given instructions regarding thresholds when to contact the clinician for abnormal values

in-person and done a physical exam. In addition to a good medical history and cardiac exam described by Dr. Lazarus, other aspects of the physical exam may be of value, such as the evaluation for possible goiter, increased liver size, lipedema, or a new murmur or dysrhythmia. Some of these physical findings are difficult to assess via telehealth alone. That said, evaluation of many of the most important aspects of a targeted physical exam for patients with obesity can be achieved via telehealth [11]. Additionally, I anticipate technology will continue to advance such that we can gather even more complex vital signs, with (hopefully) more widespread use of home electrocardiogram and other cardiac monitoring via telehealth.

Specifically regarding phentermine, I feel phentermine can be safely prescribed via telehealth, given the right patient (Table 4) and given access to applicable telehealth data. I look forward to publishing our Massachusetts General Hospital Weight Center telehealth experience, as I think it will inform the potential risks and benefits of telehealth obesity management in general, and telehealth prescribing of anti-obesity medication specifically. Being able to prescribe phentermine via telemedicine has allowed our patients improved access to treatment, and telehealth will continue to be an important way to increase access to care – beyond these times of COVID 19.

8. Practical tips in use of phentermine

Dr. Bays: Thank you Dr. Fitch. I would like to conclude with asking each of you to provide your top 3 pragmatic tips regarding the use of phentermine for patients with overweight/pre-obesity or obesity.

Dr. Fitch:

1. Pick the right drug for the right patient. Getting a good history, physical exam, and laboratory assessment [20] helps identify: (a) patients who may have a contraindication to phentermine, (b) patients where phentermine is perhaps not the best choice [10], or (c) patients who may likely be intolerant to the stimulant effects of phentermine. For example, a patient who tends to skip meals all day and eat large volumes late at night might not be a good patient for morning administered phentermine, as morning phentermine would be expected to mainly reduce daytime hunger.
2. While the effect of phentermine on mood may benefit from additional study [53], clinical experience suggests it beneficial to monitor patients for potential worsening of mood disorder, especially anxiety or bipolar disorder.
3. Use phentermine cautiously in older adults and those with increased risk for cardiovascular disease, such as patients with longstanding diabetes mellitus (See Table 3). Vital sign monitoring of patients administered phentermine include blood pressure and pulse. After initiating phentermine, we have patients send us blood pressure and pulse readings via our patient portal or connected devices. We do so for monitoring purposes, as well as to increase accountability and awareness of potential cardiovascular side effects of phentermine.

Dr. Primack:

1) While not required according to the prescribing information, I recommend obtaining an electrocardiogram prior to start of phentermine. In addition to the potential to find troubling wave patterns or cardiac dysrhythmias, having a baseline electrocardiogram may help bring piece-of-mind to patient and clinician. My experience is that other clinicians will often blame any side effect they can on phentermine and ask patients to discontinue phentermine, with such recommendations even given to patients having documented long-term health benefits with phentermine.
2) While I sometimes use ½ the dose, a great starting dose is 37.5mg once in the morning. As part of being informed about the risks and benefits of phentermine and its side effects, patients should be informed they may have trouble sleeping for 2–3 nights after initiation phentermine therapy.
3) As with any medication, consideration of anti-obesity pharmacotherapy is two-fold. First, we use clinical trial evidence to support the optimal use of a medication for the optimal patient – which is often reflected in the prescribing information indicated use. Secondly, we apply our clinical experience to inform us when to start a medication, how the drug is to be dosed, and when to stop a medication and try something else. Phentermine as a drug widely used for obesity treatment for over 60 years. It has stood the test of time. In the right patient and in the right clinical situation, phentermine is an effective anti-obesity medication for treatment of the disease of obesity, which is an epidemic affecting over 40% of US adults [11].

Dr. Lazarus:

1) Regarding the question of which is the best anti-obesity medication, phentermine is not always the best answer. We have had fantastic results in our center with other anti-obesity medications as well. It is therefore best to be aware of the risks and benefits of the full range of anti-obesity medications [10], and target the best medication using a patient centered approach [42].
2) While telehealth has expanded since the COVID-19 pandemic, the use of phentermine via telehealth has challenges (See Table 4). Phentermine is a schedule-IV controlled substance. Prior to prescribing phentermine, it is my preference to recommend an in-person visit to document weight, body mass index, blood pressure, pulse, heart exam, and an electrocardiogram.
3) Beware of people with a history of drug-addiction. While most patients do not have drug seeking behavior, people with a history of methamphetamine use are at high-risk for drug-seeking behavior if prescribed phentermine (or any other stimulant). Patients at risk for drug seeking behavior might best be treated with DEA unscheduled anti-obesity medications [10] or bariatric procedures [44].

9. Conclusion

Dr. Bays: Thanks to all of you for your unique insights. My sense is we are at a crossroads in obesity pharmacotherapeutic intervention. As with diabetes, hypertension, and dyslipidemia, I believe we are on the cusp of judging anti-obesity medications, not only by how much they improve the weight of patients, but also by how much they improve the health of patients [10]. Within the next years, we will hopefully have cardiovascular outcome trial evidence supporting some anti-obesity medications as only reducing body weight, but also reducing CVD risk [10].

Regarding the use of phentermine, an analogy for me would be prescribing of sulfonylureas for patients with type 2 diabetes mellitus. As an Endocrinologist and Diabetologist, I have prescribed sulfonylureas over the past decades. This is despite not being a fan of sulfonylureas. Sulfonylureas are obesogenic, increase the risk of hypoglycemia, and no evidence exists that they reduce the risk of CVD in a clinically meaningful way. However, sulfonylureas are generic, and they do lower blood glucose.

Within the past few years, we now have anti-diabetes medications (e.g., glucagon-like peptide-1 receptor agonists and sodium glucose transporter 2 inhibitors) that not only lower glucose levels, but also reduce body weight with a low risk of hypoglycemia. Many of these agents also reduce CVD risk. Given all these advantages, why would I ever prescribe sulfonylureas? The answer is that sometimes, sulfonylureas are the only anti-diabetes medication available to the patient to lower their blood sugar (i.e., issues regarding access and affordability).

Most formulations of phentermine are generic. Other anti-obesity medications are not always available to all patients who would benefit from them. As a clinical trialist of multiple past and ongoing cardiovascular outcomes trials, I look forward to the day when we have multiple anti-obesity medications that are safe and generally well-tolerated, and

that provide clinically meaningful weight reduction and that reduce CVD risk. Most of all, I look forward to the day when the most effective anti-obesity medications having the most favorable health outcomes are available to all patients. When that day comes, I am uncertain about the future role of phentermine. But that day is not today. Given we have patients with the disease of obesity who require treatment today, it is hoped the perspectives and variances in clinical experiences from opinion leaders, as reflected by this roundtable discussion, will allow each clinician a better perspective regarding how and when to best use phentermine – based upon the best available evidence.

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Author contribution

HEB conceptualized the submission, wrote/sent questions to the other authors, and assisted with editing the manuscript. EL, CP, and AF responded to their assigned questions, reviewed their sections for accuracy, and gave final approval of their contribution.

Ethical review

This Obesity Medicine Association Roundtable represents original works, with work and/or words of others appropriately cited or quoted in the submission. This submission did not involve human test subjects or volunteers. HEB was not involved in the peer review process, nor the acceptance/rejection of this submission. Responsibility for the editorial process for this article was delegated to an independent Editor and/or Associate Editor.

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