

# Clinical utility of phentermine/topiramate (Qsymia™) combination for the treatment of obesity

Jin Hee Shin<sup>1</sup>  
Kishore M Gadde<sup>2</sup>

<sup>1</sup>Department of Community and Family Medicine, Duke University Medical Center, <sup>2</sup>Obesity Clinical Trials Program, Duke University Medical Center, Durham, NC, USA

**Abstract:** Qsymia™ (Vivus Inc, Mountain View, CA, USA), a combination of phentermine and delayed-release topiramate, has been available in the US since September 2012 for the treatment of obesity. Phentermine is an anorexigenic agent, which is approved for the short-term treatment of obesity, while topiramate is approved for nonweight loss indications – seizure disorders and migraine prophylaxis. The amount of weight loss achieved with combination therapy is of a greater magnitude than what could be achieved with either agent alone. Adverse events that occur with the combination therapy are in line with the known side effect profiles of the constituent drugs; teratogenicity, a slight increase in heart rate, psychiatric and cognitive adverse effects, and metabolic acidosis are concerns.

**Keywords:** Qsymia, combination drug, antiobesity drugs, phentermine, topiramate, obesity, weight loss

## Introduction

Increased prevalence of obesity has become a global public health concern.<sup>1,2</sup> Obesity increases the risk for several chronic diseases such as type 2 diabetes, hypertension, and cardiovascular disease; hence, the prevalence of such obesity-related conditions is likely to increase as obesity continues to rise.<sup>3,4</sup> Over the past 2 decades, the prevalence of type 2 diabetes, which in most cases is closely linked to excess body weight, has risen rapidly. This and other obesity-related comorbidities have imposed a heavy burden on health care systems.

Diet and lifestyle modifications remain the cornerstones of weight loss therapy, but are limited by a lack of long-term success for most obese patients.<sup>5,6</sup> Furthermore, the type of intensive lifestyle interventions that have been shown to be effective in randomized controlled trials are challenging to implement in clinical settings, especially primary care practices, due to limited time, resources, and a lack of reimbursement by health insurance carriers. When obese patients fail to achieve adequate weight control with diet and lifestyle modification alone, medications and other interventions such as surgery may be indicated. Pharmaceutical interventions bridge the gap between lifestyle interventions and more invasive surgical treatments.

Unfortunately, although avidly pursued for more than half a century, very few antiobesity drugs are currently available. Several weight loss drugs have failed to get marketing approval, or have been removed from the market due to safety concerns (eg, rimonabant, sibutramine).<sup>7–9</sup> One of the challenges in the clinical development of antiobesity drugs is the view held by the regulatory agencies, which suggests that

Correspondence: Kishore M Gadde  
Box 3292, Duke University Medical  
Center, Durham, NC 27710, USA  
Email kishore.gadde@duke.edu

these drugs must have a far superior benefit-to-risk profile than for drugs approved for most other diseases.

The efficacy criteria set forth by the US Food and Drug Administration (FDA) for a drug to be approved for the treatment of obesity require that it induce a placebo-adjusted weight loss of  $\geq 5\%$  at 1 year, or that  $\geq 35\%$  of patients on the drug should achieve a  $\geq 5\%$  weight loss with at least twice as many patients losing  $\geq 5\%$  relative to those treated with placebo. Improvements in obesity-related biomarkers and risk factors such as blood pressure, lipids, and glycemia are viewed favorably. Convincing the regulatory agencies regarding drug safety in the context of demonstrated efficacy is a major challenge.

Prior to recent approval of lorcaserin (Belviq™, Eisai, Inc, Woodcliff Lake, NJ, USA) and Qsymia™ (VIVUS, Inc, Mountain View, CA, USA) in the US, and following the withdrawal of sibutramine in 2010, the only FDA-approved medication for the long-term management of obesity was orlistat, which achieves a mean placebo-subtracted weight loss of about 3 kg after 1 year;<sup>10</sup> however, the clinical utility of this gastric and pancreatic lipase inhibitor has been limited by its gastrointestinal side effects and marginal efficacy. Phentermine (PHEN) and diethylpropion, both noradrenergic drugs, are available in the US, but not in Europe, for the short-term treatment of obesity.

Obesity is a chronic medical condition. As such, treatments aimed at the management of obesity must follow the general principles of management of chronic conditions like type 2 diabetes and hypertension. When a successful weight loss intervention is stopped, the benefits of treatment are often lost; this is true for lifestyle interventions as well as medications.<sup>11–13</sup> In the absence of a continuing intervention at some level, long-term weight control is unlikely in most cases; hence, long-term treatment is imperative.<sup>14,15</sup> Since clinicians do not expect to cure diseases such as hypertension or diabetes with medication, they expect to palliate them; therefore, the same argument can apply for medications used to treat obesity to promote and maintain weight loss.

Long-term success of single-drug therapies for obesity is often limited by the counter-regulatory adaptive mechanisms of the human body, especially the processes in the central nervous system that regulate energy intake and homeostasis.<sup>16</sup> Hence, there is a growing interest in combination drug therapies, which could more effectively overcome endogenous compensatory mechanisms than treatments working via a single mechanism. A combination of drugs that target multiple pathways that regulate energy homeostasis may thus achieve more favorable long-term

weight loss outcomes than monotherapies.<sup>17</sup> Indeed, existing single mechanism approaches to obesity have rarely achieved greater than 5% placebo-adjusted weight loss over a year or longer.<sup>10,18</sup> Rationally chosen combination drug therapy may also have improved tolerability and may possibly demonstrate improved safety, although there is no evidence to support this hypothesis to date.

Qsymia™, hereafter referred to as PHEN/TPM, combines immediate-release phentermine hydrochloride (PHEN) and delayed-release topiramate beads (TPM) in a timed-release capsule form. The FDA approved this new drug therapy in July 2012, and the drug has become available in the US since September 2012.<sup>19</sup> The European Medicines Agency, however, rejected the marketing authorization application of PHEN/TPM in the European Union in October 2012 due to concerns over potential long-term cardiovascular and central nervous system effects, teratogenic potential, and the possibility of use by patients for whom this combination therapy is not indicated. In February 2013, the European Medicines Agency reconfirmed its decision of rejection, stating that a cardiovascular outcomes trial would be necessary prior to approval to establish long-term safety.

## Phentermine

PHEN is a noradrenergic drug, which is theorized to affect food intake primarily via the enhancement of norepinephrine release and possibly via the blockade of norepinephrine reuptake as well. It has been available in the US since 1959 for short-term (generally regarded as 12 weeks) treatment of obesity in dose range of 15 mg/day to 37.5 mg/day. PHEN has no serotonergic activity at clinical doses. Furthermore, unlike its congener, amphetamine, PHEN does not appear to enhance dopamine release;<sup>20</sup> therefore, its addiction potential is believed to be less than that of amphetamine.<sup>21</sup> Common adverse effects, typical of sympathomimetic amines, include dry mouth, headache, insomnia, nervousness, irritability, and constipation. More clinically significant side effects include palpitations, tachycardia, and hypertension.<sup>22</sup>

PHEN is primarily metabolized by the liver, and 70%–80% of the drug is cumulatively excreted in urine. Its elimination half-life is 19–24 hours.

## Topiramate

TPM is a fructose derivative, which was approved by the FDA for the treatment of seizure disorders (typical dose 400 mg/day) in 1996; it was also approved for migraine prophylaxis (typical dose 100 mg/day) in 2004. Weight loss, with a reduction in visceral body fat, has been observed with

TPM treatment among patients with seizure disorders and migraines.<sup>23</sup> Persistence of weight loss beyond the typical 6-month plateau was also noted. Subsequently, several randomized clinical trials examined the efficacy of TPM for weight reduction in obese patients with and without obesity-related comorbidities.<sup>24–31</sup>

TPM is a neurostabilizer that acts via modification of excitatory voltage-activated sodium and calcium channels, antagonism of alpha-amino-3-hydroxyl-4-isoxazole-propionic acid kainate (AMPA/KA) receptors, and enhancement of gamma-aminobutyric acid receptor-mediated inhibitory currents. Although the exact mechanism of action for weight loss with TPM is not known, animal experiments suggest that TPM-induced weight loss results from increased energy expenditure, decreased energetic efficiency, and decreased caloric intake as an appetite suppressant;<sup>32–34</sup> among these actions, decreased calorie intake appears to be a significant factor associated with TPM-induced weight loss in humans.<sup>25,35,36</sup> AMPA/KA receptor antagonism may lead to a reduction in compulsive or addictive food craving, as supported by an improvement in binge eating disorder;<sup>37,38</sup> Activation of gamma-aminobutyric acid receptors with TPM may decrease nightmares and sleep deprivation-induced feeding;<sup>39</sup> TPM is a potent inhibitor of carbonic anhydrase isoenzymes, thereby impeding lipogenesis.<sup>40,41</sup> The effect of TPM on carbonic anhydrase may contribute to TPM-induced hypophagia via altered taste sensitivity;<sup>42</sup> TPM may also influence body weight via its effects on hypothalamic corticotropin-releasing hormone and galanin.<sup>43</sup> Peripherally, TPM may enhance insulin action and glucose transport, as well as increase adiponectin secretion in the adipose tissue, thus potentially reducing metabolic disease.<sup>44,45</sup> Despite TPM's many favorable metabolic effects and consistent demonstration of weight loss efficacy in randomized controlled trials, its development as a monotherapy for obesity has been hindered by a high incidence of dose-dependent neuropsychiatric and cognitive adverse events such as memory and concentration impairment, language difficulties, and mood changes.<sup>46</sup>

TPM exhibits linear pharmacokinetics; elimination half-life is 19–25 hours. TPM is minimally metabolized and is primarily eliminated in the urine, unchanged, thus, it carries minimal potential for drug interactions via hepatic enzyme inhibition or induction. However, at doses greater than 200 mg/day, TPM may induce the metabolism of ethinylestradiol. In patients with severe renal impairment, due to reduced clearance of TPM, a cautious approach is recommended when using this drug at high doses.<sup>47</sup>

## Phentermine + TPM (PHEN/TPM)

The PHEN/TPM combination is a once-daily formulation designed to provide an immediate release of PHEN and a delayed release of TPM (ie, the drug combination produces peak exposure to PHEN in the morning and a peak concentration of TPM in the evening). A high-fat meal does not affect the pharmacokinetics of either PHEN or TPM when administered as PHEN/TPM at doses up to 15 mg/92 mg.<sup>48</sup> In vitro studies of PHEN and TPM indicate that these drugs are not likely to cause clinically significant interactions with drugs utilizing the cytochrome P450 enzyme pathways, or those involved in plasma protein binding displacement; however, there is evidence suggesting that ethinyl estradiol levels may be decreased by 16%, thus raising a concern about the possibility of decreased contraceptive efficacy.<sup>48</sup> In patients with moderate (creatinine clearance  $\geq 30$  to  $<50$  mL/minute) and severe renal dysfunction ( $<30$  mL/minute), the maximum dose of PHEN/TPM should not exceed 7.5/46 mg.<sup>19</sup>

## Efficacy

### Phase II trial

In this 24-week randomized clinical trial, a total of 200 patients were randomized in equal ratios to placebo, PHEN 15 mg, TPM 100 mg, or the combination of PHEN and TPM (PHEN/TPM).<sup>49</sup> PHEN was administered in the morning and TPM in the evening; commercially available preparations were used. Doses of PHEN and TPM were gradually increased to reach the full doses at week 4. A total of 79% of the randomized patients completed 24 weeks. In an intent-to-treat analysis with the last observation carried forward, body weight changes were  $-2.1\%$  for placebo,  $-4.6\%$  for PHEN,  $-6.3\%$  for TPM, and  $-10.7\%$  for PHEN/TPM. Half of the patents assigned to PHEN/TPM lost 10% or more weight; the corresponding proportions for placebo, PHEN, and TPM were 8%, 14%, and 16%, respectively. The most common adverse event was paresthesia, which was reported by 38% of patients receiving PHEN/TPM, 22% receiving TPM, 4% receiving PHEN, and 2% receiving placebo.

Subsequently, PHEN/TPM was evaluated in three Phase III trials for its long-term efficacy and safety; ancillary diet and lifestyle counseling were provided for patients in all trials.

### Phase III trials

The first of these studies was OB-301, a 28-week confirmatory trial with a factorial design involving seven treatment arms, tested two fixed-dose combinations – mid-dose PHEN/TPM (7.5/46 mg) and full-dose PHEN/TPM (15/92 mg) – as well as

mid- and full doses of the individual constituent drugs against placebo.<sup>48</sup> The study randomized 756 obese patients with a BMI range of 30–45 kg/m<sup>2</sup> to one of the seven treatment arms for 28 weeks. Patients treated with full-dose PHEN/TPM achieved an average weight change of –9.0%, as compared with –1.5% ( $P < 0.0001$ ) with placebo. Weight change with mid-dose PHEN/TPM was –8.2%. Weight changes with monotherapies were: –6.1% with TPM 92 mg, –4.9% with TPM 46 mg, –5.8% with PHEN 15 mg, and –5.2% with PHEN 7.5 mg. This trial and the subsequent 1-year trials used the once-a-day combination pill comprised of immediate-release PHEN and delayed-release TPM. Although it was anticipated that PHEN might offset TPM-induced psychiatric adverse events, this was not the case. The incidence of psychiatric adverse events was 27% with PHEN/TPM 15/92 mg, which was in contrast to 16% with TPM 92 mg. The study demonstrated that there was no evidence that PHEN/TPM could have fewer adverse effects than either drug alone.

OB-302 was a 56-week trial that randomized 1267 morbidly obese patients with a BMI  $\geq 35$  kg/m<sup>2</sup> (no BMI upper limit) without significant comorbidities to low-dose PHEN/TPM (3.7/23 mg), full-dose PHEN/TPM (15/92 mg), or placebo.<sup>50</sup> At baseline, the mean BMI for the entire study cohort was 42 kg/m<sup>2</sup>. Mean weight changes were –1.6% with placebo, –5.1% with low-dose PHEN/TPM, and –10.9% with full-dose PHEN/TPM. The proportions of patients achieving  $\geq 5\%$  weight loss were: 17% with placebo, 45% with low-dose PHEN/TPM, and 67% with full-dose PHEN/TPM (Table 1).

OB-303, the largest among the PHEN/TPM Phase III trials, randomized 2487 overweight or obese patients with a BMI of 27–45 kg/m<sup>2</sup> and two or more obesity-related comorbidities – hypertension, dyslipidemia, type 2 diabetes, prediabetes or abdominal obesity – to placebo, mid-dose PHEN/TPM (7.5/46 mg), or full-dose PHEN/TPM (15/92 mg) for 56 weeks.<sup>46</sup> Mean weight changes in the placebo, mid-dose PHEN/TPM, and full-dose PHEN/TPM

groups were –1.2%, –7.8%, and –9.8%, respectively. Weight loss of  $\geq 5\%$  was achieved by 21% of subjects assigned to placebo compared with 62% and 70% of subjects assigned to mid-dose PHEN/TPM and full-dose PHEN/TPM, respectively. Relative to placebo, there were greater reductions in systolic blood pressure, triglycerides, and fasting insulin with both doses of PHEN/TPM. A small, but statistically significant, reduction in total cholesterol was observed with both doses of PHEN/TPM. Statistically significant, albeit small, reductions in diastolic blood pressure and low-density lipoprotein-cholesterol were noted only with full-dose PHEN/TPM. High-density lipoprotein-cholesterol increased with both doses of PHEN/TPM relative to placebo (Table 2).

OB-305 was a 2-year extension of the OB-303 trial. A total of 676 patients who completed the OB-303 trial while taking the study drug were enrolled in OB-305 at selected sites.<sup>51</sup> Treatment assigned in OB-303 was continued in OB-305. Although there was weight regain in all treatment groups, the mean weight loss at the end of the 2 years was greater with mid-dose PHEN/TPM and full-dose PHEN/TPM (–9.3% and –10.5%, respectively) than with placebo (–1.8%).

### Obstructive sleep apnea trial

Patients with moderate to severe obstructive sleep apnea, confirmed with overnight polysomnography, were studied in a small Phase II trial with 23 patients randomized to full-dose PHEN/TPM and 22 to placebo; a total of 40 patients completed the full 28-week treatment.<sup>52</sup> It was reported that a change in the primary endpoint – the apnea-hypopnea index – favored PHEN/TPM over placebo with a greater reduction in events (–31.5 events versus –16.6 events).

### Safety and tolerability

In 1-year Phase III trials, twice as many patients discontinued due to an adverse event with full-dose PHEN/TPM compared with placebo (17.5% versus 8.5%); mid-dose PHEN/TPM

**Table 1** Effect of phentermine/topiramate on bodyweight at week 56 in phase III trials

Study	Treatment group	N*	Baseline mean weight, kg	Weight change	Percentage of patients with $\geq 5\%$ weight loss	Percentage of patients with $\geq 10\%$ weight loss
OB-302 <sup>50</sup>	Placebo	498	115.7	–1.6	17.3	7.4
	3.75/23 mg	234	118.6	–5.1	44.9	18.8
	15/92 mg	498	115.2	–10.9	66.7	47.2
OB-303 <sup>46</sup>	Placebo	979	103.3	–1.2	20.8	7.4
	7.5/46 mg	488	102.8	–7.8	62.1	37.3
	15/92 mg	981	103.1	–9.8	70.0	47.6

**Notes:** \*N denotes patients included in the intent-to-treat (ITT) analyses. Results are derived from intent-to-treat analyses with the last-observation-carried-forward. Weight changes shown are changes in least-squares means.

**Abbreviations:** 3.75/23 mg, phentermine 3.75 mg/topiramate 23 mg; 7.5/46 mg, phentermine 7.5 mg/topiramate 46 mg; 15/92 mg, phentermine 15 mg/topiramate 92 mg.

**Table 2** Effects of phentermine/topiramate on blood pressure and lipids at week 56 in phase III trials

Study	Treatment group	LS mean changes by ITT-LOCF					
		Blood pressure (mmHg)		Lipid parameters (%)			
		SBP	DBP	TG	HDL-C	LDL-C	TC
OB-302 <sup>50</sup>	Placebo	0.9	0.4	9.1	0	-5.5	-3.5
	3.75/23 mg	-1.8 <sup>b</sup>	-0.1 <sup>a</sup>	5.2 <sup>a</sup>	0.5 <sup>a</sup>	-7.7 <sup>a</sup>	-5.4 <sup>a</sup>
	15/92 mg	-2.9 <sup>d</sup>	-1.5 <sup>d</sup>	-5.2 <sup>d</sup>	3.5 <sup>c</sup>	-8.4 <sup>b</sup>	-6.0 <sup>b</sup>
OB-303 <sup>46</sup>	Placebo	-2.4	-2.7	4.7	1.2	-4.1	-3.3
	7.5/46 mg	-4.7 <sup>c</sup>	-3.4 <sup>a</sup>	-8.6 <sup>d</sup>	5.2 <sup>d</sup>	-3.7 <sup>a</sup>	-4.9 <sup>b</sup>
	15/92 mg	-5.6 <sup>d</sup>	-3.8 <sup>b</sup>	-10.6 <sup>d</sup>	6.8 <sup>d</sup>	-6.9 <sup>b</sup>	-6.3 <sup>d</sup>

Notes: <sup>a</sup>Not significant; <sup>b</sup>P < 0.05; <sup>c</sup>P < 0.001; <sup>d</sup>P < 0.0001.

Abbreviations: LS, least-squares; ITT-LOCF, intent-to-treat, last observation carried forward; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; 3.75/23 mg, phentermine 3.75 mg/topiramate 23 mg; 7.5/46 mg, phentermine 7.5 mg/topiramate 46 mg; 15/92 mg, phentermine 15 mg/topiramate 92 mg.

had fewer (11.5%) adverse-event related discontinuations compared with the high-dose. In addition, more patients on PHEN/TPM had dose reductions (14% with full-dose PHEN/TPM, 10% with mid-dose PHEN/TPM) than with placebo (3%). In general, adverse events occurred at a higher frequency with full-dose PHEN/TPM than with mid-dose PHEN/TPM or placebo. The most frequent adverse events of clinical interest with full-dose PHEN/TPM were paresthesia (20%), dry mouth (19%), constipation (16%), dysgeusia (9%), insomnia (9%), and dizziness (9%). Psychiatric adverse events occurred in 23% patients assigned to full-dose

PHEN/TPM, 15% on mid-dose PHEN/TPM, and 11% on placebo (Table 3).<sup>48</sup>

Regarding the safety of PHEN/TPM, the FDA expressed concerns in five areas: (1) teratogenicity; (2) cardiovascular; (3) cognitive; (4) psychiatric; and (5) metabolic acidosis.

Weight loss drugs are used disproportionately by women of childbearing potential; therefore, from a public health perspective, increased person-years of exposure among this population is a concern. Furthermore, despite precautions and the requirement for effective forms of contraception, numerous pregnancies are still reported in clinical trials

**Table 3** Most common treatment emergent adverse events in 1-year trials of phentermine/topiramate

Adverse event	Placebo N = 1,561	Treatment group		
		PHEN/TPM 3.75/23 mg N = 240	PHEN/TPM 7.5/46 mg N = 498	PHEN/TPM 15/92 mg N = 1580
Gastrointestinal events				
Dry mouth	2.8	6.7	13.5	19.1
Constipation	6.1	7.9	15.1	16.1
Nausea	4.4	5.8	3.6	7.2
Diarrhea	4.9	5.0	6.4	5.6
Nervous system events				
Paresthesia	1.9	4.2	13.7	19.9
Headache	9.3	10.4	7.0	10.6
Dysgeusia	1.1	1.3	7.4	9.4
Dizziness	3.4	2.9	7.2	8.6
Disturbance in attention	0.6	0.4	2.0	3.5
Psychiatric events				
Insomnia	4.7	5.0	5.8	9.4
Depression	2.2	3.3	2.8	4.3
Anxiety	1.9	2.9	1.8	4.1
Irritability	0.7	1.7	2.6	3.7
Other				
Fatigue	4.3	5.0	4.4	5.9
Blurred vision	3.5	6.3	4.0	5.4

Notes: Data are percentages of subjects reporting each adverse event. Shown are adverse events of clinical interest only.

Abbreviations: PHEN/TPM 3.75/23, phentermine 3.75 mg/topiramate 23 mg; PHEN/TPM 7.5/46, phentermine 7.5 mg/topiramate 46 mg; PHEN/TPM 15/92, phentermine 15 mg/topiramate 92 mg.

involving weight loss drugs. In recent years, reports have emerged indicating an increased risk of oral clefts (cleft lip and cleft palate) among infants born to mothers exposed to TPM during pregnancy. In a prospective observational study of the UK pregnancy registry, a significantly higher rate of oral clefts was observed with exposure to TPM.<sup>53</sup> In PHEN/TPM obesity trials, 34 pregnancies were reported, and the drug was discontinued soon after pregnancy became known; 19 pregnancies were carried to term, 15 births had exposure to TPM, and there were no fetal adverse outcomes.<sup>48</sup> Given the small number of pregnancies, the FDA relied on data from pregnancy registries and various surveillance programs, which indicated an increased risk of oral clefts with TPM exposure. As requested by the FDA, the manufacturer of Qsymia™ conducted a retrospective cohort study of four large health care databases to examine the prevalence of major congenital malformations and oral clefts among infants born to mothers exposed to TPM during pregnancy. The comparison group was infants of women who had previously taken antiepileptics, but not during pregnancy. Preliminary results showed a prevalence ratio of oral clefts of 2.0 (95% confidence interval, 0.7 to 5.7) in pregnancies exposed to TPM monotherapy versus those that were unexposed.<sup>54</sup> Analyses of data from the National Birth Defects Prevention Study and the Birth Defects study also showed an increased risk of oral clefts (pooled adjusted odds ratio [OR] 5.4; 95% confidence interval, 1.5 to 20.1).<sup>54</sup> An additional concern is that TPM may interfere with the pharmacokinetics of oral contraceptives, leading to failure of contraceptive protection, although such risk is unlikely at doses < 200 mg/day.

In 1-year trials, mid-dose PHEN/TPM and full-dose PHEN/TPM-treated patients experienced mean heart rate increases of 0.6 beats per minute (bpm) and 1.6 bpm, respectively, whereas there was no change in placebo-treated patients. A higher proportion of PHEN/TPM-treated patients also experienced a categorical increase in heart rate compared to placebo-treated patients (>20 bpm: 13.5% mid-dose PHEN/TPM, 19.6% full-dose PHEN/TPM versus 11.9% placebo). At 2 years, a small heart rate increase persisted with PHEN/TPM treatment, although the difference versus placebo was not statistically significant (placebo 0.4 bpm, mid-dose PHEN/TPM 1.3 bpm, full-dose PHEN/TPM 1.7 bpm).<sup>54</sup> Whereas PHEN/TPM treatment led to a small increase in heart rate, systolic and diastolic blood pressure decreased. Changes in the rate–pressure product (heart rate × systolic blood pressure),<sup>55</sup> which has been demonstrated to correlate with myocardial oxygen demand, were favorable with both

doses of PHEN/TPM and placebo.<sup>54</sup> There was no increase in the composite number of major adverse cardiac events (comprised of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) with PHEN/TPM relative to placebo.

TPM at doses used for epilepsy and migraine prophylaxis is associated with cognition-related adverse events – in particular, psychomotor slowing, difficulty with concentration and attention, memory impairment, and language difficulties.<sup>56,57</sup> PHEN/TPM treatment demonstrated the known cognitive adverse events of TPM monotherapy. In 1-year Phase III trials, the incidence of cognition-related adverse events was 1.7%, 2.0%, 5.6%, and 7.8% in the placebo, low-dose PHEN/TPM, mid-dose PHEN/TPM, and full-dose PHEN/TPM groups, respectively. The most common cognitive adverse event was disturbance in attention.<sup>48</sup> In the OB-301 trial, the Repeatable Battery for Assessment of Neuropsychological Status – a comprehensive battery to assess various aspects of cognition – was administered to examine the differences between mid- and full-doses of PHEN/TPM, as well as the individual constituents. The test results provided no compelling evidence to suggest that PHEN could mitigate the known cognitive adverse effects of TPM.<sup>48</sup>

In 1-year trials, psychiatric disorders, as a class, were twice as common with PHEN/TPM full-dose (23%) than with placebo (11%), with mid-dose PHEN/TPM falling in between at 15%. In comparison with placebo, depression-related adverse events were more frequent with full-dose PHEN/TPM, but not with the mid-dose PHEN/TPM; anxiety-related adverse events had a higher frequency with the mid-dose and full-dose. The percentages of patients who discontinued due to psychiatric adverse events were 4.8% with full-dose PHEN/TPM, 2.4% with mid-dose PHEN/TPM, and 1.2% with placebo. There was no increase in suicidality with PHEN/TPM at the doses tested.

Prior clinical trials of TPM monotherapy, as well as PHEN/TPM clinical experience, demonstrate that TPM can cause metabolic acidosis in some patients, possibly through the inhibition of carbonic anhydrase. In the 1-year safety cohort, 30% of patients treated with full-dose PHEN/TPM had serum bicarbonate levels < 21 mEq/L sometime after randomization compared to 22% on mid-dose PHEN/TPM, and 6% on placebo; this reduction in serum bicarbonate was also observed in the 2-year safety cohort (OB-305) for 30% of patients on full-dose PHEN/TPM, 23% on mid-dose PHEN/TPM, and 4% on placebo. Paresthesia, a frequently observed adverse effect of PHEN/TPM treatment, may be

related to decreased bicarbonate. Untreated chronic metabolic acidosis may increase the risk for osteomalacia, osteoporosis, and renal calculi. The incidence of kidney stones in PHEN/TPM Phase III trials was 1.2% with full-dose versus 0.3% with placebo.

## Therapeutic considerations

PHEN/TPM is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with diet and exercise. It is recommended for obese patients ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) or overweight patients ( $\text{BMI} \geq 27 \text{ kg/m}^2$ ) with obesity-related comorbidities such as hypertension, type 2 diabetes, or dyslipidemia. This combination drug therapy is available in four fixed-dose strengths: PHEN/TPM 3.75/23 mg (low dose), 7.5/46 mg (mid-dose), 11.25/69 mg (three-quarter dose), and 15/92 mg (full dose).<sup>19</sup> The recommended dose of PHEN/TPM is 7.5/46 mg; for selected patients, full-dose (15/92 mg) may be a consideration. In order to minimize adverse effects, physicians should start with the lowest dosage and slowly titrate as recommended. The proposed treatment regimen starts with low-dose PHEN/TPM, uptitrating over 2 weeks to mid-dose PHEN/TPM. Discontinuation or dose escalation should be considered for nonresponders (not achieving 3% weight loss after 3 months on the mid-dose). The three-quarter-dose is mainly intended to facilitate gradual escalation from the mid- to full-dose. PHEN/TPM should be discontinued if at least 5% weight loss is not achieved after 3 months on the full-dose. For patients on the full-dose, if a decision is made to stop, gradual discontinuation is recommended. Doses higher than 7.5/46 mg are not recommended for patients with moderate or severe hepatic or renal disease.

In compliance with the Risk Evaluation and Mitigation Strategy recommended by the FDA, PHEN/TPM is currently only available via a few pharmacies that provide home delivery. PHEN/TPM is contraindicated in pregnant women. To reduce the risk of teratogenicity, women of childbearing potential should have a negative pregnancy test prior to starting PHEN/TPM, and at monthly intervals thereafter. PHEN/TPM is not recommended for patients with recent or unstable cardiac or cerebrovascular disease; it is also contraindicated in patients with glaucoma and hyperthyroidism. Heart rate should be monitored regularly. PHEN/TPM should be avoided in patients with significant current depression, active suicidal ideation, or a history of suicide attempts. To minimize the risk of clinically significant metabolic acidosis, periodic electrolyte monitoring is prudent.

## Conclusion

PHEN/TPM combination therapy provides robust weight loss that is superior to weight loss achievable with either drug alone. Weight loss associated with PHEN/TPM may lead to improvements in some metabolic and glycemic parameters, blood pressure, and lipids. Weight loss efficacy of PHEN/TPM has been demonstrated to sustain for up to 2 years. Teratogenic potential and a slight increase in heart rate are important concerns. Psychiatric and cognitive adverse effects occur at a relatively high frequency. Patients need to be closely monitored for changes in weight, vital signs, mood, and appropriate laboratory markers, so that if a patient is not receiving the expected benefit or has significant adverse effects, treatment should be discontinued.

Although there are no head-to-head comparison trials, placebo-adjusted weight loss appears to be of a larger magnitude with PHEN/TPM than with lorcaserin, another recently approved drug to treat obesity; lorcaserin, on the other hand, appears to have superior tolerability.

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