A Review of the Combination of Phentermine and Topiramate Extended-Release for Weight Loss

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Received: August 8, 2012 / Published online: October 24, 2012
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ABSTRACT

The Food and Drug Administration recently approved the combination of phentermine and extended-release topiramate (PHN/TPM) for weight loss. This is one of only two weight-loss agents to arrive on the US market in the last decade. This product combines the anorexigenic agent, phentermine, which is approved for the short-term treatment of weight loss, with a carbonic anhydrase inhibitor, topiramate, which

is approved for non-weight loss indications, including seizure disorders and migraine headache. Although the combination is believed to be synergistic, no clinical trial data currently address this. The PHN/TPM combination is a once-daily formulation. Mean weight loss among participants who completed 1 year of PHN/TPM treatment in research trials, in combination with lifestyle modification, has ranged from approximately 7% (lower doses) to over 14% (higher doses), relative to approximately 2% with placebo. In addition to weight loss, PHN/TPM resulted in improved comorbidities and quality of life, although it has not been shown to improve mental/psychosocial issues. Among the common adverse events observed in clinical trials are paresthesia, dry mouth, constipation, and headache. Other noteworthy adverse events that occurred more commonly with PHN/TPM versus placebo included dysgeusia, insomnia, irritability, and alopecia. Laboratory abnormalities in serum bicarbonate and potassium were also observed in a subset of patients. Due to the teratogenic potential of topiramate, women of child-bearing potential are required to have a negative pregnancy test at baseline and are instructed to take monthly pregnancy tests. As part of a risk-management approach, only pharmacies certified

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by the manufacturer will be allowed to dispense PHN/TPM and will be required to provide information on birth defects. Like phentermine, the combination drug will be designated as a schedule IV medication. In comparison with other agents currently on the market, the combination of PHN/TPM appears to provide significant advantages for weight loss, while improving comorbid conditions and quality of life. Monitoring for laboratory abnormalities, adverse events, and changes in psychiatric status should occur during therapy.

Keywords: Combination; Obesity; Phentermine; Phentermine/topiramate; Topiramate; Weight loss

INTRODUCTION

Obesity leads to premature death [1] and impairs quality of life [2–4]. A representative sample of US adults in 2009–2010 indicated that 35.5% of men and 35.8% of women are obese [5]. Healthcare expenditures attributable to obesity were projected to reach \$147 billion in 2008 [6]. In 2006, per capita medical spending was \$1,429 higher for obese versus nonobese individuals [6]. Obesity is associated with several of the most common causes of mortality in the US: heart disease, stroke, certain cancers, diabetes, and renal disease [7]. One in every eight deaths is attributable to an illness directly related to obesity [8]. Despite these individual and societal burdens of obesity, treatment options remain limited.

A minority of patients is extremely successful in attaining and maintaining significant weight loss through lifestyle modification alone [9]. For the majority, however, lifestyle modification in the absence of a behavioral weight-loss program, pharmacotherapy regimen, or weight-loss surgery is inadequate. Pharmacotherapy is a much needed intermediate intervention

for those who are unsuccessful with lifestyle intervention alone and for whom weight-loss surgery is not indicated or desired. Currently, the pharmacotherapeutic options for obesity management are extremely limited. Although several drugs are in the obesity pipeline, the process for getting such drugs to market has recently proven difficult.

MATERIALS AND METHODS

Studies were found using PubMed. No limits on dates were set. Major keywords included phentermine and topiramate, phentermine, topiramate, pharmacotherapy for weight loss, lorcaserin, orlistat, and others.

INDICATIONS AND EFFICACY BENCHMARKS FOR PHARMACOTHERAPY

Pharmacotherapy for obesity is indicated for patients with a body mass index (BMI) ≥ 30 kg/m² or 27–29.9 kg/m² with a comorbid condition that increases cardiometabolic risk [10]. Pharmacotherapy is indicated in conjunction with supportive lifestyle modification counseling [11], and should be used with a reduced calorie diet and exercise regimen. Current indications for bariatric surgery include a BMI of ≥ 40 kg/m² or ≥ 35 kg/m² with significant obesity-related disorders [12]. Therefore, a substantial percentage of the population who are overweight/obese but do not meet criteria for surgery may benefit from a pharmacological intervention.

According to the US Food and Drug Administration (FDA), a weight-loss medication is deemed effective if it demonstrates one of the following after 1 year of treatment: (1) “The difference in mean weight loss between the active-product and placebo-treated groups is

at least 5% and the difference is statistically significant,” or (2) “The proportion of subjects who lose $\geq 5\%$ of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.” In addition, the FDA expects improvements in blood pressure, lipids, glycemia, or other comorbidities that are commensurate with the degree of weight lost [13].

A PERILOUS PAST FOR WEIGHT-LOSS PHARMACOTHERAPY

A historical look at the fate of some of the most commonly used prescription and herbal products for weight loss over the last three decades reveals multiple issues, which may have contributed to the FDA’s hesitancy in approving new medications. Dinitrophenol was withdrawn for risk of neuropathy and cataracts, aminorex was withdrawn due to pulmonary hypertension, and amphetamine use was discouraged due to risk of dependency and cardiac adverse events [14]. In 2004, the FDA mandated the removal of ephedrine-containing products due to cardiovascular concerns. Phenylpropanolamine, a sympathomimetic amine widely used as an appetite suppressant, was withdrawn in 2000 after being associated with intracranial hemorrhage [15].

Perhaps the most memorable pitfall in obesity pharmacotherapy involved fenfluramine-phentermine (fen-phen) in 1997. Although this combination was efficacious and widely prescribed, fenfluramine was withdrawn following FDA concerns about cardiac valve damage [16, 17].

Sibutramine was withdrawn in 2010 after results of the Sibutramine Cardiovascular Outcomes Trial (SCOUT) became available [18].

The SCOUT trial was a large, placebo-controlled, multicenter trial sponsored by the drug’s manufacturer to determine whether the drug could reduce cardiovascular mortality in a high-risk sample. Contrary to the study hypothesis, patients receiving sibutramine had a significantly higher rate of cardiovascular events versus placebo with overall incidences of 11.4% versus 10%, respectively. Although the sibutramine package labeling warned against treating patients at high cardiac risk, the FDA issued new warnings based upon these data, which ultimately led to the drug’s withdrawal.

Although never available in the US market, cannabinoid 1 receptor (CB1) antagonists, such as rimonabant, were in late-stage development by several pharmaceutical companies before being aborted due to the increased risk of depression/suicide. Rimonabant was also removed from the European market.

Other weight-loss medications and drug combinations are in the development process, including bupropion/naltrexone, bupropion/zonisamide, and tesofensine. The FDA approved Qsymia™ (Vivus, Inc., Mountain View, California, USA), a combination of phentermine and topiramate extended-release (PHN/TPM), most recently.

CURRENTLY AVAILABLE PHARMACOTHERAPY OPTIONS

In addition to phentermine, which is approved for the short-term treatment (3 months) of obesity, two additional agents are approved for longer term use. Orlistat is a lipoprotein lipase inhibitor available in prescription (120 mg) and over-the-counter formulations (60 mg), which works by inhibiting the breakdown and absorption of dietary fat. The pharmacological activity of orlistat is localized to the gastrointestinal tract, with less than 2% of the

drug being absorbed into systemic circulation [19]. This results in a toxicity profile consisting of gastrointestinal adverse effects, but relatively few serious side effects. However, the efficacy of orlistat is modest. A meta-analysis of orlistat trials of at least 12 months in duration showed a mean weight loss of 2.89 kg (95% confidence intervals [CI]: 2.27–3.51 kg) [20].

Lorcaserin is a serotonin 2C agonist that was recently approved by the FDA for weight loss at a dose of 10 mg twice daily. In three large, controlled trials lasting 52–104 weeks, including approximately 8,000 patients, placebo-subtracted weight loss was 3.0–3.7%, when combined with reduced calorie diet and exercise [21]. The most common adverse effects of lorcaserin in patients without diabetes included headache, dizziness, fatigue, nausea, dry mouth, and constipation. In diabetic patients, the most common side effects included hypoglycemia, headache, back pain, cough, and fatigue [21].

PHENTERMINE/EXTENDED-RELEASE TOPIRAMATE

In July 2010, an FDA advisory committee rejected PHN/TPM, with a vote of 10 to 6, due to concerns about increased heart rate, teratogenicity, and suicidality. In October 2010, the FDA requested additional data from Vivus, its manufacturer, to address these concerns. In February 2012, an FDA Scientific Advisory Committee recommended approval of PHN/TPM with some changes from the original submission. In July of 2012, PHN/TPM (formerly Qnexa® [Vivus, Inc.]) was approved as a schedule IV drug under the brand name, Qsymia™.

FORMULATION AND DOSAGES

PHN/TPM is a combination of an immediate-release formulation of the anorexigenic

agent, phentermine, and an extended-release formulation of the anticonvulsant medication, topiramate. Phentermine, with a history of use spanning 52 years, is currently the most widely prescribed drug for weight loss in the US with over 6.5 million prescriptions written in 2011 [22]. Topiramate has a 15-year history of use. The drug combination is formulated to produce peak exposure to phentermine in the morning and peak concentrations of topiramate in the evening [22].

The drug was approved in four dosage strengths of PHN/TPM: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg. The scientific rationale for the specific doses included in the combination is not clear, for example, 92 mg topiramate instead of the commercially available 100 mg dosage form of topiramate. The doses of topiramate used for weight loss are somewhat lower than for the other indications of the drug. The recommended migraine headache prophylaxis dose is 100 mg/day given in two divided doses [23]. The dose for partial-onset seizure and primary generalized tonic-clonic seizure is up to a maximum of 400 mg/day given in two divided doses, and similar doses are used for adjunctive therapy in these seizure disorders [24]. Topiramate doses up to 1,600 mg/day have been studied in epilepsy [23].

For weight loss, the recommended dosing is 3.75/23 mg once daily (in the morning) for 14 days with an increase to 7.5/46 mg thereafter [25]. If at least 3% of baseline body weight has not been lost after 12 weeks, the dose may be escalated or discontinued. If the dose is escalated, it should be done by prescribing the 11.25/69 mg dose for 14 days followed by increasing to the 15/92 mg dose. If after an additional 12 weeks on PHN/TPM 15/92 mg the patient has not experienced 5% weight loss, the drug should be discontinued [25]. Doses of 3.75/23 mg and 11.25/69 mg should be used for

titration purposes [25]. When discontinued, the drug should be reduced gradually by taking a dose every other day for at least a week before stopping treatment to prevent the precipitation of seizures [25]. In patients with moderate (creatinine clearance ≥ 30 to < 50 mL/min) and severe (< 30 mL/min) renal dysfunction, the maximum dose should not exceed 7.5/46 mg.

MECHANISM OF ACTION AND EFFICACY OF INDIVIDUAL AGENTS

Topiramate

It has been suggested that topiramate and phentermine may have synergistic effects toward weight loss [26], although this theory has not been tested in clinical trials. Until the combination of PHN/TPM is compared against each of the agents individually, claims of synergy cannot be addressed. Topiramate is currently FDA-approved for the treatment of seizure disorders and prophylaxis of migraine headaches [23]. The mechanism of action that contributes to weight loss is currently unclear. The pharmacology of topiramate is complex. It is known to block neuronal voltage-dependent sodium channels, antagonize 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid/kainite glutamate receptors, enhance gamma-aminobutyric acid activity, and weakly inhibit carbonic anhydrase [23].

Topiramate has been associated with weight loss in many treatment trials, including epilepsy [24], migraine headache [27, 28], bulimia nervosa [29, 30], binge-eating disorder [31, 32], antipsychotic-associated weight gain [33, 34], and obesity [35]. A recent meta-analysis [35] evaluated weight loss associated with topiramate across 10 randomized, controlled trials (RCTs) in overweight or obese patients, with or without comorbid conditions. Overall, patients lost an

average of 5.34 kg (95% CI -6.12 to -4.56 kg) beyond the loss observed with placebo [35]. This meta-analysis also showed that trials with longer treatment durations (> 28 weeks duration) demonstrated greater weight loss (6.58 kg; [95% CI -7.48 to -5.68 kg]) and that doses over 96 mg/day were associated with higher discontinuation rates in trials.

A recent 3-month study of 40 patients treated with topiramate 100 mg/day for migraine prophylaxis found no change in resting metabolic rate [36]. There were, however, statistically significant reductions in mean BMI, body fat ratio, and abdominal skin-fold measurements. The findings of this study led the authors to conclude that the anorexigenic activity of topiramate may occur through hypothalamic activity. It has been suggested that topiramate may also lead to weight loss through increased satiety due to decreased gastrointestinal motility, increased taste aversion, increased energy expenditure, and decreased caloric intake [22]. The propensity of topiramate to contribute to neuropsychiatric and cognitive events at higher dosages has hindered its development as a monotherapy for weight loss [37].

PHENTERMINE

Phentermine was approved by the FDA in 1959. Appetite reduction associated with phentermine is thought to be centrally mediated, including hypothalamic stimulation that results in norepinephrine release [23]. Phentermine is indicated for short-term use for weight reduction, in combination with a reduced calorie diet and exercise [23]. The utility of phentermine when used short-term according to its labeling is questionable.

Off-label use of phentermine has been examined in clinical trials of longer duration. A meta-analysis [20] evaluated the results

of six placebo-controlled RCTs. These trials ranged from 2–24 weeks and involved dosages of 15–30 mg/day. Lifestyle intervention was included in over 80% of patients. The average weight loss in these trials was 3.6 kg (95% CI 0.6–6.0 kg) above placebo.

Phentermine is generally well-tolerated. Common side effects are characteristic of sympathomimetic amines, including dry mouth, headache, insomnia, nervousness, irritability, and constipation. More serious side effects include palpitations, tachycardia, and hypertension [38]. Phentermine should be avoided in patients with hyperthyroidism, glaucoma, agitated states, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-severe hypertension, a history of substance abuse, or those who would have a drug interaction (e.g., monoamine oxidase inhibitors).

CLINICAL TRIALS INVOLVING PHN/TPM

Three large RCTs address the efficacy of PHN/TPM for weight loss. A fourth trial has been completed but not yet published (EQUATE). These trials provide efficacy and tolerability information regarding the effect of this drug combination on comorbid conditions. All trials were funded by Vivus, the manufacturer of the PHN/TPM combination. The published trials include: CONQUER [37], EQUIP [39], and SEQUEL [40]. The results of each of these trials will be discussed in detail and a summary of each is presented in Table 1 [37, 39, 40].

The EQUIP study [39] was a 56-week, three-arm, double-blind, parallel-group study conducted at 91 centers across the US. The study included a blinded 4-week titration period and subsequent 52-week treatment period. Patients 18–70 years of age were included who had a BMI of ≥ 35 kg/m². Patients were relatively

free of comorbid conditions. Participants were randomized in a 2:1:2 ratio to placebo ($n = 514$), PHN/TPM 3.75/23 mg ($n = 241$), and PHN/TPM 15/92 mg ($n = 512$). Participants were provided with “standardized lifestyle counseling” based upon the Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN) manual [41] and were instructed to follow a 500 kcal dietary reduction along with increased water intake with increased physical activity. Participants were mostly women (83%) and the mean total BMI was 42 kg/m².

The CONQUER study [37] was a 56-week, randomized, double-blind RCT conducted at 93 centers across the US. Participants 18–70 years of age were enrolled with a BMI ≥ 27 – ≤ 45 kg/m², with two or more comorbid conditions (hypertension, hyperlipidemia, diabetes, impaired glucose tolerance, or high waist circumference). The majority of patients in this trial were women (70%), and the mean BMI was 36.6 kg/m². Comorbidity rates were hypertension (52%), hypertriglyceridemia (36%), impaired glucose tolerance or impaired fasting glucose (68%), and type 2 diabetes (16%). Patients were randomized in a 2:1:2 ratio to either daily placebo, PHN/TPM 7.5/46 mg, or PHN/TPM 15/92 mg. As with EQUIP, participants received lifestyle counseling, and dietary and fitness instructions.

The SEQUEL study [40] assessed the efficacy and safety of PHN/TPM for longer-term use in overweight/obese individuals with existing cardiometabolic disease. This was a 52-week, placebo-controlled, double-blind, extension study following CONQUER. Participants who completed and complied with the CONQUER trial were eligible for SEQUEL. Patients continued the product to which they were originally randomized, in conjunction with lifestyle modification. Interestingly, more participants met criteria for type 2 diabetes mellitus at baseline in

Table 1 Overview of major PHN/TPM studies

Study name, primary author, year, study sponsor	Study duration, study design, intervention(s)	Participants: <i>N</i> , characteristics	Efficacy: % weight loss	Attrition and reasons
EQUIP [39]	56 weeks	plc: <i>n</i> = 514 3.75/23: <i>n</i> = 241	ITT analysis: plc: 1.6%	Completion rates: total: 53.7%
Allison et al., 2011	DB, RCT	15/92: <i>n</i> = 512	3.75/23: 5.1% 15/92: 10.9%	plc: 46.9% 3.75/23: 57.3% 15/92: 58.8%
Vivus, Inc.	Energy deficit, LEARN manual + one of three groups	M & F Age 18–70 years BMI ≥35 kg/m ²	Completer analysis: plc: 2.1% 3.75/23: 6.7% 15/92: 14.4%	Most common reasons: - lost to follow-up - withdrawal of consent - adverse events
CONQUER [37]	56 weeks	plc: <i>n</i> = 994 7.5/46: <i>n</i> = 498	ITT analysis: plc: 1.2%	Completion rates: total: 69.3%
Gadde et al., 2011	DB, RCT	15/92: <i>n</i> = 995	7.5/46: 7.8% 15/92: 9.8%	plc: 62% 7.5/46: 75.1% 15/92: 73.7%
Vivus, Inc.	Energy deficit, LEARN manual + one of three groups	BMI ≥27 and ≤45 kg/m ² + two or more comorbidities	Completer analysis: plc: 1.6% 7.5/46: 9.6% 15/92: 12.4%	
SEQUEL [40]	52-week extension after 56-week	<u><i>n</i> (% of CONQUER patients)</u>	ITT-LOCF: plc: 1.8% 7.5/46: 9.3%	Completion rates (weeks 56–108): plc: 86.3%
Garvey et al., 2012	CONQUER study	plc: 227 (69.4%) 7.5/46: 153 (79.4%) 15/92: 295 (85.5%)	15/92: 10.5%	7.5/46: 82.5% 15/92: 83.1%
Vivus, Inc.	DB, PC Lifestyle modification + continuation in one of three groups	BMI ≥22 kg/m ²	Completer analysis: plc: 2.2% 7.5/46: 9.3% 15/92: 10.7%	Most common reasons - lost to follow-up - withdrew consent - adverse event

3.75/23 phentermine 3.75 mg + topiramate 23 mg extended-release capsules, 15/92 phentermine 15 mg + topiramate 92 mg extended-release capsules, 7.5/46 phentermine 7.5 mg + topiramate 46 mg extended-release capsule, *BMI* body mass index, *DB* double-blind, *F* female, *ITT* intention to treat, *LEARN* Lifestyle, Exercise, Attitudes, Relationships, and Nutrition, *LOCF* last observation carried forward, *M* male, *PC* placebo-controlled, *PHN/TPM* phentermine and extended-release topiramate, *plc* placebo, *RCT* randomized, controlled trial

the SEQUEL extension study compared with the CONQUER cohort (21.5% vs. 15.8%). Percentage rates of participation were as follows: 15/92 mg (85.5%), 7.5/46 mg (79.4%), placebo (69.4%).

EFFICACY FOR WEIGHT LOSS

In the EQUIP trial, weight loss was highest for patients in the 15/92 mg PHN/TPM group, and both drug groups lost significantly more weight than placebo in each analysis. Study completers lost 14.4% of baseline weight on PHN/TPM 15/92 mg, 6.7% on PHN/TPM 3.75/23 mg, and 2.1% on placebo. Higher percentages of patients lost at least 5%, 10%, and 15% of baseline weight on active medication versus placebo. Weight loss $\geq 10\%$ was achieved by 67.7% of participants with PHN/TPM 15/92 mg, 27.7% with PHN/TPM 3.75/23 mg, and 13.0% with placebo.

The CONQUER trial showed significantly greater weight reductions for both drug groups versus placebo. The completer analysis showed reductions of -9.9 kg (least squares mean -9.6%), -12.9 kg (-12.4%), and -1.8 kg (-1.6%) with PHN/TPM 7.5/46 mg, 15/92 mg, and placebo, respectively. Significantly higher percentages of participants lost $\geq 10\%$ of baseline weight in the PHN/TPM groups. This threshold was reached by 37% in the PHN/TPM 7.5/46 mg group, 48% in the PHN/TPM 15/92 mg group, and 7% in the placebo group in ITT analyses.

Weight-loss efficacy in SEQUEL was greater in both medication groups versus placebo. Least squares mean percentage change in weight from baseline to week 108 in the intent-to-treat (ITT) Last Observation Carried Forward (LOCF) analysis was significantly greater in the PHN/TPM groups versus placebo: -9.3% (PHN/TPM 7.5/46 mg), -10.5% (PHN/TPM 15/92 mg), and -1.8% (placebo). A completer analysis revealed similar results. Significantly more patients in both drug groups achieved losses of 5%, 10%, and 15%

versus placebo. More patients in the 15/92 mg dose group lost 20% or more of baseline body weight versus those on placebo. In SEQUEL, the PHN/TPM 15/92 mg dose was found to be superior to the 7.5/46 mg dose and placebo for weight loss in participants with the highest BMIs (baseline BMI 40 and 45 kg/m²).

Weight loss observed in trials of PHN/TPM appears to be greater than weight loss reported in lorcaserin trials and in some of the trials of bupropion/naltrexone. In three large (approximately 8,000 patients) lorcaserin RCTs of 52–104 weeks duration, weight loss was 3.0–3.7% versus placebo when combined with reduced calorie diet and exercise [21]. Data from the first year of treatment in the large Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) and Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trials of lorcaserin showed a 5.8% weight loss [42]. In four large 56-week bupropion/naltrexone trials consisting of approximately 4,500 patients, weight loss ranged from approximately 5.0–9.3% [43].

EFFICACY FOR WEIGHT-RELATED COMORBID CONDITIONS

In EQUIP, comorbidities improved significantly with 15/92 mg PHN/TPM versus placebo for waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, triglycerides, total cholesterol/high-density lipoprotein (HDL) ratio, total cholesterol, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol. Improvements in the PHN/TPM 3.75/23 mg group did not always reach statistical significance when compared against placebo.

Comorbidities in CONQUER were also generally improved in PHN/TPM versus placebo. Significant improvements were observed for

waist circumference, blood pressure, lipids, glycemia, C-reactive protein, and adiponectin. Among patients with hypertension, those on active PHN/TPM had a greater reduction in SBP versus placebo, and patients on PHN/TPM discontinued more antihypertensive medications versus placebo. A complication in interpretation of the comorbidity data from CONQUER is that patients' comorbidities were managed according to the "standards of care" and concomitant medications could be adjusted accordingly. This makes it difficult to determine whether the PHN/TPM combination had an independent effect, or even a weight-loss mediated effect, on comorbid conditions beyond the improved monitoring and management that was provided as part of the study. The longer-term SEQUEL study found continued reduction in many comorbid conditions. Improvement in comorbidities can be reviewed in Table 2 [37, 39, 40].

ADVERSE EVENTS

When PHN/TPM data were analyzed and presented to the FDA in aggregate, the most frequently reported treatment emergent adverse events included paresthesia (17%), dry mouth (16.6%), constipation (15.1%), upper respiratory tract infection (13.5%), nasopharyngitis (10%), and headache (9.8%) [22]. Additional dose-related adverse effects that were more common in PHN/TPM versus placebo included dysgeusia, insomnia, irritability, and alopecia [22]. Additional information on study-specific adverse events may be found in Table 2.

LABORATORY ABNORMALITIES

It is thought that the inhibition in carbonic anhydrase that occurs with topiramate contributes to changes in bicarbonate,

potassium, and risk of nephrolithiasis. When looking at laboratory results overall, there were no differences between the medication and placebo groups regarding the incidence of serious laboratory-related adverse events or drug discontinuations due to laboratory adverse events [22]. There were, however, some notable laboratory findings reported in the major trials. All cases of hypokalemia associated with a potassium value <3 mmol/L plus a reduction of >0.5 mmol/L from baseline reportedly occurred in patients taking non-potassium-sparing diuretics [22]. More information on laboratory abnormalities that occurred during clinical trials can be found in Table 2.

PSYCHIATRIC AND NEUROCOGNITIVE ADVERSE EVENTS

In EQUIP, psychiatric side effects were assessed with the Patient Health Questionnaire-9 (PHQ-9) [44] and the Columbia Suicide Severity Rating Scale (C-SSRS) [45]. Mean PHQ-9 scores indicated improvements in depressive symptoms over time in all treatment groups, with no between group differences observed. No increases in suicidal ideation or behavior were identified on the C-SSRS for any participants. It should be noted that participants had minimal depressive symptoms at baseline (mean PHQ-9 = 2.8) due to exclusionary criteria (PHQ-9 >10). Data presented in study appendices reflect that there may be a small number of patients whose psychiatric function worsens while on the drug. Psychiatric and neurocognitive effects have not been specifically and thoroughly assessed in patients with clinical depression or other significant mental health disorders. Therefore, clinicians should monitor for any potential worsening of these conditions if PHN/TPM is started.

Table 2 Comorbid condition improvement and adverse events in major PHN/TPM trials (*continued on next page*)

	EQUIP [39] (ITT + LOCF)	CONQUER [37] (ITT + LOCF)	SEQUEL [40] (ITT + LOCF, weeks 0–108)
Comorbidities			
Blood pressure			
(LS mean % change), mmHg			
SBP			
15/92	2.9 ↓	5.6 ↓	4.3 ↓
3.75/23 or 7.5/46	1.8 ↓	4.7 ↓	4.7 ↓
Plc	0.9 ↑	2.4 ↓	3.2 ↓
DBP			
15/92	1.5 ↓	3.8 ↓	3.5 ↓
3.75/23 or 7.5/46	0.1 ↓	3.4 ↓	3.7 ↓
Plc	0.4 ↑	2.7 ↓	3.9 ↓
Lipids			
(LS mean % change), %			
LDL			
15/92	8.4 ↓	6.9 ↓	5.6 ↓
3.75/23 or 7.5/46	7.7 ↓	3.7 ↓	4.6 ↓
Plc	5.5 ↓	4.1 ↓	10.7 ↓
HDL			
15/92	3.5 ↑	6.8 ↑	11.9 ↑
3.75/23 or 7.5/46	0.5 ↑	5.2 ↑	7.3 ↑
Plc	0	1.2 ↑	4.7 ↑
TG			
15/92	5.2 ↓	10.6 ↓	13.7 ↓
3.75/23 or 7.5/46	5.2 ↑	8.6 ↓	12.5 ↓
Plc	9.1 ↑	4.7 ↑	0.4 ↑

Table 2 continued

	EQUIP [39] (ITT + LOCF)	CONQUER [37] (ITT + LOCF)	SEQUEL [40] (ITT + LOCF, weeks 0–108)
Glucose			
(LS mean % change)			
15/92	FG: 0.6 mg/dL↓	HbA _{1c} : 0.1%↓	HbA _{1c} (in type 2 DM subgroup): 0.2%↓
3.75/23 or 7.5/46	0.8 mg/dL↑	0%	0.4%↓
Plc	1.9 mg/dL↑	0.1%↑	0.04%↓
Adverse events	DC due to AEs:	DC due to AEs:	SAEs:
(% of subjects, except as noted)	15/92: 16%	15/92: 19.0%	15/92: 8.1%
	3.75/23: 11.3%	7.5/46: 12.0%	7.5/46: 5.9%
	plc: 8.4%	plc: 9.0%	plc: 6.2%
	Reasons for DC:	HR:	Most common AEs:
	insomnia, irritability, anxiety, headache,	15/92: 1.7 bpm↑	upper respiratory tract infection,
	attention disturbance, depression,	7.5/46: 0.1 bpm↑	constipation, paresthesia,
	dry mouth, nephrolithiasis	plc: 0.1 bpm↓	sinusitis, dry mouth
	TEAEs	SAEs:	HR:
	paresthesia (18.8% with 15/92 vs. 4.2%	nephrolithiasis > 15/92 vs. 7.5/46 and plc	15/92: 1.7 bpm↑
	with 3.75/23 vs. 1.9% plc), dry mouth,	Other dose-related trends	7.5/46: 1.3 bpm↑
	dysgeusia, insomnia	dry mouth, constipation, dysgeusia,	plc: 0.4 bpm↑
	Other AEs more common with drug:	paresthesia, insomnia, dizziness, anxiety,	Psychiatric AEs:
	alopecia (15/92: 4.3%, 3.75/23: 2.1%,	irritability, disturbance in attention	anxiety
	plc: 1%) hypoesthesia, depression,		plc: 3.1%
	irritability, anxiety, attention, disturbances,		7.5/46: 6.5%
	and other less frequent events		15/92: 9.5%
	HR:		depression
	15/92: 1.2 bpm↑		plc: 7.9%
	3.75/23: 0.3 bpm↓		7.5/46: 3.9%
	plc: 0.2 bpm↓		15/92: 8.1%

Table 2 continued

	EQUIP [39] (ITT + LOCF)	CONQUER [37] (ITT + LOCF)	SEQUEL [40] (ITT + LOCF, weeks 0–108)
Laboratory abnormalities: (% of subjects, except as noted)	Bicarbonate: 15/92: 1.7 mEq/L↓ 3.75/23: 1.6 mEq/L↓ plc: 0.3 mEq/L↓ Significant reduction in bicarbonate ^a : 15/92: 0.8% 3.75/23: 1.3% plc: 0% Serum potassium reductions: 15/92: 1.0% 3.75/23: 0.4% plc: 0%	Bicarbonate: 15/92: 1.0 mmol/L↓ 7.5/46: 0.3 mmol/L↓ plc: 0.5 mmol/L↑ Significant reduction in bicarbonate ^a : 15/92: <1% (<i>n</i> = 7) 7.5/46: <i>n</i> = 1 plc: <i>n</i> = 1 Significant reduction in potassium ^b : 15/92: 5.0% 7.5/46: 4.0% plc: 1.0%	Bicarbonate: 15/92: 0.2 mEq/L↑ 7.5/46: 0.7 mEq/L↑ plc: 2.2 mEq/L↑ Decrease in bicarbonate of >5 mEq/L × two visits: 15/92: 16.3% 7.5/46: 13.1% plc: 1.8%

3.75/23 phentermine 3.75 mg + topiramate 23 mg extended-release capsules, 15/92 phentermine 15 mg + topiramate 92 mg extended-release capsules, 7.5/46 phentermine 7.5 mg + topiramate 46 mg extended-release capsule, *AE* adverse event, *DC* discontinuation, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *FG* fasting glucose, *HbA_{1c}* hemoglobin A1c, *HDL* high density lipoprotein, *HR* heart rate, *ITT* intention to treat, *LDL* low density lipoprotein, *LOCF* last observation carried forward, *LS* least square, *PHN/TPM* phentermine and extended-release topiramate, *SAE* serious adverse event, *plc* placebo, *SBP* systolic blood pressure, *TEAE* treatment emergent adverse events-defined as those which occur more frequently with medication versus placebo and occur at a rate of >5%, *TG* triglyceride

^a Significant reduction in bicarbonate: defined as reduction to ≤17 mEq/L on two consecutive visits or at study exit

^b Significant reduction in potassium: potassium concentrations below 3.5 mmol/L on two consecutive visits or at study exit

In CONQUER, no increase in suicidality was observed with drug versus placebo. Adverse event rates due to depression in the safety sample were similar in all three treatment groups (3–4%). Anxiety and irritability were significantly more common in the PHN/TPM 15/92 mg group versus placebo (4% vs. 2% for anxiety; 3% vs. <1% for irritability). Generally, psychiatric adverse events occurred early in treatment (median 29 days in the PHN/TPM 15/92 mg group) and lasted 29 days (median) in the PHN/TPM 15/92 mg group. Disturbance in attention was observed in 4% of those in the PHN/TPM 15/92 mg group, 2% in the PHN/TPM 7.5/46 mg group, and <1% in the placebo group, differences that were significant for both drug groups versus placebo. These cognitive side effects emerged to a median of 23–25 days into treatment and lasted a median of 51 days in the PHN/TPM 7.5/46 mg group and 36 days in the PHN/TPM 15/92 mg group. In all cases, cognitive disturbances resolved after drug discontinuation.

In SEQUEL, there was no apparent increase in serious suicidal ideation or suicidal behavior as assessed during the 108 weeks of observation. Depression-related adverse events were comparable between groups. Anxiety-related adverse events correlated with higher doses. Rates of anxiety were found to be 3.1%, 6.5%, and 9.5% for placebo, PHN/TPM 7.5/46 mg, and PHN/TPM 15/92 mg, respectively. No serious anxiety-related events occurred but did lead to discontinuation in one PHN/TPM 15/92 mg patient and severe symptoms in two additional patients in the higher-dose group.

PREGNANCY OUTCOMES AND POTENTIAL TERATOGENICITY

One of the FDA Advisory Panel's major concerns with the approval of PHN/TPM involved the teratogenic potential of the drug. Topiramate is

currently marketed in Pregnancy Category D. In some cases, topiramate may be continued during pregnancy when the risk of seizures in a woman with epilepsy or severe migraines outweighs the potential for fetal malformation [22]. In the case of PHN/TPM, the plan is to have a contraindication for pregnant women and immediately discontinue the drug if a woman becomes pregnant during treatment.

The teratogenic potential of PHN/TPM continues to be investigated. A large, observational retrospective study (Fetal Outcome Retrospective TopiRamate ExpoSure Study [FORTRESS]) is underway to quantify the fetal risk associated with topiramate [22]. Other sources of data concerning fetal risk with topiramate are being evaluated. To date, it appears that during the first trimester of pregnancy, topiramate has no overall effect on the prevalence of major congenital malformations, but may increase the prevalence of oral clefts by two- to fivefold. Data are currently too limited to conclusively determine the true teratogenic potential of topiramate.

Fifteen pregnancies occurred in women randomized to PHN/TPM during EQUIP. Of these, six resulted in abortion (three spontaneous, three elective), and nine resulted in healthy live births with no evidence of congenital malformation. Two pregnancies occurred in the SEQUEL study, one in the placebo group and one in the PHN/TPM 15/92 mg group. The pregnancy in the drug group was carried to term with no evident teratogenic effects.

An additional consideration is that topiramate may interfere with the pharmacokinetics of hormonal contraceptives. Estrogen and progestin levels are reduced by topiramate, particularly at doses of >200 mg/day [23]. The dosage of topiramate in the combination of PHN/TPM 15/92 mg was found to reduce the exposure of a single dose of ethinyl estradiol 35 µg by 16% and

increase the exposure of norethindrone 1 mg by 22% [25]. The manufacturer states that these changes are unlikely to affect contraceptive effectiveness, although irregular bleeding may occur [25]. Nevertheless, the patient brochure on PHN/TPM recommends that oral contraceptives be used in combination with barrier methods of contraception. It is recommended by the manufacturer that women of childbearing potential produce a negative pregnancy test at baseline and monthly thereafter during therapy.

This drug will be dispensed only through pharmacies certified by the manufacturer. This requirement is part of a Risk Evaluation and Mitigation Strategy (REMS) to help prevent birth defects. To become certified, pharmacies must agree to dispense a patient medication guide and a brochure with each PHN/TPM prescription that specifically warns patients about birth defects with PHN/TPM, and pharmacies must agree to educate pharmacy personnel accordingly.

QUALITY OF LIFE

In the CONQUER trial, both health-related quality of life and weight-related quality of life were assessed; for EQUIP, only weight-related quality of life was assessed. The Medical Outcomes Study Short Form-36 (SF-36) [46] was used to assess health-related quality of life, and the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) was used to assess weight-related quality of life [47].

Participants receiving PHN/TPM 7.5/46 mg and 15/92 mg in both EQUIP and CONQUER trials experienced significant improvements versus placebo ($P < 0.05$) on IWQOL-Lite total score and all subscales (physical function, self-esteem, sexual life, public distress, and work). Significant differences were observed for participants on PHN/TPM 3.75/23 mg only on physical function [48]. SF-36 results (CONQUER)

indicated significant improvements for both PHN/TPM groups versus placebo ($P < 0.05$) on physical functioning, physical role, bodily pain, general health, vitality, and Physical Component Summary. When stratified by weight loss (inclusive of all groups), improvements in IWQOL-Lite and SF-36 were greater with greater weight reductions [48].

CONCLUSION

The authors identified five major points regarding PHN/TPM treatment. (1) Weight loss exceeds FDA efficacy benchmarks and appears to continue or be maintained for at least 2 years with continued use of the drug. (2) The most common adverse effects include paresthesia, dry mouth, and constipation. Among psychiatric side effects, anxiety symptoms seem to be most common. (3) Laboratory abnormalities can include reductions in bicarbonate and in some cases hypokalemia. (4) PHN/TPM should be avoided in women desiring pregnancy or becoming pregnant due to potential teratogenic effects associated with topiramate (particularly oral cleft defects). (5) Weight loss induced by PHN/TPM 7.5/46 mg and 15/92 mg improved both weight-specific and physical quality of life concerns, but did not improve general mental/psychosocial concerns.

ACKNOWLEDGMENTS

Dr. Steffen is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of Interest. Neither author received any funding/sponsorship for preparing this manuscript. Dr. Kolotkin has received financial compensation for previous consulting work for Vivus and Orexigen.

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