Drug Saf (2014) 37:693–702
DOI 10.1007/s40264-014-0206-3

REVIEW ARTICLE

Tolerability and Safety of the New Anti-Obesity Medications

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Published online: 6 August 2014

Abstract Worldwide obesity prevalence has nearly doubled since 1980. Due to numerous co-morbidities, obesity represents a serious health and socioeconomic problem worldwide. Pharmacotherapy should be an integral part of comprehensive obesity management. Drug therapy can assist in weight loss and its maintenance in those individuals who do not achieve appropriate weight loss through lifestyle interventions alone. After the withdrawal of sibutramine from the market in 2010, orlistat, a lipase inhibitor, was the only remaining prescription drug approved for the long-term treatment of obesity. In 2012, phentermine/topiramate extended-release (PHEN/TPM ER) combination and lorcaserin were approved by the US FDA as novel medications for long-term weight management. Three major phase III trials conducted with each drug confirmed their efficacy in terms of weight loss/maintenance and improvement of cardiometabolic risks. No head-to-head studies between the two new anti-obesity drugs have been carried out. However, in the existing studies PHEN/TPM ER had a superior weight loss profile to lorcaserin but the incidence of adverse effects was lower with lorcaserin. Both drugs were well-tolerated, and adverse events were modest in intensity, dose dependent, rather rare, and tended to decrease with the duration of treatment. Major safety concerns regarding PHEN/TPM ER include elevations in resting pulse rate, teratogenicity, mild metabolic acidosis, and psychiatric and cognitive adverse events. Valvulopathy, cognitive impairment, psychiatric disorders, and hypoglycemia represent major safety concerns for lorcaserin. Although existing trials have not demonstrated any significant issues with PHEN/TPM ER-induced heart rate elevation and lorcaserin-induced valvulopathy, all safety concerns should be seriously taken into account in patients treated with either of these novel anti-obesity medications.

Key Points

Both of the new anti-obesity drugs, phentermine/topiramate extended release and lorcaserin, provide additional weight loss and a reduction of cardiometabolic health risks over the results achieved by lifestyle interventions alone.

The novel drugs are well-tolerated and adverse events are reduced with the duration of treatment.

Obesity treatment should be individually tailored and specific safety concerns regarding each novel anti-obesity drug should be seriously evaluated by the prescribing physician.

1 Introduction

Worldwide obesity prevalence has nearly doubled since 1980. In 2008, more than 1.4 billion adults were overweight and over 500 million were obese [1]. Obesity is related to multiple chronic diseases such as type 2 diabetes mellitus,

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dyslipidemia, hypertension, cardiovascular diseases, arthritis, and certain cancers. Obesity decreases quality of life, reduces life expectancy, and causes considerable healthcare costs [1, 2]. A low-energy diet, increased physical activity, and cognitive–behavioral therapy represent the core components of lifestyle intervention in obesity management [3]. To achieve long-term effects, anti-obesity drugs and bariatric and/or metabolic surgery are often required. Bariatric/metabolic surgery is the most efficient method in terms of weight loss and reduction in health risks, particularly type 2 diabetes; however, specific indications and contraindications for bariatric surgery should be taken into account as well as the limited capacity of specialized bariatric facilities [4].

Meta-analysis of seven major randomized studies conducted in adults and five randomized studies performed in children demonstrated that lifestyle intervention alone is effective only if applied intensively and continuously in highly motivated individuals [5]. It is clear that such intervention is expensive and time consuming. Skepticism about the role of lifestyle intervention was further supported by the recent results of the Look AHEAD (Action for Health in Diabetes) study. Intensive lifestyle intervention over 9.6 years in type 2 diabetics did not reduce the rate of cardiovascular events in overweight and obese patients, although meaningful weight loss $\geq$5 % was achieved in 50 % of patients at 8-year follow-up [6, 7].

The objective of this review is to summarize data on the efficacy, safety, and tolerability of currently available new anti-obesity drugs (phentermine/topiramate and lorcaserin) as well as those that are expected to be approved in the near future (cetilistat, naltrexone/bupropion, liraglutide).

2 Withdrawal of Anti-Obesity Drugs Due to Adverse Events

The withdrawal of several anti-obesity drugs from the market led to disappointment regarding the role of pharmacotherapy in the treatment of obesity. Fenfluramine, dexfenfluramine, rimonabant, and sibutramine were withdrawn from the market due to safety concerns. Fenfluramine, dexfenfluramine, and a combination of fenfluramine with phentermine were voluntarily withdrawn from the market in 1997. In the drug-treated individuals, heart valve disease and pulmonary hypertension developed in response to the stimulation of serotonin 5-HT_{2B} receptors in peripheral tissues including the cardiovascular system [8]. Rimonabant, a blocker of cannabinoid receptors (CB1), affected CB1 receptors both in the brain and in peripheral tissues. This drug was approved as an anti-obesity agent only in some European countries. However, serious psychiatric adverse events such as anxiety, depression, and suicidal ideation [9] led to its withdrawal from the market in 2009. In contrast to fenfluramine, dexfenfluramine, and rimonabant, the withdrawal of sibutramine in 2010 may be considered as controversial. The reason for its voluntary withdrawal from the market both in Europe and the USA was based on the results of the costly SCOUT (Sibutramine Cardiovascular Outcomes Trial) [10]. This long-term trial in patients at high risk of cardiovascular diseases was demanded by the European Medicines Agency (EMEA). Over 10,000 overweight or obese subjects aged >55 years with known cardiovascular disease or type 2 diabetes were enrolled. It is important to mention that according to the drug labeling, more than 90 % of the recruited individuals were contraindicated. Furthermore, non-responders were not excluded from the study. These risky patients were followed for 6 years. A significantly higher incidence of non-fatal myocardial infarctions and strokes was observed in the sibutramine-treated individuals than in the placebo-administered subjects (11.4 vs. 10.0 %). After the removal of sibutramine from the market, orlistat, a lipase inhibitor, remained the only prescription drug approved for the long-term treatment of obesity [11].

Skepticism about the pharmacotherapy of obesity was further enhanced when clinical trials with several novel anti-obesity drugs (e.g., ecopipam, growth hormone analogs, topiramate, cholecystokinin agonists, neuropeptide Y antagonists, β_3-adrenoreceptor agonists) failed either due to serious adverse events or their lack of effect in terms of weight loss [12].

3 New Anti-Obesity Drugs

In 2012 the US FDA approved a phentermine/topiramate extended-release (PHEN/TPM ER) combination and lorcaserin as novel medications for long-term weight management in adults [13]. Three major clinical studies were conducted with each of the drugs: EQUIP, CONQUER, and SEQUEL with PHEN/TPM ER [14–16] and BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management), BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management), and BLOOM-DM (a trial in diabetics) with lorcaserin [17–19]. The immediately released phentermine upregulates norepinephrine, dopamine, and serotonin in the central nervous system (CNS), which suppresses appetite and increases energy expenditure. Phentermine has been used since 1959 as an anorectic drug for short-term weight management [20] and is currently the most widely prescribed anti-obesity medication in the USA. In 2008, 82 % of all weight loss drug users were prescribed phentermine and by 2010 its use had increased to 98 % [21]. Topiramate extended release has been used for the treatment of epilepsy since 1996 and for migraine prophylaxis since 2004

[22]. It affects food intake by blocking excitatory voltage-gated sodium and calcium channels, glutamate receptors, and carbonic anhydrase isoenzymes. It also increases energy expenditure by augmenting the activity of γ-aminobutyric acid. Lorcaserin selectively activates 5-HT_{2C} receptors in the CNS and therefore reduces food intake without affecting energy expenditure [23].

3.1 Efficacy of New Anti-Obesity Drugs in Terms of Weight Loss

The combination of immediately released phentermine with extended-release topiramate leads to a peak exposure to phentermine in the morning and topiramate in the evening. This combination led to a greater weight loss and to more cardiometabolic benefits and improved tolerability than monotherapy with each component [24].

All three phase III trials with PHEN/TPM ER (EQUIP, CONQUER, and SEQUEL [14–16]) administered to overweight or obese patients demonstrated statistically significant weight loss compared with placebo. Weight loss after 56 weeks of treatment achieved 5.1, 8.4, and 10.6 % with 3.75/23, 7.5/46, and 15/92 mg of PHEN/TPM ER (vs. 1.7 % in placebo), respectively. The SEQUEL study extended PHEN/TPM ER administration over 2 years and resulted in 9.3 and 10.5 % weight loss from baseline values for the dose of 7.5/46 and 15/92 mg, respectively (vs. 1.8 % in placebo) [16]. More patients treated for 1 year with the PHEN/TPM ER 15/92 mg combination achieved weight loss ≥5 % than those treated with placebo (66.7 vs. 17.3 % in EQUIP trial; 78.0 vs. 21.0 % in CONQUER trial). A significant difference in ≥5 % weight loss between drug- and placebo-treated individuals was observed in the SEQUEL study, which was carried out over 108 weeks (79.3 vs. 30.0 %).

After 1 year of therapy, more patients treated with lorcaserin 10 mg twice daily lost at least 5 % of body weight than those treated with placebo (47.2 vs. 25.0 % in BLOSSOM trial [18]; 47.5 vs. 20.3 % in BLOOM trial [17]). A greater proportion of patients who had achieved weight loss ≥5 % at year 1 and continued to receive lorcaserin for 104 weeks retained their weight loss than in those in whom lorcaserin was replaced by placebo in the second year [17]. A 1-year administration of lorcaserin 10 mg led to a mean weight loss of 4.7 % when given once a day (vs. 2.8 % in placebo) compared with 5.8 % if given twice a day (vs. 2.2 % in placebo).

3.2 Efficacy of New Anti-Obesity Drugs in Terms of Health Risk Reduction

It has been shown that a modest weight loss of 5–10 % of initial body weight results in clinical meaningful reduction in obesity-related health risks [25]. The favorable cardiometabolic effects of the new anti-obesity agents are mainly mediated through the weight loss. In response to their administration, significant decreases in waist circumference, blood pressure, fasting glucose, glycated hemoglobin, homeostasis model assessment of insulin resistance, fibrinogen, and high-sensitivity C-reactive protein as well as improvements in lipid profile were demonstrated. In addition, an increase in adiponectin levels was found in patients receiving PHEN/TPM ER [15]. Subsequent studies with PHEN/TPM ER also revealed improvements in liver function and functional tests in sleep apnea [26], and reduction of concomitant medications for cardiometabolic diseases [16]. PHEN/TPM ER prevented progression of pre-diabetes and/or metabolic syndrome to type 2 diabetes. Compared with patients receiving a placebo, reductions of 70.5 and 78.7 % in the annualized incidence rate of type 2 diabetes was demonstrated in patients treated with PHEN/TPM ER in a daily dose of 7.5/46 and 15/92 mg, respectively [27]. Subsequent analysis of the CONQUER study showed beneficial effects of the PHEN/TPM ER-induced weight loss in patients with dyslipidemia and hypertension. Patients with dyslipidemia who exhibited weight loss ≥5 % significantly reduced their triglycerides (−14.5 to −39.8 %) and non-high-density lipoprotein cholesterol (−9.4 to −14.8 %) compared with those losing <5 % of their initial weight. Similarly, patients with hypertension who achieved weight loss ≥5 % significantly reduced systolic blood pressure (−7.5 to 11.8 mmHg) compared with those who lost <5 % of their body weight [28]. Further long-term drug trials are required in order to assess clinical relevance related to cardiovascular morbidity and mortality. Scores of the impact of weight on quality of life (Lite questionnaire) were evaluated in all clinical trials conducted with both anti-obesity drugs [15, 17, 18]. An improvement in quality of life was described in response to the administration of both of these novel anti-obesity drugs.

3.3 Tolerability of New Anti-Obesity Drugs

The most common adverse events associated with PHEN/TPM ER administration were paresthesia, constipation, dry mouth, dysgeusia, insomnia, and dizziness (Table 1). However, the incidence of adverse events decreased in the second year of the treatment as shown in Table 2. Frequently reported adverse events in overweight/obese patients treated with lorcaserin (10 mg twice daily) were headache, nausea, and dizziness (Table 3). In overweight/obese patients with type 2 diabetes, the most common adverse effects due to the treatment with lorcaserin were headache, back pain, nasopharyngitis, and nausea (Table 4). As with PHEN/TPM ER, a marked reduction in the occurrence of lorcaserin-induced adverse events was observed during the second year of its administration (Table 3).

Table 1 One-year trials with phentermine/topiramate extended release: adverse events (%) occurring at a rate of ≥5 % or at least 1.5 times more frequently than placebo [14, 15]

Adverse event	EQUIP trial					CONQUER trial				
	Placebo ($n = 513$)	PHEN/TPM 3.75/23 mg ($n = 240$)	*P* value	PHEN/TPM 15/92 mg ($n = 511$)	*P* value	Placebo ($n = 993$)	PHEN/TPM 7.5/46 mg ($n = 498$)	*P* value	PHEN/TPM 15/92 mg ($n = 994$)	*P* value
Paresthesia	1.9	4.2	0.090	18.8	<0.0001	2.0	14.0	<0.0001	21.0	<0.0001
Dysgeusia	1.0	1.3	0.714	8.4	<0.0001	1.0	7.0	<0.0001	10.0	<0.0001
Dizziness	4.1	2.9	0.537	5.7	0.250	3.0	7.0	0.001	10.0	<0.0001
Insomnia	4.9	5.0	1.00	7.8	0.055	5.0	6.0	0.383	10.0	<0.0001
Dry mouth	3.7	6.7	0.093	17.0	<0.0001	2.0	13.0	<0.0001	21.0	<0.0001
Constipation	6.8	7.9	0.650	14.1	0.0001	6.0	15.0	<0.0001	17.0	<0.0001

PHEN/TPM phentermine/topiramate

Table 2 Markedly reduced incidence (%) of reported adverse events in the second year than in the first year of treatment with phentermine/topiramate extended release in the SEQUEL trial [16]

	SEQUEL trial					
	Weeks 0–56			Weeks 56–108		
	Placebo ($n = 227$)	PHEN/TPM 7.5/46 mg ($n = 153$)	PHEN/TPM 15/92 mg ($n = 295$)	Placebo ($n = 227$)	PHEN/TPM 7.5/46 mg ($n = 153$)	PHEN/TPM 15/92 mg ($n = 295$)
Paresthesia	2.6	13.7	21.0	0.0	0.7	3.4
Dysgeusia	1.8	11.8	13.2	0.0	0.7	1.0
Dizziness	2.6	5.9	6.8	0.9	1.3	0.3
Insomnia	6.6	7.8	8.1	3.5	5.9	3.7
Dry mouth	2.2	13.7	20.0	0.4	0.7	1.4
Constipation	7.1	16.3	21.0	3.1	7.2	4.1

PHEN/TPM phentermine/topiramate

Table 3 The most common adverse events (%) in overweight/obese patients treated with lorcaserin 10 mg twice daily: reduction of adverse events in the second year of treatment in the BLOOM and BLOSSOM trials [17, 18]

Adverse event	BLOOM trial				BLOSSOM trial	
	Placebo 1 year ($n = 1,584$)	Lorcaserin 1 year ($n = 1,593$)	Placebo 2 years ($n = 697$)	Lorcaserin 2 years ($n = 573$)	Placebo 1 year ($n = 1,601$)	Lorcaserin 1 year ($n = 1,602$)
Headache	11.0	18.0	4.3	7.2	9.2	15.6
Nausea	5.4	7.5	4.2	3.5	5.3	9.1
Dizziness	3.8	8.2	2.4	1.7	3.9	8.7

Table 4 The most common adverse events (%) in overweight/obese patients with type 2 diabetes mellitus treated with lorcaserin 10 mg for 1 year in the BLOOM-DM trial [19]

Adverse event	Lorcaserin 10 mg once daily ($n = 95$)	Lorcaserin 10 mg twice daily ($n = 256$)	Placebo ($n = 252$)
Headache	16.8	14.5	7.1
Back pain	8.4	11.7	7.9
Nasopharyngitis	23.2	11.3	9.9
Nausea	8.4	9.4	7.9

Discontinuation rates were similar or even lower in the groups treated with PHEN/TPM ER than in patients receiving placebo (Table 5). Discontinuations due to adverse events were low, particularly in those followed over 2 years (Table 5). Lower total discontinuation rates in patients taking PHEN/TPM ER than in those receiving placebo might be explained by the greater weight loss in drug-treated subjects as well as by a TPM-induced reduction of food craving and food-addictive behavior [29]. Discontinuation rates in major lorcaserin trials were quite high in the drug-treated individuals, but were still

Table 5 Discontinuation rates (%) in total and due to adverse events in major phentermine/topiramate extended release trials [14–16]

	PHEN/TPM 3.75/23 mg	PHEN/TPM 7.5/46 mg	PHEN/TPM 15/92 mg	Placebo
EQUIP, 56 weeks ($n = 1,267$)				
Total	39.0	–	33.6	47.1
Due to AEs	11.3	–	16.0	8.4
CONQUER, 56 weeks ($n = 2,487$)				
Total	–	31.0	36.0	43.0
Due to AEs	–	11.6	19.3	9.0
SEQUEL, 108 weeks ($n = 676$)				
Total	–	17.5	16.9	13.7
Due to AEs	–	4.5	4.4	3.1

AEs adverse events, *PHEN/TPM* phentermine/topiramate

Table 6 Discontinuation rates (%) in total and due to adverse events in major lorcaserin trials [17–19]

	Placebo	Lorcaserin 10 mg once daily	Lorcaserin 10 mg twice daily
BLOOM ($n = 3,182$)			
First year total	54.9	–	44.6
First year due to AEs	6.7	–	7.1
Second year total	27.3	–	25.7
Second year due to AEs	3.0	–	3.0
BLOSSOM ($n = 4,008$)			
Total	48.0	41.0	42.8
Due to AEs	4.6	6.2	7.2
BLOOM-DM ($n = 604$)			
Total	37.9	21.1	34.0
Due to AEs	4.3	6.3	8.6

AEs adverse events

somewhat lower than in the placebo groups (Table 6). Table 6 shows a reduction in the discontinuation rate in the second year of the trial with lorcaserin.

4 Safety Concerns with Phentermine/Topiramate Extended Release

Major safety concerns have been expressed in terms of cardioexcitatory effects of phentermine when applied as a monotherapy [30]. However, a study by Hendricks et al. [31] did not show any increase in systolic and diastolic blood pressure or heart rate in patients during long-term phentermine pharmacotherapy for obesity. In response to PHEN/TPM ER treatment, only minor increases in heart rate [0.6–1.7 beats per minute (bpm)] were noted (Table 7) [32]. This small increase in heart rate was opposed by significantly reduced systolic and diastolic blood pressure. Moreover, patients with the highest heart rate at baseline (>90 bpm) exhibited reductions in heart rate after 1-year of treatment with PHEN/TPM ER [33]. No significant effect on the QT interval was demonstrated. No increase in the number of non-fatal myocardial infarctions, non-fatal strokes, or cardiovascular deaths was reported in the PHEN/TPM ER-treated group compared with the placebo-treated cohort. A recent review by Jordan et al. [33] evaluated the cardiovascular risk/benefit profile associated with long-term administration of PHEN/TPM ER and concluded that this combination may be a safe and effective option for reducing weight even in overweight/obese patients at low-to-intermediate cardiovascular risk.

It has been shown that topiramate monotherapy for epilepsy and migraine prophylaxis is associated with cognition-related adverse events [34]. The rate of cognition-related adverse events was 2.0, 5.6, and 7.8 % with 3.75/23, 7.5/46, and 15/92 mg of PHEN/TPM ER, respectively, compared with 1.7 % in the placebo group [32]. Psychiatric adverse events such as anxiety, depression, and irritability were reported in 12.1, 7.2, and 4.8 % of individuals receiving PHEN/TPM ER 15/92, 7.5/46 mg, and placebo, respectively. Psychiatric adverse events caused discontinuation of PHEN/TPM ER treatment in 4.8, 2.4, and 1.2 %

Table 7 Modest increase in heart rate (beats per minute) with phentermine/topiramate extended release administration [32]

	Placebo	PHEN/TPM 7.5/46 mg	PHEN/TPM 15/92 mg
1-year trials	0.0	0.6	1.6
2-year trials	0.4	1.3[a]	1.7[a]

PHEN/TPM phentermine/topiramate

[a] The difference vs. placebo was not statistically significant

of patients who were assigned to full dose, mid-dose, and placebo, respectively [30]. Serious depression and anxiety was not reported and no suicidal attempts or ideation were observed in three major PHEN/TPM ER studies.

Teratogenicity manifested with oral clefts was reported in children of mothers exposed to topiramate monotherapy during the first trimester of pregnancy [35]. No fetal adverse outcomes have been reported in pregnancies of mothers exposed to PHEN/TPM ER. However, PHEN/TPM ER is contraindicated for women who are pregnant, trying to become pregnant, or are breast-feeding.

Mild metabolic acidosis is due to the inhibition of carbonic anhydrase by topiramate. Less than 1 % of the drug-treated patients exhibited substantial reductions in serum bicarbonate. However, its levels tended to return to normal over time [14–16]. Reduced bicarbonate levels induced by topiramate may explain paresthesia, which is a frequently observed adverse event with PHEN/TPM ER administration (Tables 1 and 2). The formation of kidney stones is rather rare (incidence 1 %) and is related to topiramate-induced metabolic acidosis. Mild hypokalemia was reported only in the CONQUER trial [15]. Hypokalemia occurred in 3 % of patients receiving a full dose of PHEN/TPM ER versus 1 % of patients treated with placebo.

Acute myopia and secondary angle closure glaucoma has been reported in patients treated with topiramate [36]. However, no ocular problems have been described in response to PHEN/TPM ER treatment.

5 Safety Concerns with Lorcaserin

Valvular heart disease, particularly of aortic and mitral valves, observed with administration of dexfenfluramine and fenfluramine was due to the activation of 5-HT_{2B} receptors. In contrast to fenfluramine, lorcaserin selectively activates 5-HT_{2C} receptors, which are mainly located within the brain. The rate of new valvulopathy in three phase III trials ($n = 5{,}249$) after 1 year of treatment was comparable between the lorcaserin (10 mg twice daily) and placebo groups (2.37 vs. 2.04 %) [37]. A meta-analysis of three randomized controlled trials carried out over 1 year demonstrated that lorcaserin administration is associated with a dose-dependent increase in pre-existing aortic regurgitation [38]. Lorcaserin is thus contraindicated in patients with pre-existing valvular heart disease.

No severe hypoglycemia was observed with lorcaserin treatment [39]. In diabetic patients, symptomatic hypoglycemia occurred in 7.4 % of patients on lorcaserin 10 mg twice daily, 10.5 % on lorcaserin 10 mg once daily, and 6.3 % on placebo [19].

Cognitive impairment was noted more frequently in patients who were treated with lorcaserin for $\geq$1 year than in the placebo group (1.9 vs. 0.5 %) [39]. Psychiatric disorders (hallucinations, euphoria) are associated with stimulation of the 5-HT_{2A} receptor, which can be induced by lorcaserin if its dose exceeds 20 mg/day; however, for weight management the dose of lorcaserin does not exceed 20 mg/day. Lorcaserin administration may rarely lead to an elevation of prolactin levels, a low white blood cell count, and a decreased heart rate.

Serotoninergic agents may cause pulmonary hypertension [40]. However, inconsistent data have so far been reported for lorcaserin treatment with respect to pulmonary hypertension.

An increased incidence of mammary and brain tumors demonstrated in rats was not confirmed in humans [13]. Moreover, breast tumors developed in rats were reclassified as benign. As reported by the FDA, a clinical study found that only a small amount of lorcaserin enters the CNS in humans [13].

6 Anti-Obesity Drugs Expecting Approval

Cetilistat (120 mg administered three times a day) acts in the same way as orlistat. It inhibits gastrointestinal lipase and thus induces modest weight reduction. Clinical trials with cetilistat in obese non-diabetic and diabetic patients demonstrated improvements in both glucose and lipid profiles [41, 42]. The most common cetilistat-induced adverse events were due to fat malabsorption and included increased defecations (25.8 % cetilistat group vs. 6.5 % placebo group), soft stools (28.0 vs. 7.6 %), abdominal pain (19.3 vs. 8.7 %), flatulence (16.8 vs. 10.9 %), and oily stool (13.6 vs. 1.1 %) [41]. Cetilistat was well-tolerated and led to clinically significant weight loss in the short-term 12-week study [41]. A study in obese diabetic patients demonstrated fewer adverse events and lower discontinuation rates due to adverse events in comparison with orlistat [42]. The reduced frequency of adverse events after cetilistat, as compared with orlistat, could be explained by structural differences between these two molecules and a different interaction with fat micelles within the intestine.

As cetilistat blocks the absorption of fat-soluble vitamins, their substitution during long-term treatment should be considered. Three phase III trials conducted in Japan confirmed the efficacy and safety of cetilistat in obese patients with type 2 diabetes and dyslipidemia [43]. Subsequently, cetilistat was approved in Japan in September 2013 for the treatment of obesity with both type 2 diabetes and dyslipidemia [43]. Negotiations concerning approval of cetilistat in other countries are expected in the near future.

The naltrexone sustained release 32 mg/bupropion sustained release 360 mg (NB) combination consists of two already existing drugs: an opioid antagonist naltrexone and an antidepressant bupropion. Bupropion decreases appetite and food intake by both the inhibition of dopamine and norepinephrine reuptake and stimulation of melanocortin pathways. The drug combination affects both the hypothalamic melanocortin pathway and the mesolimbic reward system. It improves control over eating and food cravings and thereby facilitates adherence to lifestyle modification. Clinical trials [COR (Contrave Obesity Research)-I, COR-II, COR-Diabetes, COR-BMOD (COR–Behavior Modification)] enrolling more than 4,500 patients revealed the efficacy of NB in terms of weight loss, reduction of visceral fat, improved lipid profile, and blood sugar control as well as weight-related quality of life [44–47]. In these clinical trials, 53.0 % of drug-treated patients and 21.0 % of those taking placebo lost ≥5 % of their initial body weight over the 12-month treatment period. Adverse events following NB administration mostly occurred during the first weeks of treatment and were usually mild to moderate in intensity and did not lead to discontinuation of treatment in most individuals. The following adverse events were reported more frequently in NB-treated groups than with placebo: nausea, constipation, headache, dry mouth, vomiting, and dizziness. No significant differences between NB-treated and placebo-treated groups were shown in the incidence of depression and suicidal ideation and in blood pressure changes. In one trial, a transient increase in systolic blood pressure was observed in the NB-treated group [44]. Only a minor increase in pulse rate (1 bpm) from baseline was observed with NB treatment. In 2011, however, the FDA declined approval of NB due to concerns about its long-term cardiovascular safety profile in overweight and obese patients. The FDA asked Orexigen Therapeutics Inc., the company that developed NB, to conduct a randomized, double-blind, placebo-controlled trial showing that the drug does not lead to an increased risk of major cardiovascular adverse events. In November 2013, Orexigen announced successful results of the interim analysis of the Light Study, an ongoing cardiovascular outcome trial which included 8,900 patients (available at http://www.orexigen.com). The analysis revealed that NB fulfilled the required criteria concerning its cardiovascular safety. Orexigen provided the results of the Light Study and submitted applications for marketing authorization for NB in the USA and Europe, with expected approval in 2014.

Liraglutide, a glucagon-like peptide-1 analog, has been approved for the treatment of type 2 diabetes. Significant weight loss and a reduction of cardiometabolic health risks was achieved in obese individuals treated with liraglutide (3 mg/day) for 2 years [48]. A higher weight loss and a greater reduction in the prevalence of prediabetes and metabolic syndrome was induced by liraglutide than by orlistat and placebo [48]. Preliminary results of the ongoing SCALE trial demonstrated that 64.0 % of drug-treated patients and 27.0 % of those taking a placebo lost ≥5 % of their initial body weight over 56 weeks [49]. In the SCALE maintenance randomized study, weight maintenance and additional weight loss was reported with liraglutide after low-calorie diet-induced weight loss [50]. The most frequent adverse events with liraglutide were transient nausea and vomiting, which were shown to contribute to weight loss. An observed increase in heart rate after liraglutide is, however, offset by its cardioprotective properties [51].

There have been several other new anti-obesity drugs, particularly among the combination drugs and the analogs of gastrointestinal hormones, which provided encouraging results in terms of efficacy and safety [12]. The possibility of reduced dosing of each component within the drug combination often results in increased efficacy and a reduction of adverse events. It should, however, be taken into account that interactions between the components may sometimes lead to potentiation of adverse effects as experienced with the fenfluramine/phentermine combination. In the case of gut hormones, their use may be limited by formation of antibodies and by a need for parenteral administration.

7 Discussion and Conclusions

FDA approval of lorcaserin and PHEN/TPM ER for the long-term treatment of obesity in combination with lifestyle modification represents an important step forward in improving the treatment of obesity and its associated cardiometabolic health risks. It is well-known that that the combination of medication and lifestyle modification results in greater weight loss than either anti-obesity drugs or lifestyle interventions alone [52]. Our recent analysis of 113 clinical trials with anti-obesity drugs clearly indicated an important role of novel anti-obesity medications, particularly combination drug therapy [12]. The benefit to risk ratio should be carefully evaluated for each novel anti-obesity drug, taking into account not only the magnitude of weight loss, but particularly the amelioration of

cardiometabolic health risks, tolerability, and safety. Recently, in association with the implementation of PHEN/TPM ER for obesity management, a complications-centric approach has been applied that emphasizes weight loss as a tool to reduce obesity-related cardiometabolic and mechanical complications and thus optimize the benefit to risk profiles [53].

Both lorcaserin and the PHEN/TPM ER combination produce meaningful weight losses. Until now, no head-to-head studies between the two new anti-obesity drugs have been carried out. However, currently available trials demonstrated that PHEN/TPM ER had a superior weight loss profile to lorcaserin but the incidence of adverse effects was lower with lorcaserin than with PHEN/TPM ER treatment. Both anti-obesity medications demonstrated beneficial influence on the lipid and glucose profile and blood pressure as well as on quality of life. In addition, PHEN/TPM ER exhibited a significant reduction in the incidence of type 2 diabetes. Adverse events were dose dependent and rather rare with both novel medications and tended to decrease with the duration of treatment. However, a somewhat higher withdrawal rate in lorcaserin than in PHEN/TPM ER trials may be due to the lower efficacy of lorcaserin in terms of weight loss.

Obesity includes multiple pathogenic entities characterized by different regulatory and/or metabolic disturbances that can be beneficially targeted by specific anti-obesity medications. Thus, treatment with anti-obesity drugs should be discontinued in non-responders, i.e., those patients who do not lose at least 5 % of their body weight over a 3-month treatment period. These new anti-obesity drugs have still not been marketed in Europe due to safety concerns. Drug-regulating agencies require trials showing the effect of anti-obesity drugs on cardiovascular morbidity and mortality in elderly obese patients with established cardiovascular disease. Studies conducted in a population at such high risk represent a distortion of reality. The question remains whether to treat elderly patients with established cardiovascular disease or whether to use anti-obesity medications for the treatment of obesity in young and middle-aged individuals to reduce their cardiometabolic health risks and thus prevent the development of cardiovascular and metabolic diseases. The risk to benefit ratio of drug treatment for obesity increases in polymorbid elderly patients who are often treated with several other medications.

In order to achieve efficient treatment of obesity, not only healthcare providers, but also medical authorities and the general public, should accept obesity as a serious complex disease. Obesity should be treated within the healthcare system as any other complex disease and cannot be perceived as a 'lifestyle' condition, but as a medical one with an important hereditary component in its pathogenesis. The drug treatment of obesity should be an integral part of comprehensive obesity management that includes diet, increased physical activity, and cognitive–behavioral therapy. Obesity treatment, and particularly the drug treatment, should be individually tailored, taking into account a large set of specific attributes for each patient such as age, sex, the degree of obesity, body fat distribution, presence of co-morbidities, metabolic and psychobehavioral characteristics, the outcome of previous weight loss attempts, etc. [54]. In order to ensure patient safety, illicit online marketing of novel anti-obesity medications must be strictly prohibited by the drug-regulating authorities [55]. The fate of the new anti-obesity drugs will be greatly affected by the experience and skills of prescribing physicians. An efficient multilevel obesity management network should ensure the right anti-obesity drugs are in the hands of the right, appropriately trained, doctors who will be responsible for adequate prescriptions only in the indicated patients [3, 56, 57].

Acknowledgments The manuscript was supported by the project of the Ministry of Health (Czech Republic) for conceptual development of research organization 00023761 (Institute of Endocrinology, Prague, Czech Republic) and by the program of the Charles University in Prague PRVOUK P31.

Conflict of interest Vojtech Hainer and Irena Aldhoon Hainerová have no conflicts of interest that are directly relevant to the content of this study.

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