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REVIEW

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Abstract

Obesity represents a major global challenge from both healthcare and economic perspectives. Although lifestyle modifications aimed at reducing calorie intake and increasing energy expenditure remain the cornerstone of obesity management, pharmacotherapy can serve as a useful adjunct. Until recently, orlistat was the only medication registered for the treatment of obesity in the European Union (EU). A deeper understanding of the complexity of energy homeostasis has resulted in new pharmacological options for weight reduction. In 2015, two new anti-obesity drugs were approved in the EU. These are a fixed combination of naltrexone/bupropion (Mysimba®) and liraglutide at a dose of 3.0 mg (Saxenda®). In addition, lorcaserin (Belviq®) and a fixed combination of phentermine/topiramate (Qsymia®) were introduced into the US market in 2012. However, the European Medicines Agency did not approve their use in the EU. The burden of previous weight loss agents that have been withdrawn due to safety concerns underlines the need for caution and close follow-up of patients undergoing pharmacological interventions for obesity treatment. This article provides an overview of the efficacy and safety of currently available weight loss pharmacotherapies.

Key words: liraglutide, naltrexone/bupropion, obesity, pharmacotherapy, weight loss

1. Introduction

The rising epidemic of obesity represents a major global challenge from both healthcare and economic perspectives. The impact of weight loss on improving the detrimental health consequences of obesity has been well documented. The role of pharmacotherapy in the management of obesity is clearly established. According to current guidelines pharmacological treatment should be considered as part of a comprehensive strategy of disease management for patients with a body mass index (BMI) ≥30 kg/m2 or a BMI ≥27 kg/m2 with an obesity-related co-morbidity such as type 2 diabetes, hypertension and/or dyslipidemia [1]. It should be emphasized that drugs are not a miraculous substitute for lifestyle change, but only an aid to facilitate the process of weight loss, as healthy eating habits and physical activity are a prerequisite for long-term weight loss maintenance. Anti-obesity drugs should be used according to their licensed indications and restrictions. The efficacy of pharmacotherapy should be evaluated after the first 3 months of therapy. If weight loss is considered unsatisfactory (<5% of weight loss), treatment should be discontinued [2].

2. History of pharmacotherapy for obesity

The history of obesity pharmacotherapy is a history of withdrawals. Amongst the drugs marketed for weight loss there have been several instances of market withdrawal due to serious adverse events. Several examples of agents involved include fenfluramine, phenylpropanolamine, amphetamines, and most recently, rimonabant and sibutramine [3]. Fenfluramine was recalled from the market due to concerns of an increased prevalence of valvular heart disease and the possible association with primary pulmonary hypertension. Phenylpropanolamine was withdrawn due to an increased risk of hemorrhagic stroke, and amphetamines due to their abuse potential. Rimonabant and sibutramine are the latest in a series of centrally acting drugs that were withdrawn from the market because of side effects. Rimonabant, a cannabinoid receptor agonist, was approved as an anti-obesity drug in 2006. However, three years later the drug was suspended from the European union (EU) market due to an increased risk of psychiatric disorders, including major depression and suicidal ideation [4]. Sibutramine is a centrally acting neurotransmitter reuptake inhibitor that reduces the reuptake of serotonin, norepinephrine, and dopamine, thereby increasing the levels of these substances in synaptic clefts. Owing to its appetite-suppressing effects, sibutramine was approved for weight management in patients unable to lose weight by diet and exercise alone. Concerns were raised regarding the safety of sibutramine, following reports of increased systolic and diastolic blood pressure and heart rate. The SCOUT (Sibutramine Cardiovascular OUTcomes) trial evaluated the long-term effects of sibutramine on the rates of cardiovascular events and death among 10742 subjects with high cardiovascular risk [5]. The risk of a primary outcome event (composite of nonfatal MI, nonfatal stroke, cardiac arrest, and CV death) was increased by 16% in the sibutramine group as compared with the placebo group. This increase was due to a higher incidence of nonfatal myocardial infarction and stroke, with no significant difference between the study groups in the incidence of cardiovascular death or death from any cause. In 2010, the European Medicines Agency (EMA) recommended suspension of marketing authorizations for sibutramine based on the SCOUT study results.

With this background, regulatory authorities demand appropriate evidence of a very favorable benefit-risk ratio for any new drug, imposing strict criteria on its effectiveness and safety. Having in mind that weight loss medication is widely used and most patients require long-term treatment, post-marketing studies, including long-term cardiovascular outcome trials are necessary to assess the effect of a drug on the risk of major adverse cardiac events.

The EMA and the US Food and Drug Administration (FDA) differ in their criteria on efficacy of anti-obesity drugs. According to the FDA, a product can be considered effective for weight management if after 1 year of treatment the difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and if the proportion of subjects who lose ≥5% of baseline body weight in the active-product group is at least 35% or approximately double the proportion in the placebo-treated group [6]. In contrast, the EMA regards weight reduction from baseline as being more clinically relevant than placebo-subtracted weight loss, and requires evidence of at least 10% weight loss from

baseline body weight at 1 year, which must also be at least 5% greater than that achieved in the placebo group. The EMA guidelines also state that when the clinical response is at least 10% weight loss from baseline body weight at the end of 1 year, the proportions of responders in various treatment arms could be considered as an alternative primary efficacy criterion [6]. Therefore, it is not surprising that drugs approved for the treatment of obesity in the US are not always available on the European market.

3. Currently approved weight loss medication

Pharmacological approaches to weight reduction focus on reducing energy intake (by decreasing food absorption or by decreasing appetite), increasing energy expenditure, or a combination of both effects [4]. There are two broad categories into which current anti-obesity agents can be divided. Centrally acting drugs modulate signaling pathways in the central nervous system (CNS) and thus suppress appetite. Peripherally acting agents promote weight loss by reducing the absorption of nutrients, as for example, orlistat (Xenical®), an inhibitor of pancreatic lipases that blocks fat absorption from the gut. Until recently, orlistat was the only medication registered for the treatment of obesity in Europe. A deeper understanding of the complex mechanisms underlying obesity lead to the development of new targets for pharmacotherapeutic interventions. After a long time, in 2015, two new anti-obesity drugs were approved in Europe. These are a fixed combination of naltrexone/bupropion (Mysimba®) and liraglutide at a dose of 3.0 mg (Saxenda®). In addition to the above-mentioned agents, two other drugs have been introduced into the US market. Although, the FDA approved lorcaserin (Belviq®) and a fixed combination of phentermine/topiramate (Qsymia®) in 2012, the EMA did not approve their use in the EU. Moreover, medications for the short-term treatment of obesity, such as diethylpropion and phentermine in monotherapy, are also available in the US, but not in the EU. However, such agents that cannot be used for longer than three months do not fit into the rational paradigm for the treatment of obesity as a chronic disease. **Table 1.** provides an overview of medications currently approved in the EU and/or US for the long-term treatment of obesity in adults.

3.1 Orlistat

Orlistat is a reversible inhibitor of pancreatic lipase, which reduces the absorption of fat from the gut. At the standard prescription dose of 120 mg three times daily before meals, orlistat prevents approximately 30% of dietary fat from being absorbed, thereby reducing caloric intake [7]. It is marketed as a prescription drug under the trade name Xenical® and is sold over-the-counter as Alli® which is one-half the strength of Xenical. The most common side effects are gastrointestinal due to unabsorbed fats in the intestine, which can include steatorrhea, frequent bowel movements, and fecal incontinence. Because the absorption of fat-soluble vitamins is inhibited by

Table 1. Medications currently approved in the European Union and/or United States for long-term obesity treatment in adults

Generic name	Trade name	Approved in EU	Approved in US
orlistat	Xenical/Alli*	YES	YES
lorcaserin	Belviq	NO	YES
phentermine/topiramate	Qsymia	NO	YES
naltrexone/bupropion	Contrave/Mysimba**	YES	YES
liraglutide 3.0 mg	Saxenda	YES	YES

*Alli® is available OTC and one-half the strength of Xenical® which is available by prescription only **Contrave® is trade name of naltrexone/bupropion in US and Mysimba® in EU

orlistat, vitamin A, D, E and K supplements should be taken when using orlistat. The effectiveness of orlistat in promoting weight loss is modest. Pooled data from clinical trials suggest that people given orlistat in addition to lifestyle modifications, such as diet and exercise, lose about 2-3 kg more than those taking placebo [8]. Orlistat modestly reduces blood pressure, has favorable effects on obesity-related metabolic disorders, and appears to prevent the onset of type 2 diabetes. Data from the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial of 3305 patients followed for up to 4 years, found that orlistat use decreased body weight by 2.7 kg (approximately 2.4% of initial body weight) more than placebo and significantly decreased the risk for developing type 2 diabetes. The cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% [9]. Unpleasant side effects and a modest weight loss significantly limit the wider use of orlistat.

3.2 Lorcaserin

Lorcaserin is a centrally acting selective agonist of the serotonin type 2 C receptor (5-HT2C) that has been designed to exhibit positive effects of serotonergic drugs, but without unwanted side effects mediated by serotonin receptor type 2A and 2B. Several clinical trials were conducted to evaluate the efficacy and safety of lorcaserin. In the 2-year, BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) trial, 3182 obese or overweight adults (mean BMI 36.2 kg/m2) were randomized to receive lorcaserin 10 mg twice daily or placebo [10]. All patients also underwent a lifestyle intervention. After one year, 47.5% of patients receiving lorcaserin had lost ≥5% of their baseline body weight, compared with 20.3% for those treated with placebo. Weight loss of at least 10% was achieved by 22.6% of patients receiving lorcaserin and 7.7% of patients in the placebo group. Patients in the lorcaserin group lost an average of 5.8 kg, as compared with 2.2 kg in the placebo group. Among patients in the lorcaserin group who had weight loss of 5% or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin for a second year than in those who switched to placebo (67.9% vs. 50.3%).

Similar results were reported in the 1-year BLOSSM trial that examined two doses of lorcaserin in a cohort of 4008 patients [11]. Significantly more patients treated with lorcaserin 10 mg/day and 20 mg/day lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%). Weight loss of ≥10% was achieved in 22.6% and 17.4% of patients receiving lorcaserin 10 mg and 20 mg, respectively, and 9.7% of patients in the placebo group.

The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study evaluated efficacy and safety of lorcaserin for weight loss in patients with type 2 diabetes [12]. Patients receiving lorcaserin 10 mg once or twice daily lost an average of 5% and 4.5% of their baseline body weight respectively, as compared with 1.5% in the placebo group. HbA1c decreased by approximately 1% with lorcaserin. Headaches, nausea, and dizziness were the most common lorcaserin-related adverse events. Importantly, there was no evidence for an increase in clinically significant valvular heart disease in lorcaserin-treated patients compared with those receiving placebo. However, the drug has not been approved in Europe.

The Committee for Medicinal Products for Human Use (CHMP) expressed concern about carcinogenic potential of lorcaserin, the development of psychiatric disorders, and possible damage to heart valves associated with its long-term use. An increased incidence of mammary adenocarcinomas was observed during animal studies in female rats, which was associated with lorcaserin plasma exposures that were 87-times the daily human clinical dose [6]. The cancer risk in animal studies was a concern of the FDA when it rejected lorcaserin the first time. The development of potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reactions have been reported during use of serotonergic drugs [13]. Based on the mechanism of action of lorcaserin and the theoretical potential for serotonin syndrome, extreme caution should be employed when used in combination with other drugs that may affect the serotonergic neurotransmitter systems, including, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants.

Although the lorcaserin-related side effects are mild and rare, relatively modest effect on weight loss and the fear of possible adverse events during long-term use make the future of lorcaserin uncertain.

3.3 Phentermine/topiramate

Fixed combination of phentermine/topiramate extended-release (Qsymia®) came to the US market in September 2012. On the basis of the weight loss achieved with phentermine and topiramate as individual agents, and the notion that a combination of these agents at low doses might have additive or synergistic effects, thereby providing improved efficacy and safety, a combination of phentermine/topiramate was developed for once-daily oral dosing to enhance weight loss and improve weight-related comorbidities [14]. In this low-dose formulation, phentermine is readily absorbed and immediately released to provide effects early in the day, whereas topiramate extended-release provides effects through later periods of the day. It is currently approved at doses of 3.75 mg/23 mg, 7.5 mg/46 mg and 15 mg/92 mg for chronic weight management in obese and overweight adults with at least one weight-related comorbidity [15].

Phentermine is a centrally acting sympathomimetic agent, which mainly acts to increase norepinephrine in the CNS, thereby suppressing appetite. Phentermine has been available as monotherapy since 1956 for the short-term treatment of obesity, mainly in markets outside of Europe. Topiramate is an antiepileptic drug marketed since 1996. Eight years later, it was approved and most frequently prescribed for the prevention of migraines. Because trials of its efficacy in patients with seizures noted significant weight loss, topiramate was further evaluated for the treatment of obesity. Although the exact mechanism of action responsible for the weight loss is not fully understood, animal studies suggest that topiramate antagonizes glutamate action at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors/kainate receptors and augments γ-aminobutyric acid (GABAA) receptor-mediated inhibitory currents [16]. Topiramate also appears to inhibit voltage-dependent sodium channels, calcium channels, and carbonic-anhydrase isoenzymes II and IV. Topiramate may decrease food intake through effects on carbonic-anhydrase by altering taste or through its effects on GABA transmission, since GABAA receptor activation and the interaction between GABA and leptin pathways are known to mediate effects on appetite and metabolism [17].

Three phase III randomized, placebo-controlled trials evaluated the safety and efficacy of phentermine-topiramate combination in the treatment of obesity. The EQUIP trial evaluated 1267 obese patients with mean baseline BMI of 42.1 kg/m2 over a 56-week period [18]. Patients were divided into 3 treatment arms: one receiving 3.75 mg/23 mg phentermine-topiramate, the second receiving 15 mg/92 mg combination, and the third receiving placebo. At 56 weeks, patients in the high dose, low dose, and placebo groups, lost 10.9%, 5.1%, and 1.6% of baseline body weight, respectively. Moreover, percentages of patients losing ≥5%, ≥10% and ≥15% of body weight were, respectively, 66.7%, 47.2%, and 32.3% on high dose; 44.9%, 18.8%, and 7.3% on low dose; and 17.3%, 7.4%, and 3.4% on placebo.

In the 56-week CONQUER trial, 2487 overweight or obese adults, with a BMI of 27-45 kg/m2 and two or more obesity-related comorbidities were randomly assigned to once-daily medium dose (7.5 mg/46.0 mg), high dose (15.0 mg/92.0 mg) phentermine/topiramate or placebo [19]. All subjects received standardized counseling for diet and lifestyle modification. The average weight loss after 56 weeks was 9.8% in the high dose phentermine/topiramate group, 7.8% in the medium dose group, and 1.2% in the placebo group. In addition, 70% and 48% of patients given high dose phentermine/topiramate, 62% and 37% given medium dose, and 21% and 7% in the placebo group, lost ≥5% and ≥10% of initial weight, respectively. The SEQUEL study, an extension of the CONQUER study, confirmed the sustained weight loss over the period of two years along with improvements in cardiometabolic profiles [20]. After two years, patients receiving medium dose and high dose phentermine/topiramate achieved a weight loss of 9.3% and 10.7%, respectively.

Side effects of combination phentermine/topiramate are consistent with previously known side effects of phentermine monotherapy (dry mouth, constipation, insomnia, palpitations) or topiramate (dizziness, paresthesia, dysguesia, disturbance of concentration,

metabolic acidosis, kidney stones). Other worrisome side effects are teratogenicity, increase in resting heart rate, anxiety, and depression.
Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate). Females of reproductive potential should have a negative pregnancy test before starting phentermine/topiramate and monthly tests thereafter during therapy. Females of reproductive potential should also use effective contraception during phentermine/topiramate therapy. If pregnancy occurs, the treatment should be discontinued immediately. A small increase in resting heart rate has been observed in clinical trials of phentermine/topiramate at higher doses, with more patients on top-dose (56.1%) than placebo (42.1%) having increases of more than 10 beats per minute, leading to some concerns regarding its potential long-term effect on cardiovascular events [21]. The labeling suggests regular monitoring of resting heart rate and recommends against prescription in patients with recent or unstable cardiac or cerebrovascular disease. Phentermine/topiramate should not be taken during or within 14 days of taking monoamine oxidase inhibitors and in patients with glaucoma.
Given the extremely favorable effect on body weight, which is significantly higher compared to other currently available anti-obesity drugs, the FDA has concluded that the benefits of the drug exceeds the potential risks and has approved its use for the treatment of obesity. However, the EMA again had a dissenting opinion highlighting concerns over possible long-term cardiovascular and CNS adverse effects, teratogenic risk, and possible drug misuse among people to whom it should not have been prescribed.

3.4 Naltrexone/bupropion

The fixed combination of naltrexone/bupropion sustained-release was approved by the FDA in September 2014 under the brand name Contrave®, and then in May 2015 in the EU where it is presently available under the name Mysimba®.
Naltrexone is an opioid antagonist with a high affinity for the μ-opioid receptor. As monotherapy, naltrexone has been approved for the treatment of alcoholism and opioid addiction. Bupropion is an atypical antidepressant, which inhibits reuptake of dopamine and norepinephrine. It is approved as an aid in smoking cessation and for the treatment of depression [22].
Neuronal networks originating in the hypothalamus play fundamental roles in the control of energy balance. The proopiomelanocortin (POMC) containing neurons are the most important source of anorexigenic signals. POMC is cleaved into peptides including α-melanocyte stimulating hormone (α-MSH) and β-endorphin, which are co-released from POMC cells. α-MSH stimulates the melanocortin-4 receptor, which leads to decreased food intake, increased energy expenditure, and weight loss. β-endorphin binds to the inhibitory μ-opioid receptor on POMC cells and acts like a brake to reduce activity of POMC cells. Bupropion stimulates activity of POMC cells, increasing POMC production and secretion of α-MSH and β-endorphin. Naltrexone blocks β-endorphin action at the μ-opioid receptor, thus preventing autoinhibition of POMC neurons. Together, the naltrexone/bupropion combination produces a greater increase in POMC activity, which leads to weight loss [23].

Several clinical trials were conducted to evaluate the efficacy and safety of fixed combination naltrexone/bupropion. In the Contrave Obesity Research-I (COR-I) trial, 1742 obese or overweight participants were randomly assigned to receive sustained-release naltrexone 32 mg plus bupropion 360 mg (NB32), sustained-release naltrexone 16 mg plus bupropion 360 mg (NB16), or placebo [24]. At 56 weeks, mean change in bodyweight was -6.1% in NB32 group, -5.0% in the NB16 group, and -1.3% in the placebo group. Weight loss of ≥ 5% was achieved by 48% of patients receiving NB32, 39% of those receiving NB16, and 16% of patients in the placebo group.
Contrave Obesity Research-II (COR-II) was a double-blind, placebo-controlled study of 1496 participants with mean baseline BMI of 36 kg/m2 who were randomized to combined naltrexone/bupropion 32 mg/360 mg (NB32) or placebo for up to 56 weeks [25]. Significantly greater weight loss was observed with NB32 versus placebo at week 28 (-6.5% vs. -1.9%) and week 56 (-6.4% vs. -1.2%). Weight loss of ≥ 5% was achieved by 55.6% of patients receiving

NB32 and 17.5% receiving placebo at week 28, and by 50.5% of patients receiving NB32 versus 17.1% of patients in the placebo group at week 56. NB32 produced greater improvements in cardiometabolic risk markers. Naltrexone/bupropion was not associated with increased depression or suicidality compared with placebo.

COR-BMOD trial examined the efficacy and safety of naltrexone plus bupropion as an adjunct to intensive behavior modification (BMOD) [26]. A total of 793 participants (mean BMI of 36.5 kg/m^2) were randomly assigned to: placebo plus BMOD or NB32 plus BMOD. Both groups were prescribed an energy-reduced diet and 28 group BMOD sessions. At week 56, weight loss was 5.1% with placebo + BMOD vs. 9.3% with NB32 + BMOD.

The most frequent adverse events of naltrexone/bupropion are nausea, headache, constipation, dizziness, vomiting, and dry mouth. Contraindications include uncontrolled hypertension, current seizure disorder or a history of seizures, CNS tumor, acute alcohol or benzodiazepine withdrawal, history of bipolar disorder, chronic opiate or opiate agonists therapy, acute opiate withdrawal, and concomitant administration of monoamine oxidase inhibitors (MAOI) [27]. At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with naltrexone/bupropion.

The combination of naltrexone/bupropion is available as sustained-release tablets containing 8 mg of naltrexone and 90 mg of bupropion. Treatment begins by taking one tablet daily, and gradually increasing doses up to 4 weeks at the recommended dose of two tablets taken twice daily. Treatment should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

3.5 Liraglutide

Incretin-based therapies represent a significant step forward in the treatment of type 2 diabetes, and most recently in the treatment of obese people with or without diabetes. Incretins are gut-derived hormones that are secreted from enteroendocrine cells into the bloodstream in response to ingestion of food. The most extensively studied incretin is glucagon-like peptide-1 (GLP-1) with a beneficial role in the control of glucose and energy homeostasis [28]. As native GLP-1 has a very short circulating half-life due to degradation by the enzyme DPP-4, degradation-resistant GLP-1 receptor agonists have been developed. Liraglutide, a long-acting GLP-1 receptor agonist with 97% homology to native GLP-1, is approved for the treatment of type 2 diabetes. It is an injectable drug that is administrated at doses up to 1.8 mg once daily. Based on the results of clinical trials in patients with type 2 diabetes, as well as studies that have investigated the therapeutic potential of higher doses of the drug in obese patients without diabetes, liraglutide at dose of 3.0 mg received approval by the FDA and EMA for treatment of obesity in adults under the brand name Saxenda®. Weight loss with liraglutide is mediated by reduced appetite and energy intake [29].

Astrup at al. conducted a double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator [30]. A total of 564 individuals were randomly assigned to one of four liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg) or to placebo administered once a day subcutaneously, or orlistat 120 mg three times a day orally. All subjects were advised to reduce daily caloric intake by 500 kcal and to increase the level of physical activity. Mean weight loss with liraglutide 1.2-3.0 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, respectively, compared with 2.8 kg with placebo and 4.1 kg with orlistat. Weight loss >5% was achieved in more patients (76%) taking liraglutide 3.0 mg than placebo (30%) or orlistat (44%).

In the SCALE trial, 3731 overweight or obese adults without diabetes were randomized to treatment with liraglutide 3.0 mg or placebo, and both groups received counseling on lifestyle modification [31]. After 56 weeks, significantly greater weight loss was observed with liraglutide as compared with placebo (-8.0% vs. -2.6%). The proportion of patients that lost ≥5% or ≥10% of body weight was 63% and 33%, respectively in the liraglutide group, and 27% and 11%, respectively, in the placebo group. Moreover, 63% and 33% in the liraglutide group, as compared with 27% and 11% in the placebo group, lost at least 5% and 10% of their body weight, respectively.

Wadden et al. assessed the efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD) [32]. Participants who lost ≥5% of initial weight during a LCD run-in were randomly assigned to liraglutide 3.0 mg per day or placebo for 56 weeks. More participants receiving liraglutide (81.4%)

maintained the ≥5% run-in weight loss, compared with those receiving placebo (48.9%), and 50.5% patients in the liraglutide group versus 21.8% of patients in the placebo group lost ≥5% of randomization weight. This study showed that liraglutide holds promise for improving weight loss maintenance.
Liraglutide is generally well tolerated. Mild to moderate nausea and vomiting are the major side effects of the drug and are usually transient, but may contribute to the greater weight loss [33]. Regarding the controversy of whether GLP-1–based therapy can increase the risk for specific malignant disease like pancreatic carcinoma and thyroid cancer, there is no firm evidence in favor of this hypothesis; however, long-term safety observations are needed [34].
The initial dose of liraglutide is 0.6 mg s.c. daily, and is increased by 0.6 mg/day in weekly intervals until a dose of 3.0 mg/day is achieved. Treatment should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

4. Conclusion

Although lifestyle modifications aimed at reducing calorie intake and increasing energy expenditure remain the cornerstone of obesity management, pharmacotherapy can serve as a useful adjunct. Recent advances in our understanding of energy homeostasis and its complexity, have resulted in the new pharmacological approaches for obesity treatment. However, our knowledge of adverse effects that result from their long-term use is still incomplete. The burden of previous weight loss pharmacotherapy that has been withdrawn due to safety concerns, underlines the need for caution and close follow-up of patients undergoing pharmacological interventions for obesity treatment.

Author contributions

SKM performed literature review, wrote the artical and gave the final aproval. ŽCO gave the idea for the article, participated in drafting the article and gave the final approval. DŠ critically revised the manuscript, gave suggestions regarding data presentation and gave the final aproval.

References

1. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et. al. Obesity Management Task Force of the European Association for the Study of Obesity. European Guidelines for Obesity Management in Adults. Obes Facts 2015;8:402-24.
http://dx.doi.org/10.1159/000442721

2. Toplak H, Woodward E, Yumuk V, Oppert JM, Halford JC, Frühbeck G. 2014 EASO Position Statement on the Use of Anti-Obesity Drugs. Obes Facts 2015;8:166-74.
http://dx.doi.org/10.1159/000430801

3. Bray GA. Medical treatment of obesity: the past, the present and the future. Best Pract Res Clin Gastroenterol 2014;28:665-84.
http://dx.doi.org/10.1016/j.bpg.2014.07.015

4. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA 2014;311:74-86.
http://dx.doi.org/10.1001/jama.2013.281361

5. Torp-Pedersen C, Caterson I, Coutinho W, Finer N, Van Gaal L, Maggioni A, et al. SCOUT Investigators. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. Eur Heart J 2007;28:2915-23.
http://dx.doi.org/10.1093/eurheartj/ehm217

6. Manning S, Pucci A, Finer N. Pharmacotherapy for obesity: novel agents and paradigms. Ther Adv Chronic Dis 2014;5:135-48.
http://dx.doi.org/10.1177/2040622314522848

7. Ballinger A. Orlistat in the treatment of obesity. Expert Opin Pharmacother 2000;1(4):841-7.
http://dx.doi.org/10.1517/14656566.1.4.841

8. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003; (4):CD004094.
http://dx.doi.org/10.1002/14651858.cd004094.pub2

9. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155-61.
http://dx.doi.org/10.2337/diacare.27.1.155

10. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363:245-56.
http://dx.doi.org/10.1056/NEJMoa0909809

11. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011;96:3067-77.
http://dx.doi.org/10.1210/jc.2011-1256

12. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426-36.
http://dx.doi.org/10.1038/oby.2012.66

13. Brashier DBS, Sharma AK, Dahiya N, Singh SK, Khadka A. Lorcaserin: A novel antiobesity drug. J Pharmacol Pharmacother 2014;5(2):175–178.
http://dx.doi.org/10.4103/0976-500X.130158

14. Singh J, Kumar R. Phentermine-topiramate: First combination drug for obesity. Int J Appl Basic Med Res 2015; 5(2): 157–158.
http://dx.doi.org/10.4103/2229-516X.157177

15. Smith SM, Meyer M, Trinkley KE. Phentermine/topiramate for the treatment of obesity. Ann Pharmacother 2013;47:340-9.
http://dx.doi.org/10.1345/aph.1R501

16. Turenius CI, Htut MM, Prodon DA, Ebersole PL, Ngo PT, Lara RN et al. GABA(A) receptors in the lateral hypothalamus as mediators of satiety and body weight regulation. Brain Res 2009;1262:16-24.
http://dx.doi.org/10.1016/j.brainres.2009.01.016

17. Xu Y, O'Brien WG, Lee CC, Myers MG Jr, Tong Q. Role of GABA release from leptin receptor-expressing neurons in body weight regulation. Endocrinology 2012;153:2223-33.
http://dx.doi.org/10.1210/en.2011-2071

18. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20:330-42.
http://dx.doi.org/10.1038/oby.2011.330

19. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:1341-52.
http://dx.doi.org/10.1016/S0140-6736(11)60205-5

20. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95:297-308.
http://dx.doi.org/10.3945/ajcn.111.024927

21. Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N. Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. J Hypertens 2014;32:1178-88.
http://dx.doi.org/10.1097/HJH.0000000000000145

22. Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss. Pharmacological Research 2014;84:1-11.
http://dx.doi.org/10.1016/j.phrs.2014.04.004

23. Caixàs A, Albert L, Capel I, Rigla M. Naltrexone sustained-release/bupropion sustained-release for the management of obesity: review of the data to date. Drug Des Devel Ther 2014;8:1419-27.
http://dx.doi.org/10.2147/DDDT.S55587

24. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376:595-605. http://dx.doi.org/10.1016/S0140-6736(10)60888-4

25. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) 2013;21:935-43. http://dx.doi.org/10.1002/oby.20309

26. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) 2011;19:110-20. http://dx.doi.org/10.1038/oby.2010.147

27. Verpeut JL, Bello NT. Drug safety evaluation of naltrexone/bupropion for the treatment of obesity. Expert Opin Drug Saf 2014;13:831–841. http://dx.doi.org/10.1517/14740338.2014.909405

28. Ahrén B. GLP-1 for type 2 diabetes. Exp Cell Res 2011;317:1239-45. http://dx.doi.org/10.1016/j.yexcr.2011.01.010

29. Ng SY, Wilding JP. Liraglutide in the treatment of obesity. Expert Opin Biol Ther 2014;14:1215-24. http://dx.doi.org/10.1517/14712598.2014.925870

30. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606-16. http://dx.doi.org/10.1016/S0140-6736(09)61375-1

31. Pi-Sunyer X, Astrup A, Fujioka K, Greenway, Halpern A, Krempf M et al.; SCALE Obesity and Prediabetes Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 2015;373:11-22. http://dx.doi.org/10.1056/NEJMoa1411892

32. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443-51. http://dx.doi.org/10.1038/ijo.2013.120

33. Lean ME, Carraro R, Finer N, Hartvig H, Lindegaard ML4, Rössner S, et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes (Lond) 2014;38:689-97. http://dx.doi.org/10.1038/ijo.2013.149

34. Chalmer T, Almdal TP, Vilsbøll T, Knop FK. Adverse drug reactions associated with the use of liraglutide in patients with type 2 diabetes-focus on pancreatitis and pancreas cancer. Expert Opin Drug Saf 2015;14:171-80. http://dx.doi.org/10.1517/14740338.2015.975205