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Pharmacological treatment of obesity in clinical practice

Omercan Topaloglu[1], Ibrahim Sahin[2]

[1]Zonguldak Bulent Ecevit University, Faculty of Medicine, Department of Endocrinology and Metabolism, Zonguldak, Turkey
[2]Inonu University, Faculty of Medicine, Department of Endocrinology and Metabolism Malatya, Turkey

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Abstract

Anti-obesity medications may be considered in the subjects with BMI ≥30 kg/m2, or with BMI 27-29.9 kg/m2 and weight-related comorbidities, whom weight reduction is not achieved via lifestyle modifications alone. If weight loss is inadequate (<4-5%) after 12 weeks of treatment, the medication should be changed. Orlistat and Liraglutide are available in our country. Orlistat inhibits pancreatic lipase, increases fat excretion, improves hypertension or lipid profile besides weight-reduction. No dosage adjustment is necessary in renal or liver impairment. Orlistat may lead flatus, intestinal cramps, fecal incontinence, oily spotting, and should not be used in malabsorption syndrome, cholestasis, or pregnancy. Liraglutide is a biochemically modified GLP1 which slows gastric emptying and decreases appetite. It is preferred as a first-line agent in most situations. It was shown to decrease major cardiovascular events. Liraglutide is initiated once a day subcutaneously 0.6 mg/day, then dose is increased up to 3mg/day. Nausea and vomiting are common with liraglutide, renal impairment, gallbladder disease or pancreatitis less common. Liraglutide is contraindicated in pregnancy, lactation, MEN 2 or medullary thyroid cancer. Phentermine/topiramate combination may be considered in subjects without any cardiovascular diseases who do not tolerate liraglutide or orlistat. It is contraindicated in pregnancy due to a risk of orofacial defects, and not recommended in hypertension, coronary heart disease, hyperthyroidism or monoamine oxidase use. Bupropion/Naltrexone combination provides anorexigenic effect by acting on feeding and reward circuitry. It may be preferred if pharmacological therapy both for smoking cessation and weight loss is desired. Vomiting, constipation, dry mouth or suicidal thoughts may be observed, and contraindicated in pregnancy, seizure, uncontrolled hypertension, opioid or monoamine oxidase inhibitor use. Phentermine, diethylpropion, benzphetamine, and phendimetrazine are used for short-term due to risk of abuse, and contraindicated in uncontrolled hypertension, coronary heart disease, or thyrotoxicosis. Safety of dietary supplements used for obesity is limited.

Keywords: Obesity, pharmacological treatment, obesity treatment, liraglutide, orlistat

Introduction

Obesity is a complex, chronic and multifactorial disease, and its prevalence has been increased worldwide. In our country, the prevalence was found as 30% in adult population, and as high as 59% in adults with type 2 diabetes mellitus (T2D) [1]. Obesity may result in a number of health consequences such as hypertension, T2D, dyslipidemia, cardiovascular disease, cerebrovascular disease, cancer, polycystic ovary syndrome, hepatosteatosis, gastroesophageal reflux disease, depression or osteoarthritis [2]. By this way, obesity may be associated with major economic burden in many countries.

***Corresponding Author:** Omercan Topaloglu, Zonguldak Bulent Ecevit University, Faculty of Medicine, Department of Endocrinology and Metabolism, Zonguldak, Turkey, E-mail: drhomercan@hotmail.com

Obesity is defined as a body mass index (BMI) of ≥30 kg/m², and severe obesity may be defined as a BMI ≥40 kg/m² or ≥35 kg/m² together with comorbidities. Weight reduction was shown to decrease morbidities associated with obesity. Weight loss may also provide a reduction in mortality associated with obesity.

By weight reducing interventions, we aim to preclude, treat and reverse the complications and comorbidities associated with obesity [3]. Lifestyle modifications, pharmacotherapy and bariatric surgery may be used sequentially according to the clinical background of the patients with obesity. We aim also to improve quality of life in the subjects with obesity. In general, lifestyle intervention may provide 5-7% weight loss, but maintenance of weight loss is difficult. Medical management in obesity aims to reduce weight by 5-10 %. In clinical studies, with medical therapy, weight loss of 4-8 % is typical [4].

An appropriate anti-obesity medication should provide a considerable weight loss, not cause tolerance to its effects,

and weight loss should be continued even after cessation of the medication. Actually, weight loss gradually diminishes and ceases even in the continuation of the medication. Weight regain is a frequent problem which may be observed after discontinuation of the medication [5,6]. Anti-obesity medication should be safe in long-term use, and not lead significant adverse effects. The response to a medication may be varied for each patient. An anti-obesity medication ideally should contribute to a decrease in health consequences associated with obesity. No medication possessing all these properties have been introduced into clinical practice [2].

Lifestyle modifications are corner-stone therapy, should be considered for every patient either alone or in combination with pharmacological treatment and/or bariatric surgery.

Pharmacological treatment of obesity may be considered in the subjects with BMI ≥30 kg/m², or those with BMI 27-29.9 kg/m² and weight-related comorbidities (such as hypertension or T2D). It should also be considered if weight reduction of at least 5% could not be achieved in the last 6 months via lifestyle modifications alone [7].

BMI, comorbidities, costs, and patient preferences should be considered in the selection of anti-obesity medications. These factors may have also a role in the adjustment of the dose or modification of treatment. Hence, medical management of the patients whom anti-obesity medications were indicated should be individualized.

Besides pharmacological treatment of obesity, medications providing weight loss, or at least weight neutral, rather than weight gain should be preferred in the management of health consequences associated with obesity.

Efficacy of pharmacotherapy should be evaluated 12 weeks after the initiation of the anti-obesity medication. If weight loss is inadequate (<4-5%), the medication should be discontinued and changed. If a patient has failed to respond to an agent, it is not certain for it to respond to another drug or combination of those. Weight loss of 5-15% at 6 months of treatment is a good response improving comorbidities. Weight management should be continued lifelong in the subjects with obesity. Every patient should be evaluated on individual basis, and pharmacotherapy may be continued up to 1 year. At the end of 2 year of treatment, if weight loss may be maintained by lifestyle interventions alone, pharmacotherapy may be cessated [2].

Pharmacological Agents Used In The Treatment Of Obesity

Several oral or injectable forms of anti-obesity medications were approved and may be used in the pharmacological treatment of obesity (Table 1). “Orlistat” and “Liraglutide” are available in our country. In meta-analyses including randomized controlled trials, medications approved by FDA (Food and Drug Administration) were shown to have weight-reducing effect comparing to placebo [4,8].

Table 1. Pharmacological agents used in obesity

Generic Name	Dosage	Side Effects	Turkey
Orlistat	120 mg tb, po, 3x1/d	Cramp, flatulence, fecal incontinence, oily spotting. Absorption of fat-soluble vitamins reduced. Rarely: severe liver injury, oxalate-induced kidney injury. Contraindicated in pregnancy.	Available
Liraglutide	Intial: 0.6 mg/day subcutaneous Weekly increase as 1.2, 1.8, 2.4 mg up to 3 mg, sc, 1x1/d	Nausea, vomiting, diarrhea, constipation. Hypoglycemia in patients using other antidiabetic medications. Monitor glucose in these. Increased lipase, increased heart rate, injection site reactions. Rarely: pancreatitis, gallbladder disease, renal impairment, suicidal thoughts. Not recommended in patients with creatinine clearance of <30 mL/minute, children/elder (<18 or >75 year-old), severe hepatic impairment. Contraindicated in pregnancy, personal/family history of medullary thyroid cancer or MEN 2A/2B	Available
Phentermine/ topiramate	Initial dose 3.75/23 mg po per day for 2 weeks. Dose increased to 7.5/46 mg for 12 weeks. Then it may be elevated to 11.25/69 mg for 14 days then to 15/92 mg	Dry mouth, taste disturbance, constipation, paresthesia, depression, anxiety, elevated heart rate, cognitive disturbances, insomnia (higher dose). Abuse potential due to phentermine component. Topiramate is teratogenic (oral cleft defects). Actions of topiramate component include inhibition of carbonic anhydrase; rarely metabolic acidosis and kidney stones may result from renal bicarbonate loss. Maximum dose with moderate hepatic or renal impairment (CrCl <50 mL/min) 7.5 mg phentermine/46 mg topiramate once daily. Upon discontinuation, tapering of dose over at least 1 week using every-other-day dosing is recommended. Contraindicated in pregnancy, hyperthyroidism, glaucoma, patients using MAO inhibitors	Not available
Bupropion/naltrexone	Naltrexone 8mg/Bupropion 90 mg 1x1 tb for 1 week, 2x1 tb/day for 2nd-3rd weeks at 4th week 2x2 tb/day	Nausea, vomiting, constipation, dizziness, dry mouth, headache. Transient increase in blood pressure and heart rate. Contraindicated in uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, MAO inhibitor use in last 14 days, pregnancy or lactation.	Not available

Noradrenergic sympathometic drugs			
Benzphetamine	Initial dose 25 mg 1x1/day. Titrate up to 25-50 mg 1-3 times a day. Maximum dose 3x50 mg/day		Not available
Diethylpropion	Immediate release 25 mg 3x1/day Controlled release 75 mg 1x1/day	Limit short-term use. Increase in heart rate, blood pressure, dry mouth, constipation, insomnia. Abuse potential	Not available
Phentermine	Immediate release 15-37.5 mg 1x1/day Oral disintegrating tablet 15-37.5 mg 1x1	Avoid in heart disease, uncontrolled hypertension, history of addiction or abuse. Contraindicated in cardiovascular disease, glaucoma, MAO inhibitor therapy, pregnancy, breast feeding, agitation.	Not available
Phendimetrazine	Immediate release 17.5-35 mg 2-3x1/day. Maximum dose 70 mg 3x1/day Sustained release 105 mg 1x1		Not available

FDA approved the use of orlistat, liraglutide, phentermine/topiramate and bupropion/naltrexone, and approved also benzphetamine, diethylpropion, phentermine, and phendimetrazine for only short-term use (12 weeks). Additionally, lorcaserin, which is serotonin type 2C receptor agonist, was assessed in several randomized clinical trials and approved by FDA a few years ago [9-12]. It was recommended at a dose of 10 mg twice daily. But, based on data suggesting an increased risk of cancer with use of lorcaserin, FDA requests the withdrawal of lorcaserin in 2020 [13].

Anti-obesity medications should be selected on the basis of body mass index, co-existent diseases, contraindications and potential adverse effects, patient preferences, costs and social insurance issues. For most patients, liraglutide is preferred as a first-line agent in the treatment of obesity.

Orlistat

Orlistat binds and inhibits pancreatic lipase in gut lumen, and hence, dietary fat cannot be completely hydrolyzed and absorbed [14]. As a result, fecal fat excretion is increased. Orlistat increases fat excretion in a dose-dependent manner, and prevents the digestion and absorption of approximately 30% of ingested fat. Almost all of orally ingested orlistat is excreted by feces, and <1% of ingested dose may be absorbed.

Efficacy was demonstrated in several randomized controlled trials [3,15]. In a meta-analysis, orlistat together with behavioral intervention was shown to provide 5-10 kg loss (8% below baseline), and more effective than placebo [16]. In Xendos, which is a double-blinded, randomized controlled trial, 3304 overweight patients were included and followed up 4 years [3]. Weight loss was observed as higher in orlistat group (11%) than in placebo group (6%) in the 1st year. In the following 3 years, small weight regain was observed. In the same study, orlistat was shown to reduce the risk of development of type 2 diabetes mellitus approximately by 37%. Other studies indicated that orlistat provided more weight loss and reductions in HbA1c levels comparing placebo [17]. Orlistat was shown to produce weight loss also in subjects having low-fat diet [18].

In several studies, orlistat was known to be effective in improving blood pressure in hypertensive obese patients. Reduction in systolic (mean -2.5 mmHg) and diastolic (mean -1.9 mmHg) blood pressure was significant in these studies. Orlistat may improve lipid profile besides its weight-reducing effect. In one study, orlistat was shown to decrease LDL cholesterol about 5-10% in patients under weight-maintaining diet [19].

Recommended oral orlistat dosage is 120 mg three times a day. Over the counter lower-dose form (60 mg) also is available in several countries. It should be taken during or shortly after (<1 hour) each main meal. Interval of 2-hour should be provided between orlistat and multivitamin doses. Due to low systemic absorption, no dosage adjustment is necessary in renal or liver impairment.

Major side effects of orlistat are gastrointestinal side effects such as flatus, intestinal cramps, borborygmus, fecal incontinence, oily spotting. The side effects may be observed in up to 30% of the patients [20]. To decrease these side effects, we recommend the patients to avoid high fat diets (>30%). Renal stone, gallstone, cardiovascular or central nervous system events were not shown to increase with orlistat use, but severe liver injury was reported. But causal relationship between liver injury and orlistat use could not be established [21].

Absorption of fat-soluble vitamins (vitamin A, D, E and K) and beta-carotene may be reduced by orlistat use [20]. Vitamin D is known as the most frequently affected vitamin. Because orlistat decreases absorption of fat-soluble vitamins, a multivitamin supplement may be advised to the patients taking orlistat. Decrease in vitamin K absorption may necessitate to reduce warfarin dose in the patients using warfarin [22]. Orlistat may decrease serum level of cyclosporine. If prescribed in the same patient, cyclosporine should be taken 3-hour after orlistat, and serum cyclosporine level should be monitored [23]. Orlistat induced fat malabsorption may lead decreased calcium-oxalate binding in intestine, and more intestinal absorption of oxalate may cause hyperoxaluria and acute kidney injury [24,25].

Orlistat should not be used in the presence of chronic malabsorption syndrome, cholestasis, in pregnancy, or in the patients with a previous history of calcium-oxalate stones.

Liraglutide

Glucagon like peptide (GLP1) and gastric inhibitory polypeptide (GIP) are incretin peptides which stimulate glucose-dependent insulin secretion. Endogenous GLP1 is secreted by intestinal L cells, and as a neurotransmitter in central nervous system. GLP1 acts on its receptor GLP-1R which is expressed predominantly in the upper gastrointestinal tract, pancreatic islets, enteric visceral afferent nerves, and throughout the brain [26]. GLP1 receptor agonists provides glucose-dependent insulin secretion, decreases glucagon secretion and may be used in the management of T2D together with oral antidiabetic medications. Liraglutide is a biochemically modified GLP1 which cannot be readily metabolized by dipeptidyl peptidase 4 enzyme, and was approved for the use in T2D and/or obesity. GLP-1 has an appetite suppressant effect and the GLP-1 response to oral glucose is obtunded in obese patients. GLP1R expressed in hypothalamic nuclei (paraventricular and arcuate nuclei) is involved in the regulation of appetite [26]. However, both peripheral and central nervous system play role in appetite regulation via GLP1. A minor portion (10–15%) of endogenous GLP1 secreted by L cells may reach the systemic circulation [26]. Circulating GLP 1 may cross blood-brain barrier and activate GLP1R in central nervous system. Liraglutide inhibits Agouti-related peptide and neuropeptide-Y (arcuate nucleus), and stimulates POMC neurons. Hence, it suppresses appetite. It also acts on mesolimbic system, decreases food-seeking behavior and food-induced reward signals [26]. Liraglutide also slows gastric emptying, and causes gastric stretch which stimulates vagal afferent signals to the solitary nucleus of the medulla and the appetite center of the hypothalamus. These signals induce satiety or nausea (area postrema). Via central mechanism, weight reducing effect of GLP1 agonists has maintained albeit lack of gastrointestinal side effects [26]. GLP1 may also be proposed to increase thermogenesis. Main mechanism of liraglutide is through decrease in energy intake via appetite suppression by acting on central nervous and gastrointestinal systems.

Liraglutide may be used at a maximum tolerated dose (≤3 mg/d) in overweight or obese patients with T2D. Similarly, at a maximum tolerated dose, liraglutide may be continued if weight loss is maintained. In 56-week clinical trial including 846 patients with T2D and obesity, liraglutide (subcutaneous 1.8 or 3 mg/d) was shown to produce significant weight loss (5 or 6.4 kg) comparing to placebo (2.2 kg) [27]. In a randomized trial, liraglutide at doses of 1.2, 1.8, 2.4 and 3 mg/day was compared with orlistat 120 mg three times daily in 564 patients with obesity but without T2D [28]. Weight loss was ranged in between 4.8-7.2 kg and increased with increasing doses of liraglutide. At higher doses of liraglutide (2.4 or 3 mg/day), weight loss was observed as higher with liraglutide (6.3 or 7.2 kg) than orlistat (4.1 kg). In another clinical study analyzing 3731 patients in whom medical treatment was indicated for obesity, liraglutide provided more weight loss comparing placebo at 56 weeks (8 vs 2.6 kg) [29]. In that study, the occurrence of T2D was lesser with liraglutide than placebo. In SCALE study, in patients losing at least 5% weight loss with diet and exercise before trial, liraglutide maintained at least 5% weight loss comparing placebo (81.4 vs 48.9%) [30].

Liraglutide was shown to decrease major cardiovascular events in the patients with T2D at a lower dose (1.8 mg/d) than the recommended dose in obesity (3 mg/d) [31]. Cardiovascular outcomes have not been studied yet in obese patients without T2D.

Liraglutide is administered once a day and subcutaneously in thigh, upper arm or abdomen. Liraglutide is initiated with low dose (0.6 mg/day) for the first week. Then the dose is increased weekly as 1.2, 1.8, 2.4 mg/day and up to 3mg/day. If there is intolerance (vomiting or profound nausea), dose-titration may be slower, and maximum tolerated dose may be continued if weight loss is maintained. It is less known about data regarding long-term (>3 year) efficacy on weight reduction [18].

Gastrointestinal side effects such as nausea and/or vomiting are common with liraglutide. Weight reducing effect of liraglutide is partially due to gastrointestinal side effects or suppression of appetite. In clinical trials, nausea is more frequent with liraglutide (2.4 or 3 mg/d) than placebo (37-47% vs 5-15%), and vomiting also more frequent with liraglutide (12-16% vs 2-4%) [28-30]. These side effects may be transient, and diminish over time. Diarrhea, anorexia, and low blood sugar also may be observed with liraglutide treatment. Less common side effects are renal impairment, gallbladder disease or pancreatitis. Pancreatitis was shown to be more frequent with liraglutide treatment, although rare, comparing to placebo [29]. In animal studies, liraglutide was shown to increase benign or malignant thyroid C-cell tumors. Due to lower expression of GLP1 receptor in C-cells and lower number of C-cells in humans, occurrence of thyroid C-cell tumors in humans might be less expected. In clinical trials, this issue is controversial [32].

Pregnancy, breastfeeding, personal or family history of MEN 2A or 2B (multiple endocrine neoplasia) or medullary thyroid cancer, or previous hypersensitivity to liraglutide are contraindications to liraglutide use. To avoid hypoglycemia in the patients using insulin secretagogue or insulin, dose reduction in these drugs may be necessary if liraglutide is added to the treatment.

Phentermine/Topiramate

Food intake is controlled via several pathways. Based on this principle, combination of two medications acting on different mechanisms may be proposed to be more effective on weight control. Several combination preparations are available.

Phentermine/extended-release topiramate combination was approved by FDA in 2012. Phentermine is a sympathomimetic amine which has central anorexic effect. Topiramate increases GABA activity. The combination is proposed to suppress appetite and increase satiety. It may be considered in the treatment of postmenopausal women or men without any cardiovascular diseases who do not tolerate liraglutide or orlistat.

In a trial including 2487 adult patients with obesity or overweight, Phentermine/Topiramate combination (7.5/46 mg or 15/92 mg) provided weight loss (8 or 10 %) comparing to placebo (1.2 %) [33]. In second year of use of this combination, it provided less weight loss. In another trial analyzing phentermine/topiramate combination (3.75/23 mg or 15/92 mg), it provided more weight loss (5.1 or 10.9 %) than placebo (1.6 %).

Initial dose is per oral 3.75/23 mg per day for 2 weeks. Then, the dose is increased to 7.5/46 mg for 12 weeks. The dose may be elevated to 11.25/69 mg for 14 days and then to 15/92 mg sequentially, if weight loss of 3% cannot be achieved in 12 weeks [34]. If 5% weight loss cannot be achieved with the highest dose after 12 weeks, the drug should be cessated gradually.

Adverse effects of this combination are dry mouth, constipation, and paresthesia [33,35]. Also, psychiatric or cognitive side effects or increased heart rate may be observed.

It is contraindicated in pregnancy due to a risk of orofacial defects (cleft lip/cleft palate). Pregnancy should be excluded before the initiation of the treatment with phentermine/topiramate in reproductive women. It is not recommended in the patients with hypertension or coronary heart disease. Hyperthyroidism, glaucoma or monoamine oxidase use are the other contraindications. Topiramate may produce renal stones, and should be cautiously used in the presence of personal history of renal stones.

Bupropion/Naltrexone

The combination was approved by the FDA in 2014 in the patients whom pharmacological treatment of obesity is indicated [36]. It is not recommended as first-line medical therapy in obesity. Bupropion is a medication available for treatment of depression, and for prevention of weight gain during cessation of smoking. Bupropion is a weak inhibitor of the neuronal reuptake of norepinephrine and dopamine [37]. Naltrexone acts as antagonist of opioid-receptor and may be used in the treatment of alcohol and opioid dependence. Bupropion/Naltrexone combination provides anorexigenic effect by acting on feeding and reward circuitry. This combination may be preferred in the smoker obese subjects who needed pharmacological therapy both for smoking cessation and weight loss.

Combination of bupropion/naltrexone was shown to provide weight loss by approximately 5% [38-42]. In a randomized clinical trial of 56 weeks, weight-reducing effect was found as higher than placebo (5-6% vs 1.3%) [38]. Although weight loss was higher with the combination, reduction in heart rate or blood pressure was greater with placebo than bupropion-naltrexone combination. Due to side effects, approximately half of the participants could not complete the treatment duration until to the end of the study.

This combination should be initiated at a daily dose of 1x1 tb containing 8 mg naltrexone and 90 mg bupropion. One week later, the dose is increased to 2x1 tb/day; and at 4th week it is increased up to 2x2 tb/day.

Nausea (30%), vomiting, constipation (15%), headache (14%), dizziness and dry mouth may be observed with the treatment with combination of bupropion/naltrexone. Because it may be associated with increase in blood pressure and heart rate, post-marketing studies should be done to evaluate cardiovascular outcomes. It may be associated also with suicidal thoughts and risk in young adults (18–24-year-old), because of containing an antidepressant, bupropion. In a report analyzing 2500 adults, no difference in suicidality or depression was found between placebo and bupropion-naltrexone combination groups [43].

Cardiovascular safety of this combination has not been established yet, and remains unknown [44]. A randomized clinical trial aiming to assess cardiovascular outcomes of this combination was terminated early, due to interim data [45].

This combination is contraindicated in pregnancy, seizure, chronic opioid use, uncontrolled hypertension, severe hepatic dysfunction, eating disorder, and in patients who did take monoamine oxidase inhibitors in the last 14 days.

Sympathomimetic Drugs

Due to potential side effects or risk for abuse, limited duration of use, FDA approved the use of phentermine, diethylpropion, benzphetamine, and phendimetrazine for short-term (up to 12 weeks). These are contraindicated in patients with uncontrolled hypertension, coronary heart disease, thyrotoxicosis, or history of drug abuse. Diethylpropion and phentermine may have potential for abuse.

These medications reach peak plasma concentrations in 1-2 hours, after they are rapidly absorbed after oral administration [46]. Plasma half-lives of these agents are short, with the exception of sibutramine which has active metabolites. They are eliminated by kidneys.

Phentermine, diethylpropion, benzphetamine, and phendimetrazine inhibit reuptake of norepinephrine and stimulate its release. Sibutramine, which was withdrawn, blocks serotonin and norepinephrine reuptake into nerve terminals. By these mechanisms, these medications decrease appetite and food intake, and all of them may be associated with increased blood pressure.

In a clinical trial analyzing 68 adult subjects with obesity, phentermine (37.5 mg/day) was observed to provide more weight loss than placebo in 12 weeks period (7.2 kg loss vs 1.9 kg) [47]. In another study investigating weight reducing effect of phentermine in obese adults with diabetes, dyslipidemia, or hypertension, phentermine was shown to lead more weight reduction (8.1 kg) than placebo (1.7 kg) in 12 weeks period [48]. Diethylpropion also was shown to provide more weight loss comparing to placebo in a clinical study of 25 weeks duration [49].

These drugs may cause elevated blood pressure or heart rate, constipation, insomnia, nervousness, or constipation. Sibutramine was shown to lead an increase in systolic and diastolic blood pressure by 1-3 mmHg, and in heart rate by 4-5 beats per minute [50]. Among approximately 10000 patients with high risk for or established cardiovascular disease, sibutramine was found to be associated with nonfatal stroke (HR 1.36), nonfatal myocardial infarction (HR 1.28) [36,51,52]. After these studies, European Medicines Agency and FDA had withdrawn sibutramine from markets [36]. However, sibutramine has been widely added to dietary supplements which did aim weight reduction. Phenylpropanolamine also had been withdrawn due to an increased risk of hemorrhagic stroke [53].

Therapies Not Approved

Lorcaserin

Lorcaserin is selective agonist of serotonine 2C receptor, and decreases appetite and provides weight reduction [54]. In a study

including 3182 subjects with obesity, lorcaserin was shown to provide >5% weight loss in higher number of patients comparing to placebo (47.5% vs 20.3%) [10]. It was shown to have beneficial effects on glycemic regulation in BLOOM-DM study [2]. It may lead headache, nausea or vertigo [10,12]. It has potential of abuse. In February 2020, by the action of FDA, due to the increased risk of cancer (lung, pancreas, colorectal), it was withdrawn from the markets [13].

Dietary Supplements

Dietary supplements have been used worldwide by many people who aimed to lose weight. The safety of these products is limited. In laboratory evaluation of these supplements, it was observed to contained many drugs such as fluoxetine, furosemide, cetilistat, phenytoin, sibutramine, bumetanide, ephedrine [36]. Green tea, Garcinia cambogia, conjugated linoleic acid, chitosan were found to be ineffective for weight loss [55,56].

Conclusion

Management of obesity necessitates multiple methods such as a combination of dietary adjustments, physical exercise, pharmacological intervention and bariatric surgery in some patients. Pharmacotherapy is a milestone in the weight management strategies. The combination of choices of anti-obesity management strategies should be based both on the clinical background of the patients, the degree of obesity, laboratory features, and patients' preferences. Cardiovascular effects of the drugs especially should be considered. The patients with obesity under pharmacological treatment should be followed up both for effectiveness of the drug (weight loss) and for development of potential side effects. In our country, Turkey, there two anti-obesity medications (Orlistat and Liraglutide) available for use in the clinical practice. In Turkey, reimbursement by social insurance is available for orlistat under certain criteria. However, liraglutide was not under reimbursement policy in our country. New medications will be more effective regarding weight reduction, and available in future both in our country and the world.

Conflict of interests
Authors declare that there is no conflict of interest.

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