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Weight Loss Pharmacotherapy of Obese Non-Diabetic and Type 2 Diabetic Patients

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Abstract

The first line in the treatment of obesity is a combination of a low calorie diet, increased physical activity and behavioural therapy. Unless these options fail, should be considered an effective and safe pharmacotherapy. The market situation in anti-obesity treatment will change in a relatively short time; the combination anti-obesity therapy is entering into clinical practice. Currently in Europe we have three drugs approved for long-term chronic treatment of obesity. In addition to the orlistat EMA approved a combination of naltrexon SR/bupropion SR and liraglutide 3.0 mg. A specific feature management of obese diabetic patients is the selection of weight neutral or weight-reducing anti-diabetic treatment (oral anti-diabetics, insulin), but also weight neutral treatment associated with co-morbidities.

Keywords: Orlistat; Naltrexon SR/bupropion SR; Liraglutide 3.0 mg; Metformin; Inhibitors DPP-4; GLP-1 RA; Inhibitors SGLT2

Introduction

The epidemic of obesity is now recognized as one of the most important public health problems facing the world today. According to World Obesity Federation (WOF) there are around 475 million obese adults with over twice that number overweight - that means around 1.5 billion adults are too fat. Globally over 200 million school-age children are overweight.

The situation in Slovakia is not different from the other world. 61.8% of Slovak adult population is overweight and obese (based on data from 2012). 23.4% has BMI (body mass index) >30 kg/m^2, 18.3% from all adults (with predominance of males) has BMI 30-35 kg/m^2, about 4% of the adult Slovak population (predominance of women) has BMI of 35-40 kg/m^2, and in the range of morbid obesity BMI > 40 kg/m^2) is more than 1% of the adult population (predominate women) [1].

Obesity increases the risk for a wide range of chronic diseases; BMI is thought to account for about 60 % of the risk of developing type 2 diabetes. In 2012 according to the National Health Information Centre (NCZI) in Slovakia there were registered 342 124 diabetic patients (7% of Slovakia's population), of which more than 300 thousand (90%) are type 2 diabetics. When viewed from the other side we see (and this is the result not only epidemiological, clinical and interventional studies, but current clinical experience) that nearly 90% of type 2 diabetics suffer from overweight or obesity [2].

According to the applicable European recommendations for the treatment of obesity first line treatment is a combination of a low calorie diet, increased physical activity and behavioral therapy (this combination is constant and integral part of a long-term treatment for obese type 2 diabetic patients). First line treatment combination leads in the general population within 3-12 months to an 8% reduction in initial weight. Motivation of risk individuals to comply with long-term, lifelong dietary and regime measures is very difficult and often fails. Then there is a place for "another line" - a safe anti-obesity therapy-aimed not only to reduce and maintain weight but also to affecting cardio-metabolic risk profile, cardiovascular morbidity and mortality. The next step in indicated cases of obese patients is a bariatric (metabolic) surgery [3].

Management of obese type 2 diabetic patients (diabesity) has its other specifics. Diabetics, in the same mode (non-pharmacological or pharmacological or a combination of both) lost less weight and gained weight more rapidly compared to non-diabetic patients. A specific management of obese diabetics is a choice of a weight-reducing or neutral anti-diabetic treatment (oral hypoglycemic agents, insulin), but also a weight neutral treatment associated with co-morbidities [4].

Pharmacotherapy of Obese Non/Diabetic Patients

Obesity pharmacotherapy is indicated for patients with a BMI ≥ 30.0 kg/m^2 or for patients with BMI of 27.0 to 29.9 kg/m^2 with co-morbidities that are not a contraindication to the administration of the medicament after the failure of essential dietary treatment, lifestyle changes and behavioral therapy in order to improve patient compliance and to keep achieved weight decreased [3,5,6].

An option of effective anti-obesity treatment remains limited at present. Not every doctor shares a positive view on medical treatment of obesity, which is understandable. In the recent past we have seen few anti-obesity medicaments, which have been withdrawn from the market: fenfluramine, dexfenfluramine (incidence of valvulopathy), rimonabant (increase in suicides, anxiety and depression) and sibutramine (increased blood pressure and increased cardiovascular risk). These events have contributed to a negative impression in regard to anti-obesity treatment. However, many doctors did not have sufficient training and experience with chronic medical treatment of obesity.

At present for chronic treatment of obesity we have only one anti-obesity agent - orlistat. It is available at doses 60 mg as an Over-The-Counter (OTC) drug. Orlistat acts as a peripheral pancreatic lipase

inhibitor, and prevents the absorption of fats in the intestine. The side effects may be: steatorrhoea, gastrointestinal discomfort, and reduced absorption of fat soluble vitamins. However, steatorrhea and gastrointestinal discomfort occur particularly in patients who are unable to reduce the daily intake of fat. In patients on warfarin treatment coagulation must be monitored because of reduction in absorption of vitamin K. The efficacy and safety of orlistat (in doses of 3 x 120 mg) has been demonstrated in long-term clinical trials of several years. In a one-year trial with orlistat there was a weight loss of 4.4 kg (-10.6 kg orlistat vs. -6.2 kg placebo). Nowadays we have acceptable data about maintaining weight loss of 2.8 kg (-5.8 kg vs. -3.0 kg) after 4 year treatment with orlistat compared to placebo [7,8].

At present, particularly in the United States for short-term obesity treatment drugs classified as either sympathomimetics (phentermine, diethylpropion, phendimetrazine and benzfetamine) are used. Phentermine is the most commonly prescribed anti-obesity agents for the short-term treatment of obesity (3 months) in the United States because it is effective and inexpensive. In Slovakia was once available as Adipex (it is not officially available in the European Union - EU).

In a relatively short time situation in anti-obesity market will change. In the United States for the long-term chronic treatment of obesity FDA (Food and Drug Administration) approved five drugs: orlistat (1997), lorcaserin, phentermine/topiramate ER (2012), naltrexone SR/bupropion SR (2014), and 3.0 mg liraglutide (2014). In the EU we have currently three EMA (European Medicine Agency) approved drugs for chronic treatment of obesity: orlistat (1997), naltrexone SR/ bupropion SR (2014) and 3.0 mg liraglutide (2015) (Table 1).

Agent/USA/EU	Mechanisms of action	Approved	
		USA (FDA)	EU (EMA)
Orlistat/Xenical/Alli	Pancreatic lipase inhibitor	1997	1997
Lorcaserin/Belviq	Selective serotonin receptor agonist 5-HT2c	2012	
Phentermine / Topiramate ER Qsymia/ Qnexa	Sympathomimetic/ anticonvulsant (GABA receptor modulator, carbonic anhydrates inhibitor, glutamate antagonist)	2012	
Naltrexone SR/ Bupropion SR/ Contrave/Mysimba	Opiod receptors antagonist/ Dopamin/noradrenalin reuptake inhibitor	2014	2014
Liraglutide 3.0 mg/ Saxenda/Saxenda	GLP-1 receptor agonist	2014	2015

Table 1: Anti-obesity treatment approved for chronic management of obesity.

In clinical practice there enters the combination anti-obesity therapy (phentermine /topiramate ER and naltrexone SR /bupropion SR), which as a combination therapy in the management of other chronic diseases (hypertension, diabetes mellitus, dyslipidaemia, cancer) is justified. Anti-obesity combination therapy results in a synergistic way to additive effects of different drugs to increase the efficacy of anti-obesity treatment. The advantage is overcoming the natural compensatory mechanisms in energy homeostasis (prevention or delay of "plateau" for weight reduction). Using lower doses of active ingredients leads to a reduction in the incidence of adverse events, which improves the tolerability of therapy and patient compliance.

The combination naltrexone SR/bupropion SR (in Europe Mysimba) is anti-obesity agent with a central mechanism of action. Synergism naltrexone SR (opioid receptor antagonist) and bupropion SR (dopamine/noradrenalin reuptake inhibitor) in dopamine areas of the brain results in the reduction of food intake. While bupropion SR led to a slight decrease in weight, naltrexone SR added to bupropion increases the weight lost. At one-year follow-up studies this combination led to a 4.8% weight loss and reduction in waist circumference. There we have the results of COR (Contrave Obesity Research) program. 4500 patients were enrolled to Phase 3 clinical trials COR-I COR-II and COR-Diabetes. The combination of naltrexone SR/bupropion SR in these studies led to weight and waist circumference loss, to improvement in cardio metabolic risk factors (favorable effect on lipids, blood glucose, fasting insulin level, systolic and diastolic blood pressure) [9-13].

Another approved medication for the chronic treatment of obesity was liraglutide 3.0 mg - GLP-1 (glucagon-like peptide-1) receptor (Saxenda). Indications include chronic weight management of subjects with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with presence at least one co-morbidity. Liraglutide has so far been adopted in the lower doses (up to 1.8 mg) for the treatment of obese type 2 diabetic patients. One-year use of liraglutide 3.0 mg resulted in a weight loss of 5.8 kg, with a further decrease in weight after two years of follow-up. Results of the Phase 3 study (The SCALE ™ Maintenance randomized study) yielded data on the effect of 3.0 mg liraglutide for other cardio-metabolic risk factors, and the ability to delay the onset of pre-diabetes (fasting hyperglycemia, impaired glucose tolerance), and delay the switch to type 2 diabetes in patients with metabolic syndrome. Liraglutide led to an improvement in the severity of obstructive sleep apnea syndrome, improving the length and quality of sleep [14,15].

A very important issue related to these new drugs for chronic long-term treatment of obesity is their actual safety and efficacy. The most frequently occurring adverse events in relation to exploited medicaments for the treatment of chronic obesity are shown in Table 2. Let us see how quickly (if at all) these new anti-obesity agents fall into our daily lives.

Orlistat	Lorcaserin	Phentermine/ Topiramate ER	Naltrexone SR/Bupropion SR	Liraglutide 3,0 mg
Steatorrhea symptoms	Headache	Paresthesias	Nausea	Nausea
	Dizziness	Dysgeusia	Vomiting	Vomiting
	Fatigue	Dizziness	Headache	Diarrhea
		Dry Mouth	Dizziness	Constipation

			Insomnia	Dyspepsia
				Abdominal Pain

Table 2: Anti-obesity drug tolerability.

Pharmacotherapy Type 2 Obese Diabetic Patients

Given the close link between obesity and type 2 diabetes (diabesity) during the whole treatment we should promote weight loss by improving lifestyle (diet and regime measures), using available safety anti-obesity treatment. In treatment of diabetes we should use oral anti-diabetic agents that do not affect weight (dipeptydilpeptidase-4 inhibitors -DPP-4 inhibitors), respectively result in weight loss (metformin, receptor agonist glucagon-like peptide1-GLP-1 RA, sodium-glucose co-transporter inhibitors – SGLT2), in the case of insulin therapy use insulin (analogues), which increase the weight as low as possible (Table 3) [4].

The expected change in weight	
Weight gain	
Sulfonylurea	+1.0 to +5.0 kg
Thiazolidinediones (pioglitazone)	+3.0 kg
Basal insulin	
Glargine	+4.0 kg
Detemir	Weight-neutral or weight gain 0 to +1.5 kg
Weight-neutral	
Alpha glucosidase inhibitors	Weight-neutral
DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin)	Weight-neutral (linagliptin -1.7 kg)
Weight decrease	
Meformin	Weight-neutral or decrease in weight 0 to -1.5 kg
Glp-1 RA (exenatide, liraglutide, lixisenatide)	Decrease in weight (-1.0 to -3.0 kg)
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	Decrease in weight (-2.0 to -5.0 kg)

Table 3: Effect of anti-diabetic therapy on weight.

Metformin is a drug of the first choice for all type 2 diabetic patients. Metformin is weight neutral, eventually leading to a decline of weight. In several studies a weight loss of 0.6 to 2.9 kilograms was demonstrated in patients on metformin monotherapy. The largest decrease in weight was achieved during the first year of treatment. Beneficial effect of metformin on weight is linked to the reduction of hyperinsulinaemia, to the decreased frequency of meals (no occurrence of hypoglycemia), to the reduced appetite in relation to its gastrointestinal effects or effects on hunger and satiety centers in the hypothalamus. According to published meta-analysis metformin in combination therapy reduces weight gain associated with other oral anti-diabetic agents (sulphonylureas - SU, thiazolidinediones) or insulin. The addition of GLP-1 RA or SGLT2 to metformin resulted in a significant reduction of weight, while the DPP-4 inhibitors are weight neutral. The effect of the weight reduction was demonstrated in patients who have had GLP-1 RA added as a third-line therapy to a combination of metformin and sulphonylurea or metformin and thiazolidinediones [4,16].

GLP-1 RA - the parenteral (subcutaneous) anti-diabetics improving the long-term metabolic control, as well as the weight of type 2 diabetes patients. Currently we have exenatide (exenatide and exenatide sustained release-EQW), liraglutide and lixisenatid, GLP-1 RA (except for the effect on glycaemia control also act centrally (stimulation of the nerve plexus in the digestive tract) thereby reducing partly appetite followed by reduction of the weight [17].

Exenatide in combination with metformin and/or with SU in 6-months clinical trials leads to a weight loss of 0.9 kg (as exenatide was added to the combination metformin/SU) to 2.5 kg (when added to metformin alone). Within the open-label extension study, three year treatment with exenatide in combination with metformin and/or SU led to progressive weight loss (mean -5.3 kg). Sustained-release exenatide resulted in a clinical trial DURATION (Diabetes Therapy Utilization: Researching Changes in A1C, Weight, and Other Factors through Intervention with Exenatide Once Weekly) 1-6 to a significant reduction in weight compared with sitagliptin; the average weight gain has been observed with pioglitazone and insulin glargine titrated to the target value.

Liraglutide (as anti-diabetic treatment in type 2 diabetic patients) is administered in doses of 0.6 to 1.8 mg. Clinical trials program LEAD (Liraglutide Effect and Action in Diabetes) documented a decrease weights and focused attention to the possibility of using liraglutide well as anti-obesity treatment (at a dose of 3.0 mg daily sc). Currently we have a lot of clinical experience in treatment of obese type 2 diabetic patients. After 6 months of treatment with liraglutide and maximum tolerated dose of metformin have experienced a significant difference in the total weight loss (-3.9 kg), in reduction of BMI (-1.6 kg/m^2) and in reduction of the waist circumference (-3.2 cm) [18].

Release of lixisenatide to the clinical practice was based on the success of the program phase 3 clinical studies (GETGOAL). Addition of lixisenatide leads to improving of glycemic control and to the decrease the projected weight gain in subjects treated in combination with SU or in combination with insulin), without the risk of hypoglycemia [17].

Another group of oral anti-diabetic agents DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and alogliptin) generally has a neutral effect on weight. Studies with linagliptin show a total weight loss -1.7 kg [19].

Both groups of anti-diabetic agents (GLP-1 RA, DPP-4 inhibitors) are very promising therapy in type 2 overweight or obese diabetic patients [17-19].

A new class of drugs with a very favorable effect on weight in type 2 diabetic patients is inhibitors of SGLT2 (canagliflozin, dapagliflozin and ertugliflozin). They lead to a reduction of glucose reabsorption in the proximal tubule of kidney resulting in increased glycosuria. Loss of 50-85 g glucose/day (glycosuria) presents loss of 200-340 kcal per day, which is about one tenth of the daily energy intake for most people. This loss of energy intake leads to a decrease in weight approximately 1 kg per month. SGLT2 sub studies focused on the body composition analysis (using CT, MRI and DXA) shows that weight reduction is caused primarily by reducing visceral and subcutaneous fatty tissue. All named SGLT2 inhibitors in clinical trials significantly reduced the weight. The best reduction is achieved as have been used alone or in combination with metformin. If used in combination with insulin or SU there has been less pronounced decrease in weight. The effect of weight loss was positive also from the long term view [4,20,21].

Dapagliflozin administered once daily 6 months in mono-therapy or in combination with metformin leads to a weight reduction approximately 2-3 kg. In patients treated with insulin in concomitant administration of dapagliflozin it leads to a reduction insulin dose, to improve of glycemic control without increasing weight [22].

In the clinical program CANTATA (CANagliflozin and Treatment Trial Analysis) the efficacy and safety of canagliflozin alone was tested, in combination with metformin, in combination with metformin and SU, metformin and pioglitazone and insulin. Canagliflozin at 100 and 300 mg daily was more effective in weight reduction compared to glimepiride (-3.7 kg, -4.0 kg vs. +0.7 kg) [21].

Also another in a series of SGLT2 inhibitors empagliflozin proved in clinical trials significantly affect not only on glycemic control, as well as weight loss (monotherapy, combination therapy with insulin or metformin). Empagliflozin monotherapy for 90 weeks leads to a decrease body weight of 2.2 to 4.0 kg, metformin about 1.3 kg, sitagliptin 0.4 kg. If empagliflozin (10 or 25 mg/day) was added to a basal insulin, after 78 weeks resulted in a decrease in body weight compared to placebo (10 mg: -2.2 kg, 25 mg: -2.0 kg, placebo: +0.7 kg) [4,21].

Conclusion

Globesity and diabesity are the real problems of our clinical practice. Weight reduction leads in both cases to a significant improvement of cardio metabolic risk factors. Current recommendations for the treatment of obese patients and obese diabetic patients are calling for personalized medicine. Part of it should be unequivocally a treatment primarily focused on weight reduction in both group - obese non-diabetics as well obese diabetic patients.

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