Current Updates in the Medical Management of Obesity

Areej Khan1, Shahzad Raza1,*, Yusra Khan2, Tulay Aksoy3, Monis Khan4, Yitzchak Weinberger1 and Joel Goldman1,5

1Department of Medicine, Brookdale University Hospital & Medical Center, Brooklyn, New York, NY 11212, USA; 2Department of Pediatrics, Bronx Lebanon Hospital, Albert Einstein School of Medicine, Bronx, New York, NY 10457, USA; 3Department of Medicine, Montefiore Medical Center, Albert Einstein School of Medicine, New York, NY 10451, USA; 4McMaster University, Hamilton, Ontario, ON L8N 3Z5, Canada; 5Division of Endocrinology, Department of Medicine, Brookdale University Hospital & Medical Center, Brooklyn, New York, NY 11212, USA

Received: February 13, 2012; Accepted: March 2, 2012; Revised: March 10, 2012

Abstract: Obesity is a chronic medical condition that is expected to become an indirect but leading cause of mortality and morbidity. Obesity results in type 2 diabetes mellitus, insulin resistance, hypertension, dyslipidemia, coronary heart disease. These factors contribute to cardiovascular disease that is a leading cause of death. Therefore, the approach to obesity therapy should be designed to reduce cardiovascular disease risk and mortality. Diet and lifestyle changes remain the cornerstones of therapy for obesity, but the resultant weight loss is often small. For more effective weight loss, individuals have shown to benefit from anti-obesity medications. Anti-Obesity therapy is considered for individuals with a body mass index greater than 30 kg/m² or ranging from 25 to 30 kg/m², or individuals with co-morbid conditions. Recent anti-obese medications affect biological mechanisms that suppress appetite and absorb nutrients to regulate body weight. In this review, we discuss the FDA approved anti-obesity drugs and recent patents which include phentermine/topiramate, pramlintide, lorcaserin, AOD9604, oleoyl-estrone, trk-beta antagonists and melanin concentrating hormone that can reduce adiposity at the molecular level.

Keywords: Exenatide, metabolic syndrome, pramlintide, phentermine, orlistat, topiramate.

1. INTRODUCTION

Increased mortality rate in obesity is due to the subsequent development of a wide range of complications that include dyslipidemia, hypertension, atherosclerosis, and type 2 diabetes. These metabolic disorders substantially increase the risk for stroke, angina and myocardial infarction [1-5]. Obesity also predisposes to breast, prostate and colorectal cancers. Non-life threatening conditions linked to obesity include sleep apnea, gallstones, osteoarthritis and gout [1, 2, 4]. Recent data suggests that over 300 million individuals are obese and an additional 800 million are overweight [2]. In the United States, Eastern Mediterranean, and Pacific Islands, the prevalence of obesity ranges from about 30% to 70% [2, 3]. Prevalence increases with age and is higher in females and ethnic groups such as American Indians, Hispanic Americans and Pacific Islanders [3, 4]. Padwal et al. [1] has attributed western diets and sedentary lifestyles throughout the world for a global rise in obesity.

Body mass index (BMI) is the most widely used measurement to quantify the degree of weight gain through the calculation of weight in kilograms divided by the square of the height in meters. According to the World Health Organization (WHO) criteria, the term overweight is defined as a BMI of 25 to 29.9 kg/m² and obesity as greater than 30 kg/m². Obesity is further subdivided into mild (30 to 34.9 kg/m²), moderate (35 to 39.9 kg/m²) and severe (40 kg/m² or greater). Mortality rates and risk of cardiovascular disease rises with increasing degrees of overweight and obesity. The risk of death occurs when BMI levels reaches 29 to 30 kg/m² or greater. Sixty-five percent of American adults are overweight and thirty-one percent are obese (BMI >30) [1, 6-8].

Table 1 describes the classification of weight according to BMI.

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>BMI kg/m²</th>
<th>Risk of Co-Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td></td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-24.9</td>
<td>Mild</td>
</tr>
<tr>
<td>Over weight</td>
<td>25-29.9</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>30.0-34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0-39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Class III</td>
<td>≥ 40</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

Type 2 diabetes mellitus is one of the most common disorders seen in obese people. It is defined as chronic hyperglycemia due to relative insulin deficiency, insulin resistance
or both [8]. Both obesity and weight gain are major risk factors for diabetes. Every 1-kg increase in weight is associated with a 9% relative increase in the prevalence of diabetes. The statistics show that eighty to ninety percent of people with type 2 diabetes are overweight [8]. Obesity increases the complications associated with diabetes through development of hyperglycemia, dyslipidemia, and hypertension [8]. The prevalence of diabetes is gradually rising and expected to increase to 300 million by 2025; an estimated increase of 42% in developed countries and 170% in developing countries [9]. This review summarizes data on currently used anti-obesity drugs and new compounds under clinical development.

2. METABOLIC SYNDROME

BMI is used as an indicator of cardiovascular risks, central or abdominal obesity and is considered a better way of assessing the risk for cardiovascular disease. The co-occurrence of abdominal obesity with hyperglycemia, dyslipidemia and hypertension is termed as metabolic syndrome [10]. Obesity is a major component of metabolic syndrome that results in diabetes, hypertension and atherosclerosis through resistance to insulin and Leptin. Leptin is a hormone secreted by fat cells and induces appetite suppression and increases thermogenesis. The hormone normally directs storage of excess calories into subcutaneous tissues and prevents abdominal fat deposition.

In obese patients, however, resistance to leptin causes fat deposition within visceral organs [10-12]. Visceral adipose tissue (VAT) contains adipocytes that are larger in size than the adipocytes in subcutaneous adipose tissue. These large visceral adipocytes cause increased lipolysis and secretion of pro-inflammatory cytokines that include leptin, adiponectin, tumor necrosis factor (TNF-α), C-reactive protein (CRP), interleukin 6 (IL-6) and elevated free fatty acid (FFA) levels. The high number of pro-inflammatory cytokines released from visceral adipose tissue result in increased atherosclerosis in obese individuals. Secretion of adipocytokines such as adiponectin may also be implicated in the pathogenesis of type 2 diabetes mellitus [13].

The toxic effects of elevated FFAs have recently become appreciated as major contributors to the development of metabolic syndrome, lipotoxicity, and cardiovascular disease. Serious consequences of abdominal obesity include: (a) resistance to insulin and leptin, (b) dyslipidemia related to increased VAT which release a wide array of proinflammatory adipokines (cytokines secreted by fat cells), which promote inflammation, recruit macrophages, and stimulate smooth muscle and fibroblast expansion. Proinflammatory adipokines and cytokines include: CRP, α-TNF, IL-1, IL-6, IL-8, IL-10 [3] chronic inflammation and [4] lipotoxic damage to tissues and vasculature. Together, these result in a dramatically increased risk of cardiovascular disease [10]. Figure 1 describes the effects of cytokines and chemokines on obesity and metabolic syndrome.

3. OBESITY AND DIABETES

While a number of co-morbidities such as hypertension and atherosclerosis are linked to obesity, type 2 diabetes is the most closely associated with obesity [10]. Weight gain and obesity leads to peripheral resistance of insulin on glucose and fatty acid utilization, resulting in type 2 diabetes. Dietary studies show that ten percent weight loss can significantly improve Hemoglobin A1C levels in type 2 diabetes [5, 10]. Weight loss can be achieved with a good exercise regimen and dietary changes. In addition to lifestyle changes, drug therapies can also be used for a more sustained weight loss in obese individuals with type 2 diabetes [9, 11]. This review

Fig. (1). Obesity and metabolic syndrome effects [10].
summarizes data on currently used anti-obesity drugs and new compounds under clinical development.

4. MEDICAL MANAGEMENT

In patients who fail behavioral therapy with regular exercise and dietary changes, adjunct treatment with drugs can help in weight reduction or maintenance while improving glycemic control and lipid profiles. The current obesity guidelines recommend drug therapy for patients with a BMI greater than or equal to 30 kg/m² or a BMI of 27 to 30 kg/m² with one or more obesity related disorders [14]. Numerous anti-obesity agents have been used for weight loss in the general populations as well as in individuals with diabetes. These drugs act through a variety of mechanisms, including increased appetite suppression (e.g., sibutramine and phen- termine), increased energy expenditure (e.g., ephedrine and caffeine), and decreased food absorption from the gastrointestinal tract (e.g., orlistat). Anti-obesity drugs may be available over-the-counter or by prescription. While some drugs are approved for safe use in weight loss (e.g., metformin), there are other drugs also capable of inducing weight loss but not approved for that purpose due to their toxic side effects (i.e., off-label usage, e.g., fluoxetine). Table 2 summarizes the data on mechanism of action and adverse effects of anti-obesity agents.

a). Sibutramine

Sibutramine is a centrally acting drug that is an inhibitor of serotonin and norepinephrine (noradrenaline) reuptake. Although pharmacological action is similar to antidepressants, sibutramine does not have antidepressant properties. Sibutramine acts primarily by increasing post-prandial satiety and is useful when lack of satiety is a problem. The drug also stimulates the sympathetic nervous system that increases thermogenesis, heart rate and blood pressure.

In Sibutramine Trial of Weight Reduction and Maintenance (STORM) study conducted in non-diabetic patients, mean weight loss of 12 percent occurred during the first 6 months [15]. Weight loss was maintained in subjects who continued to take sibutramine while weight regain occurred in subjects who switched to a placebo. Both groups shared the same diet and lifestyle during the study. In addition to weight loss, sibutramine improved lipid profile by reducing low density lipoprotein (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL) resulting in a decline in the cholesterol HDL ratio by 13.3 percent [15]. Interestingly, sibutramine have also shown decrease in the systolic blood pressure by 0.8 mm Hg and triglycerides by 0.3 mmol/L [15, 16].

The largest Sibutramine trial conducted was by Kaukua et al. [17] where patients were randomized to either sibutramine 15 mg or placebo once daily with hypo-caloric diet for a 12-month period. The subjects receiving sibutramine lost a mean weight of 7.1 kg, while the placebo group only lost a mean weight of 2.6 kg. Serrano-Rios et al. [18] also randomly assigned sulphonylurea-treated obese type 2 diabetic patients to either sibutramine 15 mg/day or to a placebo. Sibutramine treated group had significantly greater reductions in body weight, HbA1c levels and fasting serum glucose when compared to the group on placebo.

Sibutramine is contraindicated in individuals receiving monoamine oxidase inhibitors, patients hypersensitive to sibutramine or any of its inactive ingredients, individuals with anorexia nervosa and those taking other centrally acting appetite suppressants. Adverse effects of sibutramine include dry mouth, anorexia, insomnia and constipation. Other potential side effects include fever, gastroenteritis, tooth disorders, peripheral edema, arthritis, agitation, leg cramps, hypotonia, abnormal thinking, bronchitis, dyspnea, pruritus, amblyopia, menstrual disorders, seizures, ecchymosis bleeding disorders and interstitial nephritis. The Sibutramine Cardiovascular Outcomes Trial (SCOUT), demonstrated a 16% increase in the risk for serious cardiovascular events such as heart attack, stroke, the need for resuscitation after the heart stopped, and death in a cohort of patients given sibutramine compared with another given a placebo. The drug has been recently withdrawn from the market because of its severe cardiovascular side effects [3].

b). Orlistat

Orlistat is an inhibitor of gastric and pancreatic lipases that acts in the gastrointestinal tract. When administered with fat-containing foods, it partially inhibits the hydrolysis of triglycerides, thus reducing the subsequent absorption of monoglycerides and free fatty acids, leading to a reduced fat absorption by around 30% [19]. In a meta-analysis, [1] the 16 trials included 10,631 participants with an average body mass index (BMI) of 36.3 kg/m², weight of 104 kg, and age of 47 years, four orlistat weight maintenance with the dose of 120 mg three times daily, which is the standard dose recommended for use in clinical practice. All sixteen studies reported greater reductions in weight in the orlistat group compared to the placebo group. Orlistat-treated patients lost 2.9 kg (95% confidence interval (CI) 2.5 to 3.2 kg; 15 studies) or 2.9% (95% CI 2.5 to 3.4%; 13 studies) more weight than placebo-treated patients. The maximum recommended prescription duration for orlistat is 2 years. Patients with diabetes, orlistat reduced weight by 2.6% or 2.3 kg compared to placebo therapy [1, 20].

Weight reduction of approximately 5% to 10% of initial body weight is associated with improvements in blood pressure, lipid and glucose parameters. Examining the impact of weight reduction on cardiovascular events and mortality is still lacking. More recently, randomized controlled trials (RCTs) involving treatments such as intensive lifestyle modification (diet plus exercise), acarbose, metformin, orlistat, troglitazone and rosiglitazone have reduced diabetes incidence in high risk patients, the majority of whom were overweight or obese [1].

Chou et al. [21] compared the effects of sibutramine and orlistat on 34 obese, poorly controlled type 2 diabetic patients and found that the weight reduction achieved with sibutramine (2.5%) was significantly greater compared with orlistat (0.9%); however, there were no significant differences in other metabolic parameters (waist circumference, lipid levels and glucose levels). In contrast, Derosa et al. [22] after randomly assigning 141 obese diabetic patients in
Table 2. The Mechanism of Action and Adverse Effects of Anti-obesity Agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine</td>
<td>Appetite suppressant</td>
<td>Withdrawn from the market because of severe cardiovascular effects</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Gastric and pancreatic lipase inhibitor contraindicated in chronic malabsorption, cholestasis, pregnancy, breast feeding, hypersensitivity</td>
<td>FDA approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased defecation, soft stools, fatty or oily evacuation and abdominal pain or oily spotting.</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Cannabinoid type 1 receptor antagonist</td>
<td>6% patients have serious side effects like depression, anxiety, irritability, aggression. Withdrawn from the US Market</td>
</tr>
<tr>
<td>Phentermine &amp; Fenfluramine</td>
<td>Appetite suppressant</td>
<td>Withdrawn from the market. Adverse side effects like heart valve disease, pulmonary hypertension</td>
</tr>
<tr>
<td>Phentermine &amp; Topiramate</td>
<td>Appetite suppressant</td>
<td>Suicidal thoughts, heart palpitations, memory lapses and birth defects. Withdrawn from the The U.S. Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decreased hepatic synthesis of glucose and decreases peripheral insulin resistance</td>
<td>Lactic acidosis. Gastrointestinal disturbance</td>
</tr>
<tr>
<td>Naltrexone &amp; Bupropion</td>
<td>Appetite suppressant via αMSH and Pro-opiomelanocortin (POMC) neuronal stimulation</td>
<td>Depression, nausea, headache, vomiting, dizziness</td>
</tr>
<tr>
<td>Bupropion &amp; Zonisamide</td>
<td>Appetite suppressant</td>
<td>Headache, insomnia and nausea, while urticaria (hives)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Incretin hormone, slows gastric emptying, suppresses glucagon, promotes satiety, potentiates nutrient-stimulated insulin secretion</td>
<td>Major side effect is pancreatitis</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Amylin analogue</td>
<td>Allergic reaction, GI discomfort, headache, nervousness, sweating</td>
</tr>
<tr>
<td>Lorcanerin</td>
<td>5-HT1C receptor agonist, activates the proopiomelanocortin system of neurons that induces hypophagia</td>
<td>Headaches, upper respiratory tract infection, nausea and dizziness</td>
</tr>
<tr>
<td>GT 389-255</td>
<td>Pancreatic lipase inhibitor</td>
<td>GI discomfort</td>
</tr>
<tr>
<td>Cetilistat</td>
<td>Gastrointestinal and pancreatic lipase inhibitor</td>
<td>GI discomfort</td>
</tr>
<tr>
<td>AOD9604</td>
<td>Synthetically modified hGH, stimulates lipolysis</td>
<td>No major side effects</td>
</tr>
<tr>
<td>Oleoyl-estrone</td>
<td>Fatty acid ester of estrone, Selective B3 receptor agonist Induce body-fat loss Reduce energy intake</td>
<td>Phase 2a studies for oral oleoyl-estrone failed</td>
</tr>
<tr>
<td>PYY 3-36 &amp; Oxyntomodulin</td>
<td>Y2R agonist and Oxyntomodulin, a glucagon like peptide 1 (GLP-1) receptor agonist, are cosecreted by intestinal L-cells appetite suppressant</td>
<td>No major side effects</td>
</tr>
<tr>
<td>TM 30338 (Obineptide)</td>
<td>Y2-Y4 receptor agonist, appetite suppressant</td>
<td>No major side effects</td>
</tr>
<tr>
<td>Anti-ghrelin vaccine</td>
<td>Gastrointestinal peptide hormone antagonist Appetite suppressant Effective in Prader-Willi syndrome because of high ghrelin</td>
<td>No major side effects</td>
</tr>
<tr>
<td>Tyrosine kinase receptor trkB agonists</td>
<td>Appetite suppressant</td>
<td>No major side effects</td>
</tr>
<tr>
<td>Melanin concentrating hormone receptor antagonist</td>
<td>Appetite suppressant</td>
<td>Prolong QT interval</td>
</tr>
<tr>
<td>MC4 receptor antagonist</td>
<td>MK-0493, Increase energy expenditure</td>
<td>Nausea, diarrhea and loose stools</td>
</tr>
</tbody>
</table>
either orlistat treatment (360 mg daily) or sibutramine treatment (10 mg daily) for 12 months found that orlistat was slightly more efficacious than sibutramine. Miles et al. [23] conducted a 1-year, multicentre, randomized, double-blind, placebo-controlled trial of 120 mg orlistat three times daily vs. placebo combined with a low calorie diet. Weight loss in the orlistat+diet group was greater than in the placebo+diet group, p < 0.001. Shi et al. [24] randomized Chinese (n = 249) newly diagnosed type 2 diabetic patients to orlistat 120 mg or placebo and evaluated orlistat’s efficacy after 24 weeks; treatment with orlistat in conjunction with low-calorie diet significantly promoted weight loss and improved glycaemic status and cardiovascular risk factors.

Samuelsson et al. [25] reported that weight reduction was associated with decreasing (p < 0.001) levels of TNF-α and IL-6 in both orlistat and placebo groups. From these clinical trials we conclude that orlistat reduces LDL levels, glucose levels and blood pressure and is not associated with major systemic toxicities. It is likely to be most useful in patients with pre-diabetes/diabetes, elevated LDL levels or preexisting cardiovascular disease but should be avoided in patients with chronic gastrointestinal problems [1]. The side effects of orlistat are mainly gastrointestinal and notice during the first year of treatment. The most common effects are increased defecation, soft stools, fatty or oily evacuation and abdominal pain or oily spotting. Orlistat can also decrease fat-soluble vitamins [26]. Therefore, adequate vitamin supplementation may therefore be needed for patients on orlistat.

The risk of very rare liver-related side effects in association with orlistat has been under close review by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency, press release 16/2/12). The drug is contraindicated in patients with chronic malabsorption syndrome or cholestasis, in pregnancy or while breastfeeding and in patients with known hypersensitivity to orlistat or any of its component.

c). Rimonabant

The endocannabinoid system has played a significant role in the control of food intake and energy balance, as well as lipid and glucose metabolism. The endocannabinoid system is overactive in obesity, suggesting that weight loss could be induced and metabolic profiles improved if the elevated endocannabinoid tone is suppressed. Endocannabinoids act as endogenous ligands capable of activating two types of G protein-coupled cannabinoid receptors, the cannabinoid type 1 (CB1) receptor and the cannabinoid type 2 (CB2) receptor. The CB1 receptor is expressed in the central nervous system and in peripheral tissues such as adipose tissue, gastrointestinal tract, liver and muscle, which are all involved in lipid and glucose metabolism. The CB2 receptor is located in the immune and hematopoietic cells. Rimonabant, the first drug to selectively inhibit the CB1 receptor in the brain and in the periphery is aimed at preventing obesity and its associated risk factors.

The Rimonabant in Obesity (RIO)-Diabetes study showed that rimonabant exerts a favorable effect in diabetes by demonstrating a direct, weight-independent effect on the above mentioned organs. Rimonabant has been studied for two major indications: (i) the potential to induce weight loss as part of the treatment of the metabolic syndrome and (ii) the effectiveness of CB1 antagonists in smoking cessation [27].

The meta-analysis of four randomized clinical trials on rimonabant therapy show 4.7 kg weight loss compared to placebo in a 1 year follow up. Rimonabant treatment increased the number of weight-loss responders by 33% compared to subjects on placebo [1]. The drug reduced weight circumference by 3.9 cm compared to placebo. Also, Rimonabant reduced systolic blood pressure by 1.8 mmHg and diastolic blood pressure by 1.2 mm Hg. Although HbA1c dropped down only to 0.7%, no statistically significant reductions were demonstrated in other studies. [1] The drug has also increased HDL cholesterol level by 0.1 mmol/L and reduced triglyceride levels by 0.24 mmol/L.

Fourteen percent of patients on rimonabant discontinued therapy due to adverse events, which was 6% greater than placebo [1]. The most serious adverse effect was an increased incidence of psychiatric disorders (depression, anxiety, irritability, aggression), which occurred in 6% of patients receiving rimonabant and was more likely in patients receiving rimonabant compared to placebo. These adverse psychiatric events were observed in 26% of the participants in the 20 mg rimonabant group compared with 14% of those on placebo in the same four studies. The drug never received FDA approval due to its adverse psychiatric side effects [28].

d). Phentermine and Fenfluramine

Phentermine is a noradrenergic drug, which stimulates the release of noradrenaline and reduces food intake by acting on β-adrenergic receptors in the perifornical hypothalamus. Fenfluramine and dexfenfluramine (the d-isomer of fenfluramine) are serotonergic drugs, which cause the release of serotonin to suppress appetite and reduce food intake [1]. The combination of phentermine with fenfluramine or dexfenfluramine was previously used in managing obesity. In 1997, both drugs were withdrawn from the market because of damage to the heart valve and pulmonary hypertension proven via echocardiographic evidence of valvular morphology that resembled those in carcinoid or ergotamine-induced heart valve disease. More recently, Lannett has received the US Food and Drug Administration (FDA) approval for the abbreviated new drug application (ANDA) of phentermine resin extended-release capsules, 15mg and 30mg for exogenous obesity and short term use.

e). Phentermine and Topiramate

RCTs show that topiramate monotherapy produces weight loss among obese individuals of ~6-8 kg at 24 weeks and improvements in lipids, glycemic control, and blood pressure. Topiramate in rats increase extraneuronal levels of dopamine, noradrenaline and 5-Hydroxytryptophan (5-HT) receptors in the hippocampus and account for the hypophagic actions of topiramate.

A 56-week randomized phase III controlled trial was conducted to evaluate safety and efficacy of a controlled-release combination of phentermine and topiramate for weight loss and metabolic improvements. The combination was associated with 14.4% weight loss in study completers.
A study conducted by Wainstein et al. [35] on 521 patients comparing the safety and efficacy of initial treatment with combination of sitagliptin and metformin with pioglitazone monotherapy in drug-naive patients with type 2 diabetes mellitus. There was a significant reduction in HbA1c level and the between-group difference in change from baseline body weight between the sitagliptin/metformin group and the pioglitazone group was 4.5 kg [35].

The weight benefits of metformin monotherapy have been demonstrated in several trials reporting a 0.6- to 2.9-kg weight reduction in diabetic patients followed for 6 months to 5 yr; most of this weight loss occurred within the first year. In addition, switching previously diet- and glyburide-treated patients to metformin resulted in a 3.8-kg weight loss, whereas patients continuing glyburide monotherapy did not experience any significant weight change [36].

Metformin has not been recommended in non-diabetic patients for weight loss however, In the systematic review and meta-analysis conducted by Björkhem-Bergman et al. [37] metformin treatment induces weight loss and prevents weight gain in non-diabetic patients taking typical antipsychotic drugs [37]. The mean weight change in metformin-treated patients compared with placebo-treated patients was ~4.8 % of the initial body weight in adults and ~4.1% in children. Surprisingly, the beneficial effects of metformin were strikingly more pronounced in Asian patients than in Hispanic patients [35]. METS study (The Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia) will provide more information about the use of Metformin in non-diabetic patients taking anti-psychotic medications.

g). Naltrexone and Bupropion (Contrave)

Contrave is a fixed dose combination therapy for obesity in a single tablet consisting of sustained release (SR) formulations of both naltrexone and bupropion and hence may suppress appetite by the release of αMSH and Pro-opiomelanocortin (POMC) neuronal stimulation however, also results in the release of β-endorphin which is thought to act as a negative feedback control on POMC firing [38]. The concept study conducted on 238 obese subjects with a BMI averaging 35 kg/m² found that the combination treatment weight loss of 4.4 kg, compared with 3.1 kg for bupropion alone after 24 weeks [39]. The main side effect issues were nausea (31%), headache (15.7%), dizziness (9.1%) and insomnia (13.4%). A 56 week phase III double-blind study was conducted on 505 overweight or obese patients with type 2 diabetes, whose HbA1C scores averaged 8% and who were maintained to concurrent anti-diabetic medication, 44.5% of subjects lost over 5% body weight when combined naltrexone and bupropion compared with 18.9% of placebo. Significant placebo-adjusted reductions in HbA1C levels of 0.5% were observed [39]. Recent concerns of contrave include psychiatric side effects and the propensity of bupropion to elicit depressed mood are of major concern.

h). Bupropion and Zonisamide (Empatic)

Empatic is a combination of Bupropion and Zonisamide. The combination is useful for the anorexic properties of sustained release formulations of both bupropion and zonisamide. A pilot clinical study of 18 diet-restricted obese women with a mean BMI of 36.8 kg/m² was conducted over 12 weeks where subjects were treated with either zonisamide immediate release alone or a combination of zonisamide immediate release 100 mg rising to 400 mg over 4 weeks and bupropion immediate release 100 mg, rising to 200 mg after 2 weeks. Empatic containing 120mg zonisamide resulted in a 6.1% weight loss, while the 360mg zonisamide containing dose gave a 7.5% weight loss. Empatic induced weight loss was progressive and had not reached a plateau at the end of the study. Discontinuation rates were 34% for high dose empatic. Main adverse events were headache, insomnia and nausea, while urticaria (hives) also contributed to discontinuation [39].
i). Exenatide

Exenatide is a glucagon-like peptide (GLP) is an incretin hormone, a 39 amino acid peptide secreted by the enteroendocrine L cells of the small intestines. Exenatide is a homolog of GLP which is injected twice daily [3, 40]. Exenatide has a relatively short half-life of 2.4 hours and is detectable in plasma within 15 min of administration and is still detectable 15 h after a single subcutaneous injection. The predominant route of elimination is via glomerular filtration with subsequent proteolytic degradation. Exenatide slows gastric emptying, suppresses glucagon, promotes satiety and it also potentiates nutrient-stimulated insulin secretion [41]. Administered as monotherapy, exenatide is associated with weight loss of approximately 3 kg over 24 wk of treatment, with Hb1Ac reductions of 0.7 to 0.9% [42]. When added to Sulphonylurea, exenatide achieved dose-dependent weight loss (up to ~1.6 kg) and HbA1c reductions (up to ~0.86%) [43].

A recent meta-analysis by Fakhoury et al. [44] on 38 placebo-controlled clinical trials assessed the efficacy and safety of incretin-based medications in patients with type 2 diabetes. The meta-analysis confirmed a positive association between exenatide and weight loss. Weight loss ranging from 2 to 6 kg has been a consistent finding in studies designed to investigate the glycemic benefits of incretin mimetics in individuals with type 2 diabetes.

There are very limited data on the use of exenatide in nondiabetic individuals. One group reported a ~3.3 kg placebo-corrected weight loss over 24 weeks [45]. Similarly, other groups have shown that 1.2-3.0 mg liraglutide daily plus aggressive lifestyle intervention for 20 weeks was associated with dose dependent, placebo-corrected weight loss over 24 weeks [45]. The side effects include nausea (3-51%), which was transient with dose dependent, placebo-corrected weight loss [46]. The side effects include nausea (3-51%), which was transient in clinical trials, disappearing after 8 weeks, and, therefore, appeared not to have a causal relationship with reductions in weight, which were sustained for the duration of the treatment. In patients continuing treatment for up to 3 years, a sustained weight loss of ~5.3-5.7 kg has been reported [47, 48]. However, exenatide treatment can achieve a body weight reduction of 6.16 kg, greater than 3.97 kg, which was achieved with the lifestyle modification program + placebo [48].

It is important to mention that besides the improvement in glycemic control and weight reduction, exenatide has been shown to reduce blood pressure, body fat mass, including visceral fat, while lean body mass is not altered, and an improvement in the profile of circulating cardiovascular biomarkers [49].

Patent US7893080 relates to methods of treating metabolic syndrome, type 2 diabetes mellitus, atherogenic dyslipidemia and/or obesity and restoring the incretin effect, restoring physiologic control of glucagon levels, restoring first-phase insulin secretion, and the physiologic glucose-dependent insulin secretion [50].

j). Pramlintide

Amylin is a peptide hormone with glucose-regulatory and anorectic effects. Its amino acid sequence is 46% identical to that of human beta-CGRP (calcitonin-gene related peptide). It is stored in the pancreatic beta cell and it is physiologically co-secreted with insulin in response to food ingestion. Amylin acts in the hindbrain area postrema and central nucleus of the amygdala to reduce food intake, by acting as a satiety signal [51-53].

Pramlintide, a soluble amylin analogue, marketed as Symlin, is used as a supplement to insulin in the treatment of type 1 or type 2 diabetes. Pramlintide also leads to a reduction in food intake and body weight in obese humans, with or without diabetes [54]. Heptulla et al. [55] have shown that co-administration of amylin analogue with insulin to a small cohort of adolescent with type 1 diabetes induced a larger reduction in prandial hyperglycemia, with a concomitant reduction in the level of glucagon when compared to insulin monotherapy. Pramlintide, given subcutaneously at a dose of 30 μg per meal, significantly reduced body weight, HbA1c values and even the dosage of insulin [56].

In a 52-week, double-blind, placebo-controlled trial that included 480 patients, Whitehouse et al. [57] demonstrated that pramlintide 30-60 μg 4 times daily induced significant weight loss as early as 13 weeks from initiation of therapy. Similar results were noticed by Ratner et al. [58] in a 52-week double-blind, placebo-controlled trial (n = 651) during which patients received pramlintide 60 μg 3 or 4 times daily. Dunican et al. [59] reviewed all seven studies where pramlintide was studied as a potential agent for weight loss in type 1 diabetes type and nine studies where pramlintide was studied in type 2 diabetes and three trials where pramlintide was tested in non-diabetic patients. All trials included patients with at least a 1-year history of diabetes and excluded those with any additional clinically significant disease states. These trials examined changes in weight as a secondary outcome, which limits extrapolation of weight-loss findings.

Pramlintide demonstrated weight loss in all of the trials analyzed in this review. Patients with type 1 diabetes experienced weight loss of up to 1.7 kg over 1 year with pramlintide 60 μg 3 times daily. Patients with type 2 diabetes experienced even greater weight loss, with patients in one study achieving placebo-subtracted weight loss of up to 3.7 kg after 16 weeks of pramlintide 120-240 μg administered 3 times daily. It has been established that greater weight loss is associated with higher initial BMI, possibly explaining the greater weight reduction seen in patients with type 2 diabetes. Weight loss in non diabetic patients treated with pramlintide was 5-10% of their baseline body weight versus non diabetic patients treated with a placebo.

In general, use of pramlintide is limited by its formulation (injection only) and high cost. Further, use of pramlintide for weight loss is not FDA approved and lacks long-term data. Though the results of these trials are promising, trials examining the weight loss benefit and safety of pramlintide in larger cohorts of patients using standardized dosing over longer periods are warranted before pramlintide should be used exclusively for weight loss as concluded by clinical trial review [59]. A patent US7910548 describes the methods of amylin based treatment for obesity [60].

k). Lorcaserin

Lorcaserin is a novel selective serotonin 2C (5-HT2C) receptor agonist in clinical development for weight man-
agement. The 5-HT\textsubscript{2C} receptor in the hypothalamus modulates food intake by activating the proopiomelanocortin system of neurons that induces hypophagia [61]. In 4- and 12-wk randomized, double-blind, placebo-controlled studies, significant dose-responsive and progressive weight loss was observed at doses of 10 and 15 mg once daily (QD) and 10 mg twice daily (BID) [62]. These results were confirmed in a large 2-yr trial incorporating background lifestyle modification in which patients taking lorcaserin 10 mg BID lost significantly more weight than placebo-treated patients after 1 year of treatment and maintained more weight loss during year 2 [63].

A 52 week randomized, double-blind placebo-controlled, parallel-group study was conducted between December 2007 and July 2009. A total of 4008 patients, of whom 79.8% were female, were randomized; 2224 (55.5%) patients completed the trial. More patients receiving lorcaserin BID and lorcaserin QD lost at least 5% body weight at 1 yr (47.2 and 40.2%, respectively than in the placebo group. Lorcaserin BID was associated with significantly greater weight loss than lorcaserin QD (P < 0.01) [64]. Similarly, significant number of patients achieved at least 10% weight loss in the lorcaserin groups compared with placebo. Small changes in LDL cholesterol in the lorcaserin twice daily group relative to placebo were not statistically significant. The most common adverse effects that occurred more frequently in both lorcaserin groups were headache, upper respiratory infection, nausea and dizziness [64]. Importantly, at 1 yr, lorcaserin did not increase the incidence of FDA-defined cardiac valvulopathy, which can occur with nonselective agents like fenfluramine or pergolide that activate the serotonin 2B receptor. Lorcaserin used for up to 1 yr was associated with significant weight loss among obese and overweight adults. A US patent application US7977329 describes method of patent application of 5-HT\textsubscript{2C} receptor agonist in the treatment of obesity [65].

\textbf{i). GT 389-255}

GT 389-255, is a lipase inhibitor being developed by Peptimmune. This is a novel combination of an inhibitor and a polymer designed to bind the undigested triglycerides therefore allowing increased fat excretion without side effects such as oily stools that occur with Orlistat. Indeed, GT 389-255 was well tolerated in healthy volunteers. Peptimmune now has to conduct efficacy trials of GT 389-255 in obese individuals to demonstrate that the compound is actually better tolerated and perhaps more efficacious than orlistat. The development seems to be stalled as Phase 1 trials were conducted in 2004 and there has been no further human clinical development since then. In 2011, Peptimmune filed for Chapter 7 Liquidation [66].

\textbf{m). Cetilistat}

Cetilistat is a novel, highly lipophilic benzoazinone inhibitor of gastrointestinal and pancreatic lipases, for the potential treatment of obesity in patients with or without diabetes. In a 12-week, randomized, placebo-controlled, phase 2 clinical study in obese patients without pharmacologically treated co-morbidities, administration of 60, 120, or 240 mg cetilistat three times daily in combination with a hypocaloric diet produced significantly greater weight loss than placebo at all doses tested [67]. In addition, cetilistat was well tolerated, with a similar proportion of discontinuations due to adverse events which are mainly gastrointestinal in nature and mild to moderate in severity.

In a randomized, placebo-controlled, double-blind study, treatment with cetilistat (80 and 120 mg three times daily) or orlistat (120 mg three times daily) for 12 weeks, combined with a hypocaloric, moderate fat diet, produced significant reductions in body weight compared to placebo in obese patients with type 2 diabetes who were being treated with metformin. This was accompanied by improved glycemic control as evidenced by significant reductions (0.5%) in plasma HbA1C levels. There were also significant reductions in waist circumference, in the cetilistat (80 and 120 mg three times daily) and orlistat (120 mg three times daily) dose groups [68].

\textbf{n). AOD9604}

AOD9604 is a synthetically modified 15 amino acid region of human chorionic gonadotrophin hormone developed by the Australian company Metabolic Pharmaceuticals Limited. The drug acutely stimulates fatty acid oxidation, increases in \textit{vitro} lipolysis via the stimulation of hormone sensitive lipase and reduces \textit{in vivo} lipogenesis by inhibiting the activity of the rate-limiting enzyme acetyl-CoA carboxylase. Chronic administration of AOD9604 in mice results in a marked decrease in fat accumulation, decreased body weight gain, and an improvement in circulating metabolites, such as triglycerides and cholesterol [69]. A patent US7605122 describes the formulations of human chorionic gonadotropin hormone for weight loss and body contouring [70].

\textbf{o). Oleoyl-estrone}

Oleoyl-estrone (OE) is a fatty acid ester of estrone. It is a naturally circulating hormone in animals including humans. The compound was found to potently induce body-fat loss while preserving protein stores in animals which is the ultimate goal of an anti-obesity agent as body protein loss is an undesired but inevitable (to some degree) side effect of fat loss via calorie restriction. In the study conducted at the University of Barcelona, [71] the effect of Oleoyl-estrone and/or selective \beta-3-adrenergic agonist (B3A) (subcutaneous constant infusion) administration for 10 days to overweight male rats, was compared with controls. Three distinct white adipose tissue (WAT) sites: subcutaneous inguinal, retroperitoneal and epididymal were compared for tissue weight. DNA (and, from these values cellularity), cAMP content and the expression of several key energy handling metabolism and control genes were analyzed and computed in relation to the whole site mass. According to this study, OE and B3A, elicited widely different responses in WAT gene expression, end producing similar effects, such as shrinking of WAT, loss of fat, maintenance of cell numbers. OE acted essentially on the balance of lipolysis-lipogenesis and the blocking of the uptake of substrates; its decrease of synthesis favoring lipolysis. B3A induced a shotgun increase in the expression of most regulatory systems in the adipocyte, an effect that in the end favoured again the loss of lipid. However, in this study, no synergistic effect was noted between OE and B3A.
in WAT, but their combined action increased WAT energy waste. A US patent no US6689800 describes the use of selective beta3 adrenergic agonists in the treatment of obesity [72].

p). PYY 3-36 and Oxyntomodulin

Food intake is regulated by the hypothalamus, including the melanocortin and neuropeptide Y (NPY) systems in the arcuate nucleus. The NPY Y2 receptor (Y2R), a putative inhibitory presynaptic receptor, is highly expressed on NPY neurons in the arcuate nucleus, which is accessible to peripheral hormones. Peptide YY (3-36) (PYY(3-36)), a Y2R agonist, is released from the gastrointestinal tract postprandially in proportion to the calorie content of a meal. PYY 3-36 and Oxyntomodulin, a glucagon like peptide 1 (GLP-1) receptor agonist, are co-secreted by intestinal L-cells after each meal can be additive in their effect on food intake in overweight and obese humans resulting in statistically significant reduction in energy intake of 42.7% in comparison with that on the saline control day [73].

Phase I clinical trials indicate that PYY 3-36 is safe, well-tolerated and shows evidence of reducing caloric intake, moderating appetite and demonstrating weight loss in human subjects. All PYY-related adverse events were mild or moderate in severity and resolved spontaneously without treatment. Recently, Nestech has announced the completion of enrolment for its Phase II clinical trial of PYY3-36 Nasal Spray to treat obesity. The study has enrolled 551 obese patients at multiple clinical sites in the United States for a six-month, randomized, placebo-controlled dose ranging study. The study is designed to evaluate three different doses of PYY3-36 Nasal Spray compared to placebo.

q). TM30338

TM30338 (Obinepitide), a dual Y2-Y4 receptor agonist developed for the treatment of obesity and related diseases. Obinepitide is derived from pancreatic hormone by having Gln-63. A first-in-man Phase I/II clinical study demonstrated that TM30338 is safe and well tolerated in man. Importantly, in obese human subjects once-a-day subcutaneous dosing of Obinepitide inhibited food intake at a statistically significant level up to 9 hours. Single subcutaneous doses of TM30338 administered to healthy human subjects with normal body weight were safe and well tolerated and allowed a maximal well tolerated dose to be defined. TM30338 administered to healthy obese subjects both once-a-day and twice-a-day for multiple days was also safe and well tolerated. There were no withdrawals due to adverse events and no serious adverse events were reported [74]. There were no apparent trends in the clinical laboratory data across the entire single dose range or following the multiple once- or twice-a-day dose regimens. Neither were there any apparent trends in, for example, the vital signs or electrocardiography parameters in subjects exposed to TM30338. In a double-blind, cross-over design performed in healthy obese subjects food intake was statistically significantly suppressed by TM30338 as compared to placebo. This was observed both in the once-a-day and twice-a-day treatment regimen. Importantly, in the once-a-day regimen the compound was administered more than 9 hours prior to the test meal [74]. At the end of the treatment period, drug treated mice had 22-26% lower body weights than placebo treated mice while drug treated rats had 14% lower body weights than placebo treated rats.

r). Anti-ghrelin Vaccines

Ghrelin is a gastrointestinal peptide hormone produced primarily by endocrine cells in the gastric fundus that is post-translationally acylated by the addition of an N-octanoic acid moiety required for binding to its receptor. Ghrelin hormone acts in the arcuate nucleus of the basal hypothalamus, stimulating the production and release of neuropeptide Y and suppressing proopiomelanocortin. Usage of ghrelin receptor antagonists, GSH-R1a, triggered a decrease in food intake, bodyweight and an improvement in glucose tolerance due to increased glucose-dependent insulin secretion, thus confirming the potential of ghrelin blocking as a potential treatment target for obesity [75]. In the study conducted by Ghosh et al. [76] an anti-ghrelin vaccine by chemical conjugation of active ghrelin with protein tubules of NS1 of the bovine bluetongue virus; while this protein is not part of the viral capsid, behaves like classical VLPs, protein capsid of the virus only. The vaccine was found to be effective in decreasing acute food intake and increasing energy expenditure which are important contributions to establish a negative energy balance and promote weight loss and maintenance; nevertheless, there was no change in bodyweight over the study span. Besides Prader-Willi syndrome where ghrelin levels are usually high who could benefit from anti-gherin vaccine [77], most obese patients have low ghrelin levels [78]. Therefore, the vaccine is not expected to be effective in the absence of a diet-induced ghrelin rise, and thus an anti-ghrelin vaccine would benefit patients enrolling in a diet and exercise program as adjuvant therapy for weight loss and bodyweight control.

s). Tyrosine Kinase Receptor TrkB Agonists

Mutations in the tyrosine kinase receptor TrkB or in one of its natural ligands, brain-derived neurotrophic factor (BDNF), lead to severe hyperphagia and obesity in rodents and/or humans by directly modulating appetite, metabolism, and taste preference downstream of the leptin and melanocortin 4 receptor via hypothalamus. The trkB agonists mediate anorexic and weight-reducing effects independent of stress induction, visceral discomfort, or pain sensitization and thus emerge as a potential therapeutic for metabolic disorders. However, the studies on humans are yet to be undertaken prior to any conclusion. A patent US7935342 describes the method of treating obesity by administering a trkB antagonist [79].

t). Melanin Concentrating Hormone (MCH)

Over the past decade, a number of neuropeptides have been identified as regulators of food intake and energy metabolism, most of them originating from the hypothalamus. Examples include alpha-melanocyte stimulating hormone (aMSH) and cocaine- and amphetamine-regulated transcript (CART) as anorexigenic peptides, and neuropeptide Y (NPY), agouti-gene-related peptide (AgRP), orexin, and melanin concentrating hormone (MCH) as orexigenic ones [80].
MCH is a 19-amino-acid cyclic peptide synthesized from precursor protein, prepro-MCH, by posttranslational cleavage along with the production of two additional peptides named neuropeptide E-I (NEI) and neuropeptide G-E (NGE) [81]. The MCH receptor (MCH-R1) with G-Protein coupled receptor is particularly high in abundance in the hypothalamus, thalamus, olfactory cortex, amygdala, and hippocampus. Marsh et al. [82] have shown that targeted disruption of the MCH-R1 gene results in resistance to diet-induced obesity and hyperphagia. Recent reports of the anorectic and antiobesity effects like increase energy expenditure of the MCH-R1 antagonists in vivo further confirmed the importance of MCH in the regulation of body weight. Neurogen researchers have reported several small molecule antagonists of MCH-R1, and among those, a piperazine compound 1 (NGD-4715) is most advanced to phase I study.

Interestingly, MCH-R1 antagonists have anxiolytic and antidepressant properties in addition to anorectic and antiobesity effects. One major issue has been the high affinity of many analogues for the human ether-a-go-go-related gene which encodes a K+ channel that is critical for heart electrical activity. Binding activity is associated with prolongation of the QTc interval. This may provide exciting clinical utility as an antiobesity drug, although cardiotoxicity need to be evaluated in clinical trials. A patent US20080255218 provides the methods for Melanin-concentrating hormone receptor antagonist [83].

**u. MC4 Receptor Antagonist**

More recently, a non-peptide melanocortin receptor agonist (MC4), MK-0493, was developed that caused increased energy expenditure and weight loss in diet-induced obese rats. Melanocortin are expressed in brain areas, particularly the arcuate nucleus of the hypothalamus and hindbrain, associated with the regulation of feeding. When administered acutely to human, only a marginally significant increase in energy expenditure was observed [84]. When administered over 12 or 18 weeks to obese subjects in a double-blind, placebo controlled trial with a 2 week run in period, no significant drug induced weight loss was observed. The compound was well tolerated with principle adverse events of nausea (16.5% vs 3.6% of controls), diarrhea and loose stools (37% vs. 14% of controls) and skin rash [38, 85].

The failure to observe efficacy in the trial with MK-0493 may reflect the low doses tolerability issues. As one role of leptin is to activate the melanocortin system in leptin resistance which may compromise the effect of MC4 agonist. Alternatively, it may reflect the leptin resistance in obese patients [38].

**4. CURRENT & FUTURE DEVELOPMENTS**

Long term goals in the management of obesity are very difficult to achieve with the present treatment options despite the transcendence of the problem, there are not many pharmacological options available for this issue, many of which have several side effects and cannot be used on a long term basis. Several previously approved drugs have been withdrawn from the market because of potential side effects like Sibutramine. Only one anti-obesity medications orlistat is currently approved by the FDA for long term use. Other medications like Exenatide and metformin which are approved for diabetes type 2 has shown substantial weight loss in some patients.

The current global epidemic of obesity is one of the most important challenges to our times requiring new treatment developments. Other drugs which decrease appetite and nutrient absorption are also effective with mild to moderate adverse effects. Recently, the U.S. Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee recommended the combination of “phentermine and topiramate” be granted marketing approval by the FDA for the treatment of obesity in adults. The Committee has recommended for an approval based on a favorable benefit-risk profile. In view of recent studies, it is important to investigate the combination therapies and long-term management for obesity in order to achieve sustained success.

**ACKNOWLEDGEMENTS**

We acknowledge Dr. Barbara J. Berger for her valuable suggestions in preparing the manuscript.

**CONFLICT OF INTEREST**

We have no conflict of interest

**REFERENCES**


