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REVIEWS

Targeting Obesity in PCOS: A Review of Current Pharmacological Interventions and Future Directions

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Abstract

Obesity is a common and significant comorbidity of Polycystic Ovary Syndrome (PCOS), contributing to a range of metabolic and reproductive complications. The rising prevalence of obesity, particularly among women of reproductive age, exacerbates the symptoms of PCOS, such as Insulin Resistance (IR), hyperandrogenism, and menstrual irregularities, while increasing the risk of long-term conditions like Type 2 Diabetes Mellitus (T2DM), cardiovascular disease, and infertility. Despite the importance of addressing obesity in PCOS, current pharmacological treatments remain limited and often ineffective in providing sustained weight loss and metabolic improvements. This review aims to evaluate the available pharmacological options for managing obesity in women with PCOS, including well-established treatments such as *Metformin*, *Orlistat*, *Liraglutide* and *Tirzepatide*, as well as emerging therapies like *Semaglutide*, *Cagrilintide*, *Bimagrumab* and Leptin Sensitizers. These therapies target key mechanisms of obesity, including IR, appetite regulation and fat metabolism. While promising, these emerging therapies require further clinical investigation to confirm their long-term safety and efficacy. Additionally, the role of lifestyle interventions, such as dietary changes and physical activity, in combination with pharmacological treatments, is discussed to optimize outcomes for patients. The review also highlights the need for personalized treatment approaches that consider the complex metabolic and hormonal dysfunctions associated with PCOS. Finally, the article calls for future research to explore combination therapies and novel pharmacological agents, as well as the potential for multidisciplinary approaches in clinical trials. Addressing obesity in PCOS remains a critical public health challenge and ongoing advancements in treatment options are essential to improving the health and quality of life for affected women.

Keywords: Obesity, PCOS, Pharmacotherapy, Polycystic Ovary Syndrome, Weight Management

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INTRODUCTION

Since the late 20th century, obesity and its related health issues have been increasing worldwide, with 650 million people were affected by obesity in 2016, a figure projected to quadruple by 2030. The WHO characterizes obesity as people with Body Mass Index (BMI) above 30 kg/m^2, indicating an excessive buildup of body fat that could pose health risks[1]. Obesity refers to the excessive accumulation of body fat, which significantly increases the risk of various complications. It is a leading cause of numerous metabolic and endocrine disorders[2].

The obesity prevalence among females has risen to 26%, with estimated prevalence among adolescent girls was 18%. Obesity was labelled as a prevailing global pandemic since 21st century, as it increasingly affects both adolescents and adults largely due to the consumption of junk food. Junk food is characterized by its high calorie content, rich in fats, salt, cholesterol and sugar, while offering little nutritional value. These foods also tend to contain large amounts of refined carbohydrates, sodium and preservatives, including items such as candy, refined grains, potato chips, chocolate, high fructose corn syrup and trans-fat. Higher BMI is strongly linked to various gynaecological and metabolic problems in women including infertility, Abnormal Uterine Bleeding (AUB), miscarriage and Polycystic Ovary Syndrome (PCOS). PCOS is a significant and common comorbidity linked to obesity, affecting girls and women with a genetic susceptibility to the condition[3-6]. PCOS impacts approximately 6%-10% of women of reproductive age12-15 years and frequently emerges during adolescence[7-9].

The development of obesity in PCOS begins during late prenatal and early postnatal life. Initially, there is a mismatch between reduced weight gain during pregnancy and increased weight gain after birth. This mismatch involves early subcutaneous fat development followed by later lipogenesis as the body shifts towards storing excess fat. The greater the genetic predisposition to obesity, more the fat mass is gained during infancy increasing the risk of this upward mismatch. A way to assess this mismatch is by comparing the changes in weight percentiles from birth to childhood BMI. Girls who experience this mismatch often accumulate fat in abnormal areas of viscera like liver leading to Insulin Resistance (IR), central obesity and elevated Blood Pressure (BP) by early childhood (ages 3–6 years)[10-16].

PCOS is diagnosed by evaluating clinical signs, such as irregular periods and symptoms of excess androgens, alongside measuring hormonal levels and identifying ovarian cysts through ultrasound imaging. The Rotterdam criteria state the need for at least any two of the key factors for probable diagnosis of PCOS: 1) evidence of hyperandrogenism (either clinical or biochemical); 2) anovulation or presence of oligo-ovulation; and 3) ultrasound findings of multiple cysts in ovaries, defined by approximately ≥10 mL of volume in ovaries and/or follicles of 2 to 9 mm in diameter which are ≥12 in number[17]. Further, polycystic ovaries, biochemical markers highlighting hyperandrogenism and menstrual irregularities are crucial diagnostic factors for PCOS[18]. Furthermore, evidence-based guidelines on PCOS have mentioned Anti-Mullerian Hormone (AMH) might contribute as alternative testing to ultrasound, offering a more affordable and convenient diagnostic approach for PCOS patients[19].

The increasing prevalence of obesity among individuals with PCOS has made addressing this condition a critical public health concern[20]. Often, obesity worsens symptoms pertaining to PCOS such as menstrual irregularities, hyperandrogenism and IR that heightens the future risk of developing long-term complications such as Type 2 Diabetes Mellitus (T2DM), cardiovascular diseases and infertility. Despite the recognition of this interconnectedness, current treatment options for managing obesity in PCOS are limited and often ineffective in achieving sustained weight loss and metabolic improvements.

As such, there is a growing need for a comprehensive review of existing pharmacological treatments and emerging therapies to provide healthcare providers with up-to-date evidence on effective strategies for managing obesity in this patient population. This review would serve as an essential resource for clinicians, guiding them in selecting the most appropriate therapies while highlighting new promising treatment options that could offer better outcomes for women struggling with both obesity and PCOS.

The primary objective of the current review article is to offer a thorough evaluation of the present pharmacological treatments for managing obesity in women with diagnosed of PCOS, focusing on their efficacy, safety and limitations. Given the increasing cases of obesity in women with PCOS and its impact on the severity of the condition, effective management strategies are crucial for improving both metabolic and reproductive outcomes. This review will also explore emerging therapies and novel treatment options under investigation for obesity management in PCOS, discussing their potential benefits and challenges. The article will evaluate the impact of these treatments on other PCOS-related symptoms, including insulin resistance, menstrual irregularities, and fertility, emphasizing the importance of an integrated treatment approach. Furthermore, it will highlight the challenges clinicians face in managing obesity in PCOS and the need for personalized, individualized treatment plans that address both metabolic and hormonal imbalances. Finally, the review will identify promising areas of future research and potential advancements in the development of new pharmacological solutions or combination therapies for addressing obesity in women with PCOS, underscoring the urgent need for effective treatments to reduce the long-term health risks associated with this condition.

PATHOPHYSIOLOGY OF OBESITY IN PCOS:

Genetic & Environmental Factors:
Genetic predisposition and environmental factors contribute to PCOS onset, leading to issues in steroidogenesis, insulin signaling and Oxidative Stress (OS)[21-25].

Ovarian Dysfunction:
Intrinsic defect in theca cells leads to excessive androgen production despite the absence of trophic factors, causing hyperandrogenism. Granulosa cells produce up to 4x higher AMH levels in women with PCOS. Presence of multiple pre-antral and small antral follicles observed[26-30].

Insulin Resistance (IR):
IR is a core component of PCOS, regardless of obesity status[31,32]. Pathogenesis of IR involves decreased insulin sensitivity due to defects in insulin receptor signalling[33,34], increased circulating insulin levels (hyperinsulinemia), insulin exacerbates hyperandrogenism by stimulating theca cells and amplifying LH-mediated androgen secretion, increased peripheral conversion of androgens to estrogen in adipose tissue, causing elevated estrone (E1) levels and estrogen dominance[35].

Hyperandrogenism:
Ovarian origin involves defective steroidogenesis in theca cells that increases androgen production due to the increased activity of enzymes like cholesterol-desmolase and 17α-hydroxylase[36]. Insulin synergy indicated by high levels of insulin, enhance the ovarian production of androgen[37,38]. Adrenal contribution in which minor contribution to hyperandrogenism, related to CYP17α1 overactivation[39].

Hormonal Imbalance:
LH/FSH imbalance involves high LH and low FSH levels that disrupt follicular maturation, leading to anovulation[40,41]. Elevated E1 levels promote chronic hyperestrogenism, increasing the risk of endometrial proliferation and cancer. Chronic anovulation results in decreased progesterone secretion, contributing to endometrial hyperplasia[42].

Obesity and IR Amplification:
Increased BMI and abdominal fat leads to excessive fat accumulation that worsens IR, particularly abdominal obesity leading to further metabolic dysfunction[43]. Dysfunctional adipocytes produce inflammatory cytokines like TNF-α, exacerbating IR[44,45]. Obesity in PCOS can worsen metabolic abnormalities such as T2DM, IR and cardiovascular risk factors[46,47]. Association between seborrhoea, hirsutism, androgenic alopecia (SAHA) syndrome and acne with individuals with high IR, suggest an increased threat of metabolic abnormalities[48].

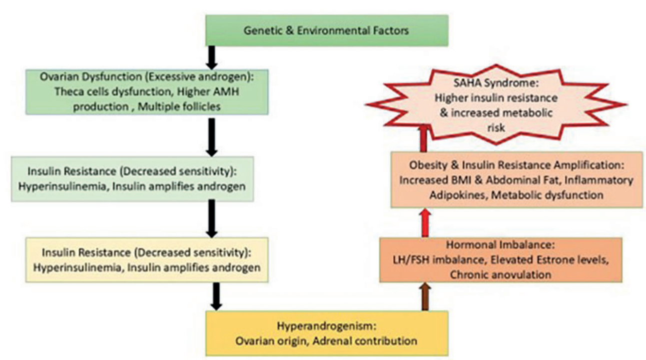

Fig. 1 Pathophysiology of Obesity in PCOS

CURRENT PHARMACOLOGICAL TREATMENTS FOR OBESITY IN PCOS:

***Metformin*:**
The medication which is commonly used for treatment T2DM is Metformin and has also been investigated for its potential to manage obesity in women with PCOS. It is a biguanide class of drug and primarily acts by improving insulin sensitivity and reducing IR, which are key factors in PCOS-related obesity. The typical starting dose of *Metformin* is 500 mg once per day or twice per day with a steady increase to an utmost dose

of 2,000-2,500 mg per day. It typically acts by reducing hepatic production of glucose, enhancing peripheral glucose uptake and reducing food intake. Additionally, it has been shown to affect gastrointestinal physiology and circadian rhythms, potentially influencing oxidation of fat and storage in the organs like skeletal muscle, liver and adipose tissue.

It can lead to side effects, especially at higher doses. The reported side effects include nausea, abdominal discomfort and diarrhea. In rare instances, *Metformin* can cause lactic acidosis, a serious condition though this is uncommon in patients with normal renal function. Despite its benefits in improving IR and contributing to modest weight loss, the effects of *Metformin* on BMI in PCOS patients typically plateau after six months and the decrease in weight gets limited beyond this period. However, when combined with lifestyle interventions such as diet and exercise, *Metformin* has been shown to help sustain weight loss over longer periods, making it a valuable treatment option for managing obesity in women with PCOS[49-60].

***Orlistat*:**

Orlistat, a lipase inhibitor is used to treat obesity by preventing the absorption of dietary fats in the gastrointestinal tract. By blocking about 30% of fat digestion, *Orlistat* helps reduce overall caloric intake, contributing to weight loss. It is administered at a dose of 120 mg, taken thrice daily with fat containing meals. This mechanism is particularly beneficial for managing obesity in women with PCOS, where obesity is a common concern.

Several studies have evaluated *Orlistat*'s effectiveness in women with PCOS. A trial comparing lifestyle changes along with administration of 120mg of *Orlistat* to a placebo plus lifestyle intervention over three months showed that *Orlistat* significantly improved anthropometric outcomes. The *Orlistat* group experienced greater reductions in weight and Waist-Hip Ratio (WHR). Additionally, *Orlistat* treatment led to improved lipid profiles. Nevertheless, no notable differences were seen between the groups for metabolic outcomes such as fasting blood glucose or insulin levels[61].

Another study involving *Orlistat* (120 mg three times daily) combined with lifestyle changes and Combined Oral Contraceptive Pill (COCP) compared to COCP alone showed that *Orlistat* plus lifestyle was superior in improving levels of Sex Hormone Binding Globulin (SHBG) and reducing body fat percentage. In a comparison between *Orlistat* and *Metformin* (1.5 g/day), no significant differences were observed for anthropometric or biochemical outcomes, including body weight, BMI and lipid profiles. Furthermore, when *Orlistat* was combined with *Metformin* and COCP, it was found to be superior to *Metformin* alone in reducing body fat percentage[62].

The commonly reported side effects were flatulence, oily stools, abdominal discomfort and diarrhea, particularly when high-fat meals are consumed. These side effects are a result of the unabsorbed fats being excreted. Some patients also report oily spotting or urgency to use the bathroom. Despite these issues, *Orlistat* remains an effective treatment for obesity in PCOS when combined with lifestyle modifications.

***Liraglutide*:**

It is a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA), was originally developed for the treatment of DM. Its efficacy in promoting weight loss led to the development of a higher-dose formulation specifically for weight management[63]. *Liraglutide* acts by mimicking the hormone Glucagon-Like Peptide-1 (GLP-1), which has a key role in controlling blood sugar, insulin secretion and appetite. By activating GLP-1 receptors, *Liraglutide* promotes satiety, reduces hunger, slows gastric emptying and enhances insulin secretion in response to meals. This mechanism is especially helpful for women having obesity and PCOS, as it helps decrease body weight and improve metabolic health. Studies show that *Liraglutide* at dose of 1.2–1.8 mg, result in significant weight loss and improvements in metabolic markers when used alone or with *Metformin*. For instance, a 6-month controlled trial of *Liraglutide* (1.8 mg) in women with obesity and PCOS showed a 3% to 4% weight loss alongside reductions in inflammation and improved endothelial function[64]. Another study compared *Liraglutide* (1.2 mg) with *Metformin* in 45 women with PCOS, finding greater reductions in BMI, improved body composition, particularly in visceral fat and positive changes in metabolic health[65]. Additionally, a double-blind trial with 72 women demonstrated that *Liraglutide* not only reduced weight but also improved reproductive parameters, including regularized menstrual cycles and normalized hormone levels[66].

Gastrointestinal side effects such as diarrhea, nausea, constipation and vomiting particularly during the initial stages of treatment. More serious but rare adverse effects may include pancreatitis, thyroid C-cell tumors and renal impairment. Despite these risks, *Liraglutide* remains a potential therapeutic avenue for managing metabolic disturbances like obesity in women with

PCOS.

***Tirzepatide*:**

It is a dual agonist of Gastric Inhibitory Peptide (GIP) and GLP-1 RA. These combined actions enable *Tirzepatide* to mimic the effects of key gastrointestinal hormones that regulate insulin secretion and glucose metabolism[67,68].

Tirzepatide is used to manage obesity and improve IR in patients with PCOS[69]. Its potential also extends to improving insulin sensitivity and addressing gut dysbiosis, a factor linked to PCOS.

The usual recommended dose to start with *Tirzepatide* is 2.5 mg once weekly, with the possibility of gradual dose escalation up to a maximum of 15 mg once weekly. This flexible dosing regimen helps tailor treatment to individual needs, particularly in patients with obesity associated with PCOS.

Tirzepatide mimics the actions of both GIP and GLP-1, two important gastrointestinal hormones that regulate insulin secretion and glucose metabolism. Its unique structure enhances albumin binding, prolonging its half-life and supporting weekly dosing. This dual mechanism allows *Tirzepatide* to exert a synergistic effect on weight reduction and glucose control while minimizing gastrointestinal side effects typically seen with GLP-1 RA.

The commonly reported side effects are gastrointestinal upset. However, due to its dual action, *Tirzepatide* may have a lower incidence of these side effects compared to other GLP-1-based therapies. Caution is also advised regarding potential interactions with COCP and concerns over teratogenic effects in women of childbearing age, necessitating further research on the drug's safety in this demographic[70-72].

In clinical trials, *Tirzepatide* has demonstrated significant weight loss, with approximately 95% of obese patients achieving weight reduction after 72 weeks of treatment[73]. Nevertheless, further research is required to completely explore its potential benefits and long-term safety in women of reproductive age, especially with respect to its impact on oral contraceptive efficacy.

Table 1 Current pharmacological treatment options to treat obesity in PCOS

Drug Category	Drug	Mechanism of action	Dose	Cost	Side effects	Selection of patient	Reference number
Biguanides	*Metformin*	Improves insulin sensitivity, reduces insulin resistance, lowers production of hepatic glucose, improves peripheral uptake of glucose, reduces food intake.	500 mg once or twice daily, increase to 2,000-2,500 mg/day based on tolerance.	Moderate	Gastrointestinal issues (nausea, diarrhea, abdominal discomfort), lactic acidosis (rare).	Ideal for patients with insulin resistance or pre-diabetes, especially those with elevated BMI and PCOS-related metabolic disturbances.	[49-60]
Lipase Inhibitors	*Orlistat*	Inhibits lipase, reducing fat absorption by ~30%, reducing caloric intake.	120 mg given with fat containing meals for three times per day.	Moderate	Gastrointestinal issues (oily stools, flatulence, diarrhea, abdominal discomfort).	Best suited for obese patients with PCOS, particularly those with high fat intake and less metabolic involvement.	[61,62]
GLP-1 Receptor Agonists	*Liraglutide*	Mimics GLP-1 hormone, promotes satiety, reduces hunger, slows gastric emptying, enhances insulin secretion.	1.2 – 1.8 mg, subcutaneously once daily.	High	Gastrointestinal issues (nausea, vomiting, diarrhea, constipation), headache, dizziness, rare pancreatitis, thyroid tumors, renal impairment.	Ideal for overweight/obese patients with PCOS and insulin resistance or metabolic syndrome, especially those seeking weight loss and metabolic improvement.	[63-66]
GLP-1 & GIP Receptor Agonists	*Tirzepatide*	Dual action on GIP and GLP-1 receptors, improves insulin secretion, enhances glucose metabolism, reduces appetite.	Started as 2.5 mg per week and increased up to 15 mg per week based on tolerance.	High	Gastrointestinal issues (nausea, vomiting, diarrhea, decreased appetite), potential interactions with oral contraceptives, teratogenic concerns in women of childbearing age.	Suitable for obese patients with PCOS, especially those with severe insulin resistance and difficulty achieving weight loss with other therapies.	[67-73]

Critical analysis:
The current pharmacological treatments for obesity in PCOS, including *Metformin*, *Orlistat*, *Liraglutide* and *Tirzepatide*, each offer varying degrees of efficacy and tolerability. *Metformin*, commonly used for its insulin-sensitizing effects, helps reduce obesity by improving IR but offers only modest and short-term weight loss, with gastrointestinal side effects like diarrhea that limits long-term patient compliance. *Orlistat* is a lipase inhibitor, effectively decreases absorption of fat and aids in weight loss but is linked to gastrointestinal adverse effects such as oily stools and diarrhea, and it has limited impact on metabolic outcomes like glucose control or insulin sensitivity.

Liraglutide, a GLP-1 RA provides more significant weight loss and metabolic improvements, including reductions in visceral fat and enhanced insulin sensitivity but is also prone to gastrointestinal side effects and has rare but serious risks, such as pancreatitis and thyroid tumors. *Tirzepatide*, a newer dual agonist of GLP-1 and GIP receptors, shows the most promising results, with significant weight loss and improved insulin sensitivity. However, *Tirzepatide*'s long-term safety, particularly concerning its impact on COCP and teratogenic risks in women of childbearing age, remains uncertain.

Despite their benefits, all these treatments are most effective when combined with lifestyle changes and the choice of therapy should be tailored to individual patient needs, balancing efficacy with tolerability.

EMERGING PHARMACOLOGICAL THERAPIES:

***Semaglutide*:**
Semaglutide, a GLP-1 RA, is used primarily to manage obesity and T2DM. It is a agonist of GLP-1, which is a hormone that controls insulin secretion, appetite and glucose metabolism. In treating obesity in PCOS, *Semaglutide* is typically administered at a dose of 1 mg once weekly. This medication helps in decreasing weight by enhancing satiety, delaying gastric emptying and decreasing intake of food. It has been shown to be especially effective in patients who have not responded to other lifestyle interventions, with many experiencing significant weight loss and normalization of menstrual cycles. *Semaglutide* has also demonstrated beneficial effects on IR and fasting glucose levels in patients with Impaired Fasting Glucose (IFG) and PCOS[74].

A study comparing *Semaglutide* (1 mg weekly) to a placebo over 16 weeks in 25 participants found that *Semaglutide* was superior for all anthropometric outcomes. The group treated with *Semaglutide* was found to have significant decrease in BMI, body weight, waist circumference and visceral body fat. Additionally, *Semaglutide* was superior for metabolic outcomes, including fasting insulin levels, 2-hour glucose levels and HDL cholesterol. However, there were no notable differences between the two study groups for fasting blood glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), 2-hour insulin levels or other lipid parameters[75].

Although *Semaglutide* can cause minor side effects, with nausea being the commonly reported particularly in the early stages of treatment. Other potential side effects include constipation, vomiting, diarrhea and abdominal pain. These side effects are usually temporary and might improve as the body gets adjusted to the medication. Despite these adverse effects, *Semaglutide* remains an effective and well-tolerated option for decreasing weight and metabolic improvements in women with obesity and PCOS.

Exenatide:
Exenatide is a known GLP-1 RA that mimics the naturally occurring hormone GLP-1, that has a crucial role in the glucose metabolism regulation and insulin secretion. Originally developed for the management of T2DM, it has also shown significant benefits in treating obesity and metabolic issues associated with PCOS. *Exenatide* is administered as an injectable medication, typically in doses of 10–20 μg daily for short-term use (12 weeks) or 2 mg weekly for longer-term management. When used in combination with other treatments, like *Metformin*, the daily dose of *Exenatide* remains in the 10–20 μg range. *Exenatide* acts as a GLP-1 RA and helps to improve the insulin secretion in a glucose-dependent way, preventing glucagon release and delaying gastric emptying. These actions collectively help lower blood glucose levels, particularly postprandial glucose spikes. Additionally, GLP-1 RA such as *Exenatide* have been shown to reduce appetite, which aids in weight loss. This makes it particularly useful in managing obesity and metabolic disorders in patients with PCOS, including improvements in HOMA-IR and fasting insulin levels. Nausea, diarrhea and vomiting are the commonly reported adverse effects related to *Exenatide*. These effects are more pronounced at higher doses and during the initial stages of treatment. While *Exenatide* helps with weight loss, the nausea and gastrointestinal issues

are frequent reasons for treatment discontinuation. In terms of safety, there is a risk of hypoglycemia, particularly when used with other insulin-sensitizing drugs like *Metformin*[76-78].

***Dulaglutide*:**

Dulaglutide is a once-weekly GLP-1 RA used to manage obesity and improve insulin sensitivity in conditions like PCOS and T2DM. This medication offers a significant advantage in patient adherence compared to other GLP-1 RA, which require daily injections as its weekly dosing schedule enhances compliance and potentially improves long-term treatment outcomes. The initiating dose of *Dulaglutide* is 0.75 mg administered once a week, which may be titrated to 1.5 mg once weekly based on patient response and tolerance. *Dulaglutide* also acts by mimicking GLP-1 hormone. This mechanism leads to enhanced satiety, slowed gastric emptying and improved insulin sensitivity, making it particularly beneficial for women with PCOS who often have IR and obesity.

Clinical studies have demonstrated *Dulaglutide*'s effectiveness in reducing weight and improving metabolic parameters in women with PCOS. A study comparing *Dulaglutide* with a Calorie-Restricted Diet (CRD) showed that, while both interventions resulted in similar weight loss, *Dulaglutide* led to more pronounced reductions in visceral fat thereby helpful in reaching target weight loss. Additionally, *Dulaglutide* significantly improved HbA1c and Post-Prandial Glucose (PPG) levels, indicating better glucose control. Both interventions also led to improvements in menstrual frequency, reductions abdominal Subcutaneous Adipose Tissue (SAT) mass and total fat mass. These findings suggest that while dietary interventions are crucial as first-line treatment for obesity in PCOS, GLP-1 RA therapy like *Dulaglutide* can serve as an effective adjunct to further support weight management and metabolic improvements in obese PCOS patients[79].

During the initiation of treatment, *Dulaglutide* might lead to side effects like abdominal discomfort, diarrhea and nausea. These side effects are usually transient but can limit its use in some patients. Rare but serious adverse effects include pancreatitis, thyroid C-cell tumors and renal impairment. Despite these risks, *Dulaglutide* remains a promising option for managing obesity and associated metabolic dysfunction in women with PCOS.

***Bupropion/Naltrexone*:**

Bupropion/Naltrexone is a combination medication consisting of *bupropion*, a Norepinephrine-Dopamine Reuptake Inhibitor (NDRI) and *Naltrexone* is an opioid antagonist. This combination is primarily used for weight loss and managing overeating behaviors such as binge eating and emotional eating which are common in individuals with PCOS. The typical starting dose for *Bupropion/Naltrexone* is 8 mg of *Naltrexone* and 90 mg of *Bupropion*, taken once daily. The dose is eventually titrated to a maximum dose of 32 mg of *Naltrexone* and 360 mg of *Bupropion* per day, depending on patient tolerance and response. *Bupropion/Naltrexone* works by targeting the hypothalamus-regulated reward circuits involved in appetite regulation. *Bupropion* increases the levels of dopamine and norepinephrine, which helps reduce cravings and emotional eating, while *Naltrexone* modulates the reward system to decrease the urge to overeat, particularly following meals. This dual action is beneficial in addressing overeating and binge eating behaviors, common in women with PCOS. The combination of these mechanisms helps control appetite and eating patterns by acting on the brain's reward and hunger pathways[80,81].

Commonly reported adverse effects are headache, constipation, nausea, insomnia and dizziness. As *Bupropion* increases the risk of seizures, it should be avoided in patients who are a known case eating disorders, seizures or alcohol/substance abuse. *Naltrexone* may cause liver toxicity at higher doses, necessitating monitoring of liver function during treatment. Despite these risks, *Bupropion/Naltrexone* remains a potentially useful option for managing overeating behaviors and supporting weight loss in women with PCOS[82].

***Phentermine/ Topiramate*:**

Phentermine is a sympathomimetic agent, while *Topiramate* is an antiepileptic drug. The combination of these two drugs, *Phentermine/Topiramate*, is used for obesity management, specifically for individuals who struggle with weight management, including women with PCOS.

Phentermine/Topiramate is primarily used for weight loss in obese patients and it has proven to be a useful drug for managing obesity in women with PCOS. It helps reduce appetite through *Phentermine*, while *Topiramate* contributes to appetite control and improved metabolic functions. The combination is beneficial when paired with a low-calorie diet and, in some cases, *Metformin* for better weight management outcomes in PCOS patients.

Phentermine/Topiramate is taken once daily, with doses of *Phentermine* typically up to 37.5 mg and *Topiramate* up to 400 mg per day. However, the

Extended-Release (ER) formulation used for obesity management utilizes lower doses to maximize weight loss while minimizing side effects. *Phentermine* works as an appetite suppressant by stimulating the release of norepinephrine, which helps reduce hunger. *Topiramate*, while originally used for epilepsy, helps with weight loss by affecting neurotransmitters that regulate hunger and it also improves insulin sensitivity, making it beneficial in metabolic conditions like PCOS. Common side effects of *Phentermine/Topiramate* may include dry mouth, constipation, insomnia and dizziness. These reported side effects are usually mild and controllable, especially with the ER formulation, which aims to minimize adverse effects while maintaining efficacy for weight loss[83,84].

SGLT-2 Inhibitors:

SGLT-2 inhibitors are a group of medications used primarily to treat T2DM, but they may also be beneficial for women with PCOS because of its significant effect on cardiovascular and metabolic profile. These drugs target SGLT-2 receptors in the kidneys and may offer therapeutic advantages for managing obesity and other metabolic disturbances common in PCOS.

SGLT-2 inhibitors like *Empagliflozin*, *Dapagliflozin* and *Canagliflozin* is being studied largely. While these medications are primarily used to control blood sugar in diabetic patients, emerging evidence suggests they may also help with weight loss and improve metabolic function in PCOS patients.

Empagliflozin is commonly prescribed at a dosage of 25 mg once a day, while other SGLT-2 inhibitors, such as *Canagliflozin*, typically begin at 100 mg per day and can be adjusted based on patient response and tolerability[85].

SGLT-2 inhibitors decrease blood glucose by blocking reabsorption of glucose and sodium in the kidneys, leading to glucose being excreted in the urine. The action of these drugs is independent of insulin secretion, which makes them useful in addressing IR and promoting weight loss. Furthermore, they improve insulin sensitivity and help with glucose uptake in muscles, decrease liver glucose production and improve lipid profiles[86,87].

A RCT comparing *Empagliflozin* (25 mg) and *Metformin* (1500 mg) in 39 women with PCOS revealed that *Empagliflozin* led to greater decrease in BMI, weight, hip circumference, waist circumference and shows decrease in body fat compared to *Metformin*. However, no significant differences were observed in metabolic markers such as IR or androgen levels[88].

It was found that combining *Metformin* with *Empagliflozin* has resulted in decrease in of body mass, fat levels and BMI in patients with PCOS[89,90,91]. Also, SGLT-2i was found to reduce BP and the level of HbA1C[92].

Studies have shown that *Empagliflozin* reduces the quantity of fat, leptin level and BP in PCOS animal model, but was not found to improve albuminuria and IR. *Licogliflozin* was found to lower hyperandrogenism and hyperinsulinism[93].

A study using *Canagliflozin* on 53 PCOS patients has found that it is effective like *Metformin* in reducing hormonal, metabolic and anthropometric profile[94]. *Canagliflozin* was not found to be inferior to treatment with *Metformin*[95]. *Metformin* when given along with *Canagliflozin* in PCOS can cause greater decrease in free testosterone, better control of glucose metabolism and greater reduction in body weight.

Dapagliflozin when given for 2 weeks, was found to enhance metabolic parameters like control of blood glucose levels, improve HOMA-IR and reduction in body weight. Additionally, it has resulted in better DHEAS values, while no significant reduction in SHBG or testosterone level was found[96]. DHEAS was known to be high in PCOS, which when regulated by SGLT-2i could potentially reduce hyperinsulinism caused by high DHEAS. Hence, this could break the chain in the cycle of hyperandrogenism and hyperinsulinism in PCOS which left untreated can result in T2DM[97].

Studies have found that SGLT2i can improve the metabolism of androgen and decrease lipotoxicity[98]. Further, it can cause reduction of 1.6 to 2.5 kg in lean mass by affecting the adipocytes particularly and could potentially increase the levels of High-Density Lipoprotein (HDL)[99], while simultaneously decreasing Low-Density Lipoprotein (LDL) and total cholesterol levels[99]. *Empagliflozin* act on the small adipocytes and decreases the quantity of adipose tissue which results in reduction of leptin levels[100,101].

Pruett and coworkers in their study in context of adipocyte mitochondrial function in a PCOS animal model, have found that *Empagliflozin* could increase the mitochondrial and cytosolic SOD expression[102-106]. *Empagliflozin* was found to decrease inflammation due to oxygen radicals and also involved in reducing Sodium Hydrogen Exchange (NHE). They stated that SGLT-2i can be given with insulin sensitizers, as it can reduce the body weight by fixing the small adipocytes frequency in visceral adipose tissue. Additionally, studies have concluded that treatment with *Empagliflozin* can reduce the renal resistivity index and proteinuria, thereby decreasing the harmful hemodynamic stress[107-109].

Commonly reported adverse effects are urinary tract infections, genital infections, dehydration and possible electrolyte imbalances due to the increased excretion of glucose. Despite these risks, these drugs' benefits especially their ability to assist with weight loss and improve metabolic health can make them an appealing option for managing PCOS[110].

TABLE 2 Emerging pharmacological therapies to treat obesity in PCOS

Drug category	Drug	Mechanism of action	Dose	Side effects	Study outcome	Reference number
GLP-1 Receptor Agonist	*Semaglutide*	Mimics the role of GLP-, controlling insulin secretion, glucose metabolism and appetite. Enhances satiety, decreases food intake.	1 mg weekly	Nausea, vomiting, diarrhea, constipation, abdominal pain	Significant weight loss, improved insulin resistance, and menstrual cycle normalization. Reduced BMI, waist circumference, and visceral fat.	[74,75]
GLP-1 Receptor Agonist	*Exenatide*	GLP-1 receptor agonist, delays gastric emptying, improves insulin secretion and prevent glucagon.	10-20 µg daily, or 2 mg weekly	Nausea, vomiting, diarrhea, hypoglycemia (especially with metformin), injection site reactions	Improved insulin resistance, weight loss, and reduced appetite. Significant reductions in fasting insulin, glucose, and postprandial glucose levels.	[76-78]
GLP-1 Receptor Agonist	*Dulaglutide*	GLP-1 receptor agonist, enhances insulin sensitivity, improves satiety and slows gastric emptying.	0.75 mg weekly (may increase to 1.5 mg)	Nausea, diarrhea, abdominal discomfort, rare pancreatitis, thyroid C-cell tumors, renal impairment	Reduced body weight, improved glucose control (HbA1c, post-prandial glucose), and improved metabolic parameters. Significant reduction in visceral fat.	[79]
Combination Therapy	*Bupropion/ Naltrexone*	Increases dopamine and norepinephrine, reduces appetite, controls overeating. Naltrexone modulates reward system.	8 mg naltrexone and 90 mg bupropion daily as initial dose and titrated to 32 mg naltrexone, 360 mg bupropion	Nausea, constipation, headache, insomnia, dizziness, increased risk of seizures, liver toxicity in high doses.	Helps manage overeating and emotional eating in PCOS. Supports weight loss.	[80-82]
Appetite Suppressant	*Phentermine/ Topiramate*	Phentermine suppresses appetite through norepinephrine release, Topiramate affects neurotransmitters to control hunger.	Phentermine: 37.5 mg daily, Topiramate: up to 400 mg daily	Dry mouth, constipation, insomnia, dizziness	Supports weight reduction. Reduces appetite and improves metabolic functions. Enhances insulin sensitivity.	[83,84]
SGLT-2 Inhibitors	*Empagliflozin*	Blocks glucose and sodium reabsorption in kidneys, promotes glucose excretion, improves insulin sensitivity.	25 mg daily	Urinary tract infections, genital infections, dehydration, electrolyte imbalances, kidney impairment, increased risk of ketoacidosis	Significant reduction in weight, waist circumference, BMI and body fat. Enhanced metabolic parameters, though no significant changes in insulin resistance or androgens.	
SGLT-2 Inhibitors	*Canagliflozin*	Blocks glucose reabsorption in kidneys, enhances glucose excretion, reduces body fat, improves insulin sensitivity.	100 mg daily (adjustable)	Genital infections, urinary tract infections, dehydration, risk of bone fractures, ketoacidosis	Similar efficacy to metformin in reducing weight, BMI, and improving metabolic parameters. Some reduction in free testosterone.	[85-110]

SGLT-2 Inhibitors	*Dapagliflozin*	Similar to other SGLT-2 inhibitors, promotes glucose excretion and improves insulin sensitivity.	5-10 mg daily	Genital infections, urinary tract infections, dehydration, electrolyte imbalances, risk of ketoacidosis	Significant improvements in weight, glucose regulation, and insulin resistance. Minor effect on DHEAS and testosterone levels.	[85-110]

Critical analysis of emerging therapies:

Emerging therapies for managing obesity in women with PCOS show significant promise, particularly in addressing the metabolic disturbances often associated with the condition, such as IR and dysregulated appetite. *Semaglutide*, a GLP-1 RA, is particularly efficient in enhancing insulin sensitivity and providing significant weight loss. This property positions it as a strong contender in managing obesity in PCOS. Clinical studies further support its benefits in improving metabolic outcomes like fasting glucose and insulin levels, although gastrointestinal side effects, notably nausea, remain a concern for some patients. Similarly, other GLP-1 RA drugs like *Exenatide* and *Dulaglutide*, offer distinct advantages in terms of patient adherence, especially *Dulaglutide*'s once-weekly dosing. These therapies help reduce body weight and improve insulin sensitivity, with *Dulaglutide* showing notable reductions in visceral fat compared to diet alone. However, the gastrointestinal side effects across these agents can be a significant limiting factor in long-term use.

The combination of *Bupropion* and *Naltrexone* presents another novel approach, targeting the brain's reward system to modulate appetite and eating behaviors, which is particularly beneficial in PCOS patients with binge or emotional eating patterns. Although promising, the side effects especially nausea and the potential for liver toxicity with *Naltrexone* require careful patient monitoring. *Phentermine/Topiramate*, another combination treatment, can also help with appetite control and metabolic regulation, but side effects like insomnia and dry mouth may affect patient adherence.

SGLT-2 inhibitors, including *Empagliflozin* and *Canagliflozin*, offer a different mechanism by improving insulin sensitivity and promoting weight loss through glucose excretion. While these drugs demonstrate potential in managing obesity in PCOS by reducing body weight and improving metabolic parameters, they are not yet officially approved for this indication. Furthermore, their side effects such as an increased risk of urinary tract infections, dehydration and potential renal concerns warrant careful consideration. However, studies suggest that SGLT-2 inhibitors could be an effective adjunct to other therapies, particularly in addressing metabolic and cardiovascular risks associated with PCOS.

In conclusion, while emerging therapies for managing obesity in PCOS such as GLP-1 RA, combination medications and SGLT-2i show significant efficacy, challenges related to side effects and long-term adherence persist. Future research into their long-term benefits and safety profiles, as well as personalized approaches based on patient characteristics will be essential for optimizing treatment outcomes in this complex metabolic disorder.

DRUGS IN CLINICAL TRIALS:

***Setmelanotide*:**

Setmelanotide is a synthetic, highly selective Melanocortin-4 Receptor (MC4R) agonist. It belongs to the class of Melanocortin Receptor Agonists, which target G protein-coupled receptors to regulate various physiological processes, including appetite control, energy metabolism and pigmentation[111-116].

The typical dosing of *Setmelanotide* varies. In the phase III trials for MC4R-related obesity, doses were titrated up to a maximum dose of 3 mg per day. For children, the initial dose is often lower (0.5 mg), with gradual adjustments based on tolerance and therapeutic response. These trials involved treatment durations ranging from 12 weeks to 1 year, depending on the study design[117].

Setmelanotide works by activating the MC4R, which is crucial for regulating appetite and energy balance in the hypothalamus. By binding to MC4R, it compensates for defects in the melanocortin signaling pathway, often seen in genetic forms of obesity (such as those involving POMC, LEPR, and other MC4R pathway-related mutations). This activation results in appetite suppression, improved insulin sensitivity and an increase in resting energy expenditure making it an effective therapeutic for severe obesity associated to these genetic defects. Importantly, *Setmelanotide* has resulted in reduced risk of adverse effects on heart rate and BP compared to first-generation MC4R agonists[118,119].

Setmelanotide has demonstrated significant efficacy in clinical trials, especially in patients with rare genetic forms of obesity. Key results from recent clinical trials show significant outcomes for *Setmelanotide* in patients with various conditions. In a small Phase II study involving patients with POMC deficiency, *Setmelanotide* led to substantial weight loss of up to 51.0 kg and a marked reduction in hunger scores[120-123]. In Phase III trials for POMC deficiency, 80% of participants achieved at least a 10% weight loss after one year of treatment, with an average body weight reduction of 25.6%. Additionally, in the LEPR deficiency cohort, 45% of participants reached the same threshold of at least 10% weight loss[124,125]. In a Phase III study of patients with Bardet-Biedl Syndrome (BBS), 32.2% of participants lost at least 10% of their body weight after one year, accompanied by a significant decrease in hunger[126-130].

These results underline *setmelanotide*'s potential in managing severe obesity in genetically predisposed individuals, although more research is needed for broader indications such as in patients with PCOS.

Setmelanotide is usually well-tolerated, but there are few side effects include mild to moderate injection site reactions, headache and nausea. Serious side effects may include changes in pigmentation, with some individuals experiencing hyperpigmentation due to the activation of the MC1R. However, cardiovascular effects such as increased heart rate and BP, which are typical of first-generation MC4R agonists, do not appear to be a concern with *Setmelanotide*. Other potential effects, similar to other melanocortin receptor agonists, may include transient changes in mood and possible impacts on the immune system and skin pigmentation[131-135].

In summary, *Setmelanotide* shows promising results for treating obesity associated with genetic defects and its ongoing evaluation may extend its use to other forms of obesity including potential applications for PCOS, where metabolic and appetite dysregulation are prominent.

***Cagrilintide*:**

Cagrilintide is a known long-acting amylin analogue, studied for weight management. It has shown efficacy in treating obesity, including in conditions like PCOS[136-138]. In a 26-week study, treatment with *Cagrilintide*, when combined with lifestyle interventions resulted in dose-dependent clinically relevant decrease in WC and body weight in participants with overweight or obesity without T2DM[139]. The study found that *Cagrilintide* 4.5 mg resulted in 7.8% of weight loss, which was higher than when compared to liraglutide 3.0 mg.

The weight loss reported from the study with *Cagrilintide* was greater than other obesity medications, including *Naltrexone-Bupropion* (4.8%), *Liraglutide* 3.0 mg (5.4%) and *Orlistat* (3.0%). But it was reported to be lower than *Phentermine/Topiramate* (9.0%)[140-144]. Also, *Cagrilintide* produces greater weight loss than *Pramlintide*, which reported to achieve 5.6-6.8% reduction in weight[145,146]. However, weight loss with *Cagrilintide* 4.5 mg was lower when compared to participants using *Semaglutide* 2.4 mg lost 10.2–12.4% of their body weight after 68 weeks. Despite this, *Cagrilintide* demonstrated continuous weight loss throughout the 26 weeks, without plateauing making it a promising option for sustained weight management in obesity-related conditions like PCOS. Longer studies are required to confirm whether these changes are sustained.

In terms of safety, *Cagrilintide* was well tolerated across all doses. The commonly observe adverse events were mild or moderate nausea and in few cases with injection site reactions. While higher doses of *Cagrilintide* led to a higher occurrence of anti-*Cagrilintide* antibodies, these antibodies were not neutralizing and did not affect the drug's efficacy or cause serious allergic reactions[147,148]. Similar to native amylin, *Cagrilintide* caused transient activation of renin and aldosterone without altering BP or electrolytes.

Given its novel mechanism of action, which targets both the homeostatic and hedonic regions of the brain to reduce food intake and regulate appetite, *Cagrilintide* presents a potential new treatment for weight management in individuals with PCOS. Further research effects of drug on food preferences, eating behaviors and long-term weight loss, especially in PCOS patients who are often resistant to other weight management therapies is needed. Additionally, combining *Cagrilintide* with other agents, such as *Semaglutide*, has shown promise in preliminary trials, suggesting a potential additive effect on weight loss. As research continues, *Cagrilintide*'s role in the treatment of obesity, particularly in PCOS could provide an important new pharmacotherapy for those struggling with weight-related complications.

***Bimagrumab*:**

Bimagrumab, a monoclonal antibody has shown potential in treating obesity and related metabolic issues in patients with PCOS. By binding to the activin type II receptor, *Bimagrumab* promotes skeletal muscle growth and has been found to reduce body fat mass and increase lean mass[149,150]. In a Phase 2 study obesity and type 2 diabetes, *Bimagrumab* administration led to decrease in total body fat mass by 20.5% and a 3.6% increase in lean mass when studied along with lifestyle intervention. This resulted in a 6.5% reduction in body weight. *Bimagrumab* also improved insulin sensitivity, as seen by a reduction in HbA1c levels. These findings suggest that *Bimagrumab* could be effective for not only weight management but also improving glycemic control in PCOS-related obesity[151]. Common side effects included diarrhea, muscle spasms and transient elevations in pancreatic and liver enzymes, with two cases of acute pancreatitis reported[152]. However, future research is required to study the benefits of *Bimagrumab* in managing PCOS-related obesity.

Leptin sensitizers:

Leptin sensitizers are a class of medications that aim to improve leptin sensitivity, which can help with weight loss and improve metabolic health. Fat cells secrete a hormone called as Leptin which controls energy metabolism and balance. In people with obesity, leptin levels are often high but the body becomes resistant to its effects. Leptin sensitizers work by increasing the body's response to leptin, allowing it to more effectively regulate energy balance and promote weight loss.

Examples of leptin sensitizers include *Metreleptin*, a recombinant human leptin analog that has been approved for the treatment of leptin deficiency. Another example is *Amlexanox*, a medication that is known to enhance leptin sensitivity and contribute to weight loss. Additionally, *Resveratrol* a natural compound found in grapes and other plants, was found to reduce weight by enhancing leptin sensitivity.

Leptin sensitizers may offer several potential benefits, including promoting weight loss by enhancing the leptin action in body, improving insulin sensitivity to reduce the risk of developing T2DM and helping to reduce inflammation which is linked to various chronic diseases. Leptin sensitizers may have potential side effects, including headaches, nausea and fatigue in some individuals.

Leptin sensitizers, such as *Metreleptin*, are a potential therapeutic option for treating obesity in PCOS patients. As a recombinant human leptin analog, *Metreleptin* works by improving leptin sensitivity, which can help regulate energy balance and metabolism. *Metreleptin* can enhance sensitivity of insulin and its secretion, reduce body weight and BMI and decrease serum triglycerides levels in patients with lipodystrophic syndromes and diabetes[153,154]. In PCOS patients, increased serum leptin levels are significantly linked with the potential of developing metabolic disorders[155]. Therefore, *Metreleptin* may be a promising treatment option for PCOS-related obesity in future.

Table 2 Drugs in clinical trials to treat obesity in PCOS

Drug Name	Mechanism of Action	Typical Dosage	Efficacy in Obesity Treatment	Potential in Treating PCOS	Common Side Effects	Reference No.	Reason for Delay in Trial
Setmelanotide	Synthetic melanocortin-4 receptor (MC4R) agonist; controls appetite, energy metabolism, and pigmentation by activating MC4R in the hypothalamus	Initial dose 0.5 mg (children), titrated up to 3 mg daily in adults. Trial durations: 12 weeks - 1 year.	Significant weight loss (up to 51 kg in some studies), with up to 80% of patients achieving ≥10% weight loss in genetic obesity (POMC, LEPR, BBS).	Shows promise for genetically predisposed obesity. Research needed for broader indications, including PCOS where metabolic dysregulation and appetite control are concerns.	Injection site reactions, headache, nausea, hyperpigmentation, mood changes.	111-138	Delays often linked to the difficulty in expanding patient populations to include non-genetic forms of obesity like PCOS, and regulatory hurdles for broader approval.
Cagrilintide	Long-acting amylin analogue; reduces food intake and regulates appetite by acting on homeostatic and hedonic brain regions.	Doses up to 4.5 mg, studied for 26 weeks.	Significant placebo-subtracted weight loss (7.8% with 4.5 mg); continuous weight loss with no plateau.	Promising for sustained weight management in PCOS, as it targets both appetite and food preferences. Studies needed to confirm long-term weight loss, particularly in PCOS patients resistant to other therapies.	Gastrointestinal issues (nausea), injection site reactions, mild activation of renin/aldosterone.	136-148	Delay due to complications in finding ideal patient population and the need for more data on safety and long-term effectiveness, particularly in PCOS.

Bimagrumab	Monoclonal antibody targeting activin type II receptor to promote skeletal muscle growth, reduce body fat, and increase lean mass.	Monthly doses for 48 weeks.	6.5% weight loss (compared to 0.8% with placebo), with a significant reduction in body fat mass and enhanced insulin sensitivity.	Potential for improving both weight and insulin sensitivity in PCOS-related obesity, especially for metabolic issues and muscle mass concerns.	Diarrhea, muscle spasms, elevated pancreatic and liver enzymes, risk of pancreatitis.	149-152	Delays related to the complexity of conducting long-term trials for a biologic and concerns regarding safety, including elevated pancreatic enzymes and the risk of pancreatitis.
Leptin Sensitizers (e.g., *Metreleptin*)	Improves leptin sensitivity, helping regulate energy balance and metabolism by enhancing leptin's effects in the body.	Dosing varies by treatment protocol; typically involves regular administration for optimal results.	Leptin sensitizers promote weight loss by enhancing leptin response, improving insulin sensitivity, and reducing inflammation.	*Metreleptin* is a promising therapeutic for PCOS-related obesity, improving insulin sensitivity and reducing body weight and triglycerides. Further research required for its use in PCOS.	Headache, nausea, fatigue, possible injection site reactions.	153-155	Delays due to challenges with study design, including achieving sufficient patient recruitment for PCOS-specific trials, as well as regulatory approval hurdles for biologic agents in this indication.

Critical analysis of drugs in clinical trials:

The treatment of obesity in PCOS is a challenging because of its multifaceted pathophysiology, involving metabolic, hormonal and genetic factors. Several drugs currently in clinical trials show promise for addressing obesity in PCOS, including *Setmelanotide*, *Cagrilintide, Bimagrumab* and Leptin Sensitizers. *Setmelanotide* is a melanocortin-4 receptor (MC4R) agonist that targets energy balance regulation and appetite. It has shown significant efficacy in rare genetic obesity syndromes, such as POMC and LEPR deficiencies, by suppressing appetite and increasing energy expenditure. Its promising results in genetic obesity raise the possibility of its application to PCOS, where metabolic dysregulation and appetite issues are common. However, while it appears to have a favourable safety profile, including fewer cardiovascular risks compared to first-generation MC4R agonists, future research is required to optimize its efficacy and safety in management of PCOS.

Cagrilintide, a long-acting amylin analogue, has also demonstrated promising results in managing obesity. It acts specifically on both homeostatic and hedonic regions of the brain to control appetite and food intake, offering continuous weight loss without plateau, which is often seen with other treatments. In clinical trials, *Cagrilintide* showed superior weight loss to *Liraglutide*, but its weight loss effects were lower than those observed with *Semaglutide*. Despite this, its novel mechanism and sustained weight loss potential make it a promising candidate for PCOS treatment. However, longer-term studies are required to confirm whether the weight loss is maintainable and to assess its long-term safety. *Bimagrumab*, a monoclonal antibody that targets the activin type II receptor to promote muscle growth, has shown the ability to reduce fat mass and increase lean muscle in clinical trials along with improvements in insulin sensitivity. This could be particularly beneficial for PCOS patients, who often suffer from IR. While the reduction in fat mass and improvement in body composition is promising, the side effects including muscle spasms and elevated pancreatic and liver enzymes, along with the limited long-term data, necessitate further investigation.

Finally, Leptin Sensitizers such as *Metreleptin*, work by improving leptin sensitivity which is impaired in obesity and has a critical role in controlling energy balance. Since leptin resistance is a major issue in PCOS, leptin sensitizers hold potential for restoring normal appetite regulation and improving metabolic health. These drugs have been reported to enhance insulin sensitivity and weight management in other obesity-related conditions, but future trial is required to affirm their specific efficacy and safety in PCOS. In summary, while all these drugs show significant promise for treating obesity in PCOS, substantial future studies are needed to determine their long-term efficacy, safety, and potential role in improving both weight management and metabolic health for PCOS patients. Each of these treatment targets different aspects of the obesity and metabolic dysregulation seen in PCOS, and ongoing clinical trials will help clarify their therapeutic potential.

FUTURE DIRECTIONS:

Research Area	Current/Existing Therapies	Limitations	Emerging Therapies	Key Areas for Future Research
Pharmacological Options	*Metformin, Orlistat, Liraglutide, Tirzepatide*	- Modest weight loss with Metformin - Gastrointestinal side effects of Orlistat and Liraglutide - Long-term safety concerns with Tirzepatide	*Semaglutide, Cagrilintide, Bimagrumab*, Leptin Sensitizers (e.g., *Metreleptin*)	- Long-term safety and efficacy of *Setmelanotide*, *Cagrilintide*, and *Bimagrumab* in PCOS - Clinical trials to assess efficacy in PCOS patients - Investigate Leptin Sensitizers' potential for leptin resistance in PCOS
Target Areas	- Insulin Resistance (IR) - Appetite regulation - Fat metabolism	- Limited efficacy in addressing all aspects of obesity in PCOS	- Mechanisms targeting appetite regulation, IR, and fat metabolism	- Investigate combination therapies (e.g., GLP-1 agonists with amylin analogues or SGLT-2 inhibitors) - Explore personalized treatments for metabolic profiles (IR, appetite regulation, fat distribution) - Genetic studies for identifying responsive subgroups
Lifestyle Modifications	- Diet - Exercise regimens - Behavioral therapies	- No specific mention of integration with pharmacotherapy	- Combination of drugs with lifestyle interventions	- Examine the impact of combining drugs with lifestyle modifications for enhanced long-term weight management
Multidisciplinary Approaches	- Focus on weight loss	- Lack of consideration for broader metabolic health and overall well-being	- Focus on metabolic health, IR, lipid profiles, cardiovascular risk	- Incorporate improvements in fertility, reduced hirsutism, and quality of life in clinical trials
Key Research Focus	- Development of more effective pharmacological treatments	- Need for better efficacy and tolerability	- Exploration of promising therapies such as *Semaglutide*	- Focus on individualized, targeted therapies addressing metabolic and hormonal dysfunctions - Long-term clinical trials for safer, sustainable treatments

CONCLUSION

The current and emerging therapies for obesity in PCOS, while promising, still have limitations in terms of efficacy, side effects, and long-term sustainability. Future research is needed to explore new drug classes, including dual agonists and melanocortin receptor modulators, and repurpose existing drugs for enhanced therapeutic benefit. Personalized medicine approaches, considering the genetic and metabolic diversity of PCOS, will be essential to improving treatment outcomes. By addressing these research gaps, there is potential for more effective, sustainable, and individualized treatments for managing obesity in PCOS.

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