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REVIEW

The Role of Antiobesity Agents in the Management of Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age. Obesity is frequently present in these patients and plays a key role in the pathogenesis of both the endocrine and metabolic abnormalities of the syndrome, particularly infertility, hyperandrogenism and insulin resistance (IR). Diet and exercise is the mainstay of management of obesity in patients with PCOS. In contrast, the effects of antiobesity agents on weight and on the obesity-related characteristics of the syndrome remain unclear. The aim of the present review is to summarize the current data on the effects of antiobesity drugs approved in Europe (orlistat, liraglutide 3 mg od and naltrexone/bupropion) on weight loss in patients with PCOS and to discuss their impact on the endocrine, reproductive and metabolic abnormalities of this population. Several studies reported that orlistat induces weight loss, improves IR and reduces androgen levels in PCOS. In contrast, data regarding the effects of the dose of liraglutide that is approved for the treatment of obesity (3 mg od) are very limited. Liraglutide 1.2-1.8 mg od results in weight loss in these patients but does not affect IR or androgen levels. Finally, there are no studies that evaluated naltrexone/bupropion in patients with PCOS and early studies reported conflicting results regarding the effects of naltrexone monotherapy on weight, IR and androgen levels. In conclusion, orlistat appears to have a role in the management of overweight and obese patients with PCOS whereas more studies are needed to clarify the role of liraglutide and naltrexone/bupropion.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age, affecting approximately 6% - 10% of this population.[1] Obesity characterizes 40%-70% of patients with PCOS and plays a key role in the pathogenesis of both the endocrine and metabolic abnormalities of the syndrome, particularly infertility, hyperandrogenism and insulin resistance (IR).[2]

According to current guidelines, diet and exercise is the mainstay of management of obesity in patients with PCOS.[3] In contrast, the effects of antiobesity agents on weight and on the obesity-related characteristics of the syndrome remains unclear, since relevant studies are limited in number, small and with a short duration of follow-up.[3] Moreover, two antiobesity agents, sibutramine and rimonabant, which showed promising results in patients with PCOS[4-6], have been withdrawn from the market due to their unfavorable safety profile[7,8].

The aim of the present review is to summarize the current data on the effects of antiobesity drugs currently approved in Europe (i.e. orlistat, liraglutide 3 mg od and naltrexone/bupropion) on weight loss in patients with PCOS and to discuss their impact on the endocrine, reproductive and metabolic abnormalities of this population.

Orlistat

Orlistat inhibits pancreatic lipase, resulting in a 30% reduction in the absorption of ingested fat and in weight loss.[9] Several uncontrolled studies reported that orlistat induces weight loss, improves markers of IR and reduces circulating androgen levels in patients with PCOS (**Table**).[6,10-12] In the largest study to date that evaluated the effects of orlistat

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in patients with PCOS, 101 women with PCOS and 29 body mass index (BMI)-matched healthy women were prescribed an energy-restricted diet, were instructed to perform moderate intensity aerobic exercise 3 days a week for 1 hour, and were given orlistat 120 mg tid for 6 months.[13] In patients with PCOS, treatment with orlistat resulted in a 12.9% weight loss.[13] A reduction in waist circumference and waist/hip ratio was also observed.[13] Markers of IR improved and circulating androgens decreased.[13] Systolic and diastolic blood pressure (BP) also decreased.[13] Regarding the effect on the lipid profile, serum low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels decreased whereas serum high-density lipoprotein cholesterol (HDL-C) levels did not change.[13] The prevalence of metabolic syndrome decreased by 54.4% (from 43.2% at baseline to 19.7% at 6 months; $p = 0.003$).[13]

In the only randomized study that compared orlistat with placebo in patients with PCOS ($n = 100$), orlistat reduced weight by 6.4%, reduced testosterone levels, lowered serum levels of LDL-C and TG and increased serum levels of HDL-C.[14] However, orlistat had no effect on markers of IR

Table. Effects of antiobesity agents on body weight, insulin resistance, circulating androgens and other parameters in patients with polycystic ovary syndrome

Agent	Body weight	Insulin resistance	Circulating androgens	Other parameters
Orlistat	↓	↓→	↓	↓ blood pressure
				↓→ low-density lipoprotein cholesterol
				↑→ high-density lipoprotein cholesterol
				↓→ triglycerides
				↓ leptin and advanced glycation end-products
				↑ anti-Müllerian hormone
Liraglutide	↓	↓→	↓→	↓ visceral abdominal tissue and liver fat content
				↓ leptin and urinary isoprostanes
				↑ heart rate
				↓ high-sensitivity C-reactive protein levels
				↓ platelet activation, P-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1
				↓ procollagen type 3 amino-terminal peptide
				↓ uncontrolled and emotional eating
Naltrexone/ bupropion	↓→	↓→	↓→	↓ beta-cell hyper-responsiveness to glucose loading
				↑hepatic removal of insulin
				↓amplitude of luteinizing hormone pulses
				↑ the frequency of luteinizing hormone pulses
				Normalizes the LH response to GnRH stimulation test

↓ reduction; ↑ increase; ↓→ reduction or no change; GnRH: gonadotropin-releasing hormone.

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and did not improve menstrual cycle abnormalities.[14]

Several randomized studies compared the effects of orlistat (120 mg tid) and metformin (500 mg tid) in patients with PCOS. In an early small study (n = 21), treatment with orlistat for 3 months induced greater weight loss than metformin (4.7 vs. 1.0%, respectively).[15] The 2 agents yielded comparable reductions in serum testosterone levels.[15] In contrast, neither treatment affected markers of IR or the lipid profile.[15] In another study in 40 obese anovulatory patients (87% with PCOS), orlistat 120 mg bid and metformin 1000-2000 mg per day for 3 months induced comparable reductions in BMI, waist circumference and circulating androgens.[16] Interestingly, menstrual cyclicity and androgenic symptoms improved in both treatment groups.[16] In addition, 25 and 5% of patients in the orlistat group experienced ovulation or managed to conceive; similar rates were observed in the metformin group (40 and 25%, respectively, p = NS).[16] In a larger study (n = 80), treatment with orlistat 120 mg bid or metformin 500 mg tid for 3 months induced comparable reductions in weight (3.9 vs. 5.0%, respectively), waist circumference and TG levels.[17] However, only orlistat reduced serum testosterone and total cholesterol levels whereas metformin had no effect.[17] Ovulation was achieved in 15 and 30% of patients treated with orlistat and metformin, respectively (p = NS).[17] In a more recent study, 90 patients with PCOS were assigned to receive lifestyle interventions alone (hypocaloric diet and aerobic exercise) or in combination with either orlistat 120 mg bid or metformin 500 mg tid for 3 months.[18] Orlistat and metformin induced comparable reductions in weight and waist circumference, which were larger than with lifestyle intervention alone, but only orlistat reduced the waist/hip ratio.[18] In addition, only orlistat reduced LDL-C and TG levels whereas none of the treatments affected HDL-C levels.[18] In contrast, reductions in testosterone levels were similar in the 3 groups.[18] Markers of IR did not change in any of the groups.[18] Ovulation rates were similar in patients treated with metformin or orlistat and higher than in those who received lifestyle interventions alone.[18] Interestingly, conception rates were higher in the orlistat group than in the metformin or lifestyle group (40.0, 16.7 and 3.3%, respectively; p = 0.003).[18]

Very few studies compared orlistat with other agents in patients with PCOS. In an early randomized, open-label study, 30 patients were assigned to receive orlistat 120 mg tid, metformin 500 mg tid or pioglitazone 45 mg od for 12 weeks after an 8-week run-in period where they were given dietary advice.[19] BMI showed a comparable reduction in patients treated with orlistat and metformin (5.7 vs. 3.4%, respectively) and did not change in the pioglitazone group.[19] Orlistat reduced IR less than pioglitazone whereas metformin had no effect.[19] The 3 agents induced comparable decreases in serum testosterone levels.[19] In a post-hoc analysis of 2 randomized studies (n = 50), orlistat 120 mg tid reduced weight by 5.7% whereas metformin 500 mg tid and pioglitazone 45 mg od had no effect.[20] Orlistat and pioglitazone yielded similar improvements in markers of IR whereas metformin did not affect IR.[20] The 3 agents induced comparable reductions in the free androgen index but none affected the lipid profile.[20] Pioglitazone also reduced high-sensitivity C-reactive protein (hs-CRP) levels, a marker of subclinical inflammation and increased cardiovascular risk[21], whereas orlistat and metformin had no effect[20]. In a more recent large randomized study (n = 149), orlistat combined with lifestyle modification (caloric restriction and increased physical activity) for 16 weeks induced similar reductions in weight with orlistat and lifestyle modification combined with oral contraceptive pills (OCP, ethinyl estradiol 20 mcg/1 mg norethindrone acetate) and greater than OCP alone (6.2, 6.4 and 1.0%, respectively).[22] Serum testosterone and TG levels did not change in the group that received only orlistat and lifestyle advice but increased in the group that received only OCP.[22] In addition, markers of IR improved in the former and worsened in the latter group.[22] Quality of life improved to a similar degree in the 2 groups.[22] Rates of ovulation, conception, clinical pregnancy and live birth did not differ between the 2 groups but fecundity per patient who ovulated was higher in the group that received only orlistat and lifestyle advice than in the group that received only OCP.[22]

In addition to its effects on weight, IR and androgen levels, uncontrolled studied reported other potentially beneficial effects of this agent in patients with PCOS. Indeed, orlistat reduced serum leptin levels, which is intimately involved in body weight regulation.[10] An increase in serum anti-Müllerian hormone levels, a key regulator of folliculogenesis, was also reported during treatment with orlistat.[11] Moreover, a decrease in serum levels of advanced glycation end-products, which induce oxidative stress, inflammation and atherosclerosis, was observed during treatment with orlistat.[12]

Regarding the safety profile of orlistat, this agent

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is associated with a higher incidence of acute kidney injury and hepatic impairment than placebo. The absorption of fat-soluble vitamins and other fat-soluble nutrients is reduced by the use of orlistat. Multivitamins containing vitamins A, D, E, K and beta-carotene must be taken once a day at bedtime in patients using orlistat.[9]

In conclusion, orlistat induces substantial weight loss in patients with PCOS and also improves IR and reduces circulating androgens. A reduction in BP and an improvement in the lipid profile have also been reported during treatment with this agent. Orlistat appears to be equally effective with metformin in reducing weight, IR and testosterone levels but has not been compared with other antiobesity agents.

Liraglutide

Liraglutide at a dose of 3 mg od has been approved in Europe in 2015 for the management of patients with BMI > 30 kg/m^2 or BMI 27-30 kg/m^2 and obesity-related comorbidities.[23] Liraglutide induces weight loss by suppressing appetite and by increasing postprandial satiety and fullness.[24]

In the only study that evaluated liraglutide 3 mg od in PCOS, 30 patients were randomized to receive liraglutide 3 mg or liraglutide 1.2 mg od combined with metformin 1,000 mg bid for 12 weeks (**Table**).[25] Liraglutide 3 mg od induced similar weight loss with liraglutide combined with metformin (6.3 vs. 3.6 kg, respectively; p = 0.062).[25] However, waist circumference was reduced more in the former group.[25] Both treatments induced similar reductions in markers of IR.[25] Combination treatment reduced serum testosterone and LDL-C levels whereas liraglutide monotherapy had no effect; neither treatment affected TG or HDL-C levels.[25]

All the other studies that assessed liraglutide in patients with PCOS evaluated lower doses than the recommended for the management of obesity. In the only placebo-controlled study, 72 patients were randomized to receive liraglutide 1.8 mg od or placebo in a 2:1 ratio for 26 weeks.[26] Patients treated with liraglutide lost a mean of 5.2 kg and also experienced reductions in waist circumference.[26] In contrast, markers of IR did not change.[26] Changes in prothrombotic mediators (thrombin, plasminogen activator-inhibitor 1, von Willebrand factor) and hs-CRP levels were also similar in the liraglutide and placebo group.[26] In a secondary analysis, liraglutide reduced visceral abdominal tissue, liver fat content and the prevalence of nonalcoholic fatty liver disease (NAFLD) more than placebo.[27] NAFLD is highly prevalent in patients with PCOS and is associated with increased cardiovascular risk.[28,29] A reduction in HbA_{1c} and in plasma glucose and leptin levels was also observed in the liraglutide group.[27] In contrast, changes in lipid profile, BP and estimated glomerular filtration rate were similar in the liraglutide and placebo group and the heart rate increased more in the former.[27] In another analysis of the same study, androgen levels declined more and menstrual bleeding occurred more frequently in patients treated with liraglutide.[30]

Two 12-week, randomized, open-label studies compared liraglutide with metformin in patients with PCOS.[31,32] In an early small study (n = 32), liraglutide 1.2 mg od induced similar weight loss with metformin 1,000 mg bid (3.0 and 2.3 kg, respectively).[31] However, in patients with IR and metabolic syndrome, liraglutide was more effective in reducing weight.[31] The 2 treatments also resulted in comparable reductions in waist circumference.[31] However, neither agent affected fat mass, markers of IR, circulating androgens, lipid profile, BP or menstrual pattern.[31] In addition, only metformin reduced testosterone levels whereas liraglutide had no effect.[31] In a more recent and larger study (n = 45), liraglutide 1.2 mg od induced greater weight loss than metformin 1,000 mg bid (3.1 and 0.2 kg, respectively).[32] Liraglutide also reduced waist circumference and visceral adipose tissue more than metformin.[32] The 2 agents induced comparable improvements in IR but neither affected circulating androgens or the menstrual pattern.[32]

Two 12-week, randomized, open-label studies compared liraglutide monotherapy with liraglutide plus metformin combination therapy in patients with PCOS.[33,34] In an early study (n = 40), liraglutide 1.2 mg od combined with metformin 1,000 mg bid induced similar weight loss with monotherapy with liraglutide 1.2 mg od and greater than monotherapy with metformin 1,000 mg bid (6.5, 3.8 and 1.2 kg, respectively).[33] None of the treatments affected visceral adipose tissue, markers of IR, circulating androgens, lipid profile, BP or the menstrual pattern.[33] In contrast, in a more recent study (n = 44), liraglutide 1.2 mg od combined with metformin 1,000 mg bid induced greater weight loss than monotherapy with liraglutide 1.2 mg od (6.2 vs. 3.8 kg, respectively).[34] In contrast, the 2 treatments resulted in similar reductions in waist circumference and visceral adipose tissue, markers of IR and glucose levels, and serum free testosterone levels.[34] However, the prevalence of metabolic syndrome

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was reduced more with combination treatment.[34]

In a meta-analysis of randomized controlled studies that evaluated the effects of liraglutide in patients with PCOS, a reduction in weight and in circulating androgens was observed but markers of IR did not change.[35]

Uncontrolled studies also reported reductions in weight, waist circumference and visceral adipose tissue after treatment with liraglutide 1.2-1.8 mg od.[36-39] A reduction in urinary isoprostanes, a marker of oxidative stress, and hsCRP levels was also observed in patients treated with liraglutide.[38,39] Interestingly, platelet activation was reduced and serum levels of P-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which are markers of endothelial dysfunction, decreased after treatment with liraglutide for 6 months but no effect on carotid intima-media thickness was observed.[38] Liraglutide also reduced serum levels of procollagen type 3 amino-terminal peptide, a marker of liver fibrosis.[39] In addition, liraglutide reduced uncontrolled and emotional eating.[36]

Interestingly, polymorphisms in the gene encoding GLP-1 receptor modulate the effects of liraglutide on weight.[37] Carriers of the rs10305420 T allele or the rs6923761 A allele experienced smaller and larger weight loss, respectively, during treatment with liraglutide.[37]

Regarding the safety of liraglutide, it should be mentioned that this agent should not be used during pregnancy. If a patient wishes to become pregnant or if pregnancy occurs, therapy should be discontinued. Animal studies have shown a toxic effect on the embryo and early spontaneous abortions. There are no randomized studies of the effect on pregnant women. Liraglutide is also associated with higher incidence of pancreatitis and non-lethal thyroid C-cell tumors.[23]

In conclusion, liraglutide induces weight loss and reduces testosterone levels in patients with PCOS but does not appear to affect IR. Liraglutide appears to be more effective than metformin in inducing weight loss and the combination of the 2 agents is more effective in inducing weight loss than monotherapy with liraglutide. However, almost all studies evaluated a smaller dose of liraglutide than the one recommended for the management of obesity (i.e. 3 mg daily).

Naltrexone-bupropion

Naltrexone-bupropion was approved in Europe in 2015 for the management of patients with BMI > 30 kg/m^2 or patients with BMI 27-30 kg/m^2 and obesity-related comorbidities.[40] Bupropion inhibits the reuptake of dopamine and noradrenaline, thus activating the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, which secrete α-melanocyte stimulating hormone (α-MSH); α-MSH inhibits food intake.[41] Naltrexone is an opioid antagonist that blocks the effects of β-endorphin, which is released by POMC neurons concurrently with α-MSH; β-endorphin both inhibits the secretion of α-MSH and stimulates appetite.[41]

There are no studies that assessed the effects of naltrexone-bupropion in patients with PCOS. However, several small studies evaluated the effects of naltrexone 50 mg od in these patients (**Table**). In some reports, treatment with naltrexone for 3-6 months reduced BMI by 3.9-4.2 kg/m^2.[42,43] However, other studies reported no change in BMI during treatment with naltrexone.[44,45]

Several studies showed that naltrexone attenuates the beta-cell hyper-responsiveness to glucose loading, which characterizes patients with PCOS.[45,46] In addition, naltrexone increases hepatic removal of insulin, which is reduced in PCOS and plays a role in the pathogenesis of hyperinsulinemia in this population.[44] On the other hand, naltrexone does not appear to affect peripheral insulin sensitivity or insulin secretion.[44] Indeed, most studies reported no change in IR during treatment with naltrexone[44,45] although others reported an improvement[42,43].

Early studies reported that treatment with naltrexone decreases the amplitude of luteinizing hormone (LH) pulses[47] and increases their frequency[48]. Moreover, naltrexone normalizes the LH response to gonadotropin-releasing hormone (GnRH) stimulation test.[49] The latter effect appears to be mediated by decreased insulin secretion.[49] In contrast, serum androgen levels were not affected by naltrexone in most studies[45] even though others reported a reduction[42,43]. However, naltrexone reduces the androgen response to adrenocorticotropic hormone stimulation test.[46] Moreover, naltrexone reduced the severity of hirsutism and acne and also improved menstrual cyclicity.[42,43] However, other studies reported no change in hirsutism during treatment with naltrexone.[44,45] More importantly, treatment with naltrexone appears to increase ovulation rates in patients with PCOS undergoing pulsatile GnRH treatment for ovulation induction.[49] Treatment with naltrexone also appears to increase ovulation and conception rates of patients who receive clomiphene.[43]

In the only comparative study, 29 patients with

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PCOS were randomized to receive naltrexone, metformin 500 mg tid, or a combination of an OCP (35 μg of ethinyl estradiol and 2 mg cyproterone acetate) and prednisolone 5 mg od for 3 months.[50] The 3 treatments induced similar reductions in circulating androgens.[50] In contrast, markers of IR did not change in any of the groups.[50] Metformin reduced both systolic BP and total cholesterol levels whereas the other treatments had no effect.[50]

Regarding the safety of naltrexone-bupropion, this combination is associated with renal and hepatic impairment, headache, dizziness, insomnia, convulsions, neuropathic reactions, hypertension and / or tachycardia, elevation of intraocular pressure, warm waves and sweat, tremor, allergic reactions and increased tendency for self-harm. There are no data from the use of naltrexone/bupropion in pregnant women and belongs to risk category X. The combination has not been studied with regard to reproductive toxicity. Animal studies with naltrexone show reproductive toxicity.[40]

In conclusion, monotherapy with naltrexone reduces body weight in patients with PCOS but does not appear to affect IR or androgen levels. There are no studies that evaluated the effects of naltrexone-bupropion combination in this population.

CONCLUSIONS

Several studies consistently reported that orlistat induces weight loss, improves IR and reduces androgen levels in PCOS. In contrast, data regarding the effects of the dose of liraglutide that is approved for the treatment of obesity (i.e. 3 mg od) are very limited. Liraglutide 1.2-1.8 mg od results in weight loss in these patients but does not affect IR or androgen levels. Finally, there are no studies that evaluated naltrexone/bupropion in patients with PCOS and early studies reported conflicting results regarding the effects of naltrexone monotherapy on weight, IR and androgen levels. Therefore, orlistat appears to have a role in the management of overweight and obese patients with PCOS whereas more studies are needed to clarify the role of liraglutide and naltrexone/bupropion in this population.

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Роль препаратов против ожирения в лечении синдрома поликистозных яичников

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Синдром поликистозных яичников (СПКЯ) является наиболее распространённым эндокринным заболеванием у женщин репродуктивного возраста. У этих больных часто наблюдается ожирение, которое играет ключевую роль в патогенезе как эндокринных, так и метаболических нарушений синдрома, таких в частности как бесплодие, гиперандрогения и резистентность к инсулину (РИ). Диета и физическая активность являются основными столбами в борьбе с ожирением у пациентов с СПКЯ. С другой стороны, воздействие препаратов против ожирения на вес и связанных с ожирением характеристики синдрома, остаётся неясным. Целью данного обзора является обобщение имеющихся данных о воздействии лекарств против ожирения, утверждённых в Европе (орлистат, лираглутид 3 мг. пероральной дозы и налтрексон / бупропион) у больных с СПКЯ и обсудить их влияние на эндокринные, репродуктивные и метаболические нарушения среди нашего населения. В нескольких исследованиях сообщалось, что орлистат приводит к потере веса, улучшает РИ и снижает уровень андрогенов при СПКЯ. С другой стороны, данные о влиянии дозировки лираглутида, утверждённой для лечения ожирения (3 мг. пероральной дозы) являются очень скудными. Лираглутид 1,2-1,8 мг. пероральной дозы приводит к потере веса у этих пациентов, но не оказывает никакого влияния на РИ или на уровни андрогенов. Кроме того нет исследований, оценивающих воздействие налтрексона / бупропиона на больных с синдромом поликистозных яичников, а более ранние исследования содержат противоречивые результаты относительно влияния монотерапии налтрексона на вес, РИ и уровни андрогенов. В заключение можно сказать, что орлистат по всей вероятности играет роль при лечении пациентов с избыточной массой тела и ожирением с СПКЯ, но необходимо провести дополнительные исследования для уточнения роли лираглутида и налтрексона / бупропиона.

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