META-ANALYSIS

Effects of orlistat vs. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis

S. K. Graff,1 F. M. Mario,1,2 P. Ziegelmann,3 P. M. Spritzer1,4

SUMMARY

Aims: The aim of this study was to assess the effects of orlistat on weight loss-related clinical variables in overweight/obese women with polycystic ovary syndrome (PCOS) and to compare treatment with orlistat vs. metformin in this group.

Methods: We conducted a systematic review and meta-analysis of the evidence about the use of orlistat in women with PCOS. We searched the literature published until May 2015 in MEDLINE, Cochrane Central Register of Controlled Trials and LILACS.

Results: Of 3951 studies identified, nine were included in the systematic review (three prospective, non-randomised studies and six randomised control trials). Eight studies used the Rotterdam criteria and 1 used NIH criteria to diagnose PCOS. Data suggest that orlistat promotes a significant reduction in BMI/weight in overweight/obese PCOS women. Eight studies evaluated orlistat impact on testosterone. Seven reported an improvement in testosterone levels. Eight studies evaluated impact on insulin resistance, and five reported improvement. Finally, five studies evaluated impact on lipid profile, and four reported improvement.

Three randomised control trials were included in the fixed effects model meta-analysis for a total of 121 women with PCOS. Orlistat and metformin had similar positive effects on BMI (−0.65%, 95% CI: −2.03 to 0.73), HOMA (−3.60%, 95% CI: −16.99 to 9.78), testosterone (−2.08%, 95% CI: −13.08 to 8.93) and insulin (−5.61%, 95% CI: −22.27 to 11.26).

Conclusion(s): The present results suggest that orlistat leads to significant reduction in BMI/body weight in PCOS. In addition, the available evidence indicates that orlistat and metformin have similar effects in reducing BMI, HOMA, testosterone and insulin in overweight/obese PCOS women. This study was registered in PROSPERO under number CRD42014012877.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition primarily characterised by hyperandrogenism and ovulatory dysfunction (1–3), with associated metabolic disturbances including insulin resistance, dyslipidaemia and type 2 diabetes mellitus (DM2) (1,2,4,5). The prevalence of PCOS in women of reproductive age varies from 9% to 18% depending on diagnostic criteria (3,6,7).

Obesity and greater abdominal adiposity are also typical of PCOS and may accentuate reproductive and metabolic issues (8–15). Therefore, lifestyle measures for weight loss are the first-line treatment in obese women with PCOS (12,16,17). However, lifestyle changes may not be sufficient to promote significant weight loss, and pharmaceutical interventions may be required (18). Metformin, an oral antidiabetic drug that reduces glucose levels by improving insulin action, has been considered a second-line treatment for PCOS women presenting insulin resistance (19–24). While its main mechanism of action involves an improvement on insulin action, leading to an amelioration of menstrual cycles and reduction in testosterone levels, in some, but not all, insulin-resistant PCOS women these effects are similar to those obtained with weight loss (20).

The lipase inhibitor orlistat is currently the sole anti-obesity agent available in many countries. Orlistat does not have systemic adverse effects and has been shown to produce significant and sustained weight loss, with improvement in cardiovascular risk factors including DM2, hypertension and dyslipidaemia in different populations (25–30). Nevertheless,
only a few studies including small samples are available in the literature regarding the effects of orlistat on weight loss in women with PCOS. Therefore, the aim of this systematic review and meta-analysis was to assess the effects of orlistat on weight loss-associated clinical variables such as weight/BMI, waist circumference, insulin resistance markers, total testosterone, lipid profile, and menstrual cyclicity and to compare these effects to those obtained with metformin treatment in overweight/obese women with PCOS.

Methods

Search strategy and study selection
The following databases were searched for prospective studies and randomised clinical trials (RCTs) published until May 2015: Medline, Cochrane Central Register of Controlled Trials, and LILACS. No limits were set on publication date or language. This systematic review was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under number CRD42014012877. The following basic search strategy was developed for PubMed and modified as needed for other databases: "Polycystic Ovary Syndrome" or "Ovary Syndrome, Polycystic" or "Syndrome, Polycystic Ovary" or "Stein-Leventhal Syndrome" or "Stein-Leventhal Syndrome" or "Syndrome, Stein-Leventhal" or "Sclerocystic Ovarian Degeneration" or "Ovarian Degeneration, Sclerocystic" or "Sclerocystic Ovary Syndrome" or "Ovarian Syndrome, Polycystic" or "Ovarian Syndrome, Polyovary" or "Ovary, Sclerocystic" or "Sclerocystic Ovary" and tetrahydrolipstatin or THLP or 1-(3-hexyl-4-oxo-2-oxetanyl)methyl]docetyl-2-formamido-4-methylvalerate or tetrahydrolipstatin or Xenical or "Roche brand of orlistat" or "Hoffmann-La Roche brand of orlistat" or Alli or "GlaxoSmithKline brand of orlistat."

The selection criteria for the studies were as follows: diagnosis of PCOS using Rotterdam (31) or NIH criteria (32), intervention with any dose of orlistat for at least 8 weeks, and comparison of orlistat with placebo or metformin or any anti-obesity drug. Regarding the studies comparing orlistat with anti-obesity drugs other than metformin in PCOS, or comparing the use of orlistat in PCOS women vs. healthy controls, only the results from the PCOS/orlistat arm were considered in the present systematic review. Studies with lifestyle interventions associated with pharmacological treatment were also included in the systematic review if all the groups in the study received the same intervention.

Primary outcomes were changes in body mass index (BMI), weight, waist circumference, insulin resistance markers and total testosterone levels following orlistat treatment. Secondary outcomes were changes in lipid profile and menstrual cyclicity, ovulation rate and ovarian morphology at ultrasound and adverse effects.

In addition, the reference lists of identified studies were searched. The most complete study was chosen to avoid duplication if the same patient populations were reported in several publications. Whenever necessary, authors were contacted to obtain additional data from published materials.

Data extraction and quality control assessment
Two reviewers (SKG and FMM) independently screened titles/abstracts for selection of articles for full text review. Disagreements were resolved by a third reviewer (PMS) or consensus discussion. The full text of selected articles was independently reviewed by the two initial reviewers. Cochrane Collaboration tools for assessing the risk of bias in randomised trials (33) were also independently applied by two reviewers (SKG and FMM), with disagreements resolved by a third reviewer (PMS) or consensus discussion. The following information was extracted from studies: name of first author, publication year, country, PCOS diagnostic criteria, type of study, intervention, number of subjects in each arm, age, length of study and lifestyle intervention.

Statistical analysis
Data are presented as mean (±SEM) at baseline and after treatment. The comparison between baseline and after-treatment data within each arm (orlistat or metformin) is presented as mean percentage change from baseline (±SEM). Data from RCTs comparing the effects of orlistat vs. metformin were combined by fixed effects model meta-analysis. Variables of interest expressed as mean (±SEM) were included in the meta-analysis if they were present in at least two studies with the same unit of measurement. Mean percentage changes from baseline achieved with orlistat or metformin were recorded for each variable/outcome, and the difference (orlistat minus metformin) between these percentage changes was considered as the effect size. Therefore, results are presented as mean differences with 95% confidence intervals (95% CI). A p-value < 0.05 was considered statistically significant. Heterogeneity was assessed using the I² statistics and Cochran’s Q test. It was not possible to meta-analyse the effect of orlistat vs. placebo on clinical variables associated with weight loss because we found only one study comparing orlistat with placebo. All analyses were conducted using the Meta package from R software version 3.0.
Results

Flow chart of study selection

Figure 1 provides details of the study selection. The primary search identified 3951 articles. After title and abstract screening, 14 potentially eligible studies were retrieved for full text review. Of these 14 articles, five were excluded: one did not meet the inclusion criteria and four overlapped with other studies. Therefore, nine studies were included in the systematic review: three prospective, non-randomised studies comparing the use of orlistat in PCOS women and healthy controls (34–36) and six RCTs (four studies comparing orlistat with metformin in PCOS women, one comparing orlistat with sibutramine in PCOS women, and one comparing orlistat with placebo in PCOS women) (37–42).

Characteristics of included studies

Table 1 summarises the characteristics of the nine studies included in the systematic review. Two studies focused on Caucasian women from the UK (37,38), two on Iranian women (39,41), one on Indian women (42) and four on Greek women (34–36,40). Eight of these studies employed Rotterdam criteria for diagnosis of PCOS and one used NIH criteria (hyperandrogenemia (free androgen index > 8) and history of oligomenorrhoea (cycle length, < 21 days or > 35 days; < 8 cycles per year) or amenorrhea and hirsutism (Ferriman-Gallwey score > 8)) (37).

All nine studies included overweight/obese PCOS women. In four, orlistat was compared with metformin (37–39,42). One study compared orlistat and sibutramine (40). In that study, a normal weight PCOS group receiving metformin for 6 months was also included. Another study compared orlistat and placebo (41). Finally, three studies compared orlistat in overweight/obese PCOS women vs. overweight/obese healthy controls (34–36).

Four studies (comparing orlistat vs. metformin or vs. sibutramine) (37–40) did not report the mean age for each group separately. Only the mean age for the overall participants was presented, and that ranged from 25.7 to 27.0 years. One study (42) included women younger than 40 years of age. In the study comparing orlistat vs. placebo (41), the mean age was 26.8 ± 5.2 in PCOS women treated with orlistat and 27.4 ± 3.3 in the placebo group. In the studies comparing PCOS and healthy controls (34–36), the age of PCOS women ranged from 25.4 to 26.1 years, vs. 30.6 to 32.1 years for controls, and study
| Name, Year          | Ethnicity (country) | PCOS criteria | Types of studies and intervention                                                                 | Dosage                                                                 | Length (weeks) | N (PCOS-orlistat/comparison group) | Age (PCOS-orlistat group vs. comparison group) Mean ± SD | Lifestyle intervention |
|---------------------|--------------------|---------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------|-----------------------------------|----------------------------------------------------------|------------------------|
| Cho et al., 2009 (38) | Caucasian (UK)     | Rotterdam     | Randomised, open-label parallel study comparing the use of orlistat with metformin in obese PCOS women | Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period | 12             | 10/10                             | 26.4 ± 6.7 (all participants)                           | No                     |
| Diamanti-Kandarakis et al., 2007 (34) | European (Greece) | Rotterdam     | Prospective study comparing the use of orlistat in obese PCOS women and obese healthy controls     | Orlistat: 120 mg three times per day                                    | 12/24          | 29/18                             | 25.5 ± 5.8 vs. 32.1 ± 5.6                               | Normal protein, energy-restricted diet (BMR – 600 kcal; 50% CHO, 30% FAT, 20% PTN) No |
| Ghandi et al., 2011 (39) | Iranian (Iran)     | Rotterdam     | Randomised, open-label parallel study comparing the use of orlistat with metformin in obese PCOS women | Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period | 12             | 40/40                             | 27.0 ± 44.0 (all participants)                          | Weight maintenance diet (50% CHO, 30% FAT, 20% PTN, 300 mg cholesterol) |
| Jayagopal et al., 2005 (37) | Caucasian (UK)     | *             | Prospective, randomised, open-label study comparing the use of orlistat with metformin in overweight/obese PCOS women | Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period | 12             | 10/11                             | 27.0 ± 4.12 (all participants)                          | Normal protein, energy-restricted diet (BMR – 600 kcal; 50% CHO, 30% FAT, 20% PTN) and instruction for exercise (moderate intensity aerobic exercise) for at least 3 h/week |
| Koiou et al., 2013 (40) | European (Greece) | Rotterdam     | Prospective, randomised study comparing the use of orlistat with sibutramine in PCOS overweight/obese women | Orlistat: 120 mg three times per day; Sibutramine: 10 mg qd | 24             | 22/28                             | 25.7 ± 5.9 (all participants)                          | Normal protein, energy-restricted diet (BMR – 600 kcal; 50% CHO, 30% FAT, 20% PTN) and instruction for exercise (moderate intensity aerobic exercise) for at least 3 h/week |
| Name, Year                  | Ethnicity (country) | PCOS criteria | Types of studies and intervention                                                                 | Dosage                                                                 | Length (weeks) | N (PCOS-orlistat/comparison group) | Age (PCOS-orlistat group vs. comparison group) Mean ± SD | Lifestyle intervention                                                                 |
|----------------------------|--------------------|--------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------|-----------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------|
| Kumar and Arora, 2014 (42) | Indian             | Rotterdam    | Randomised controlled trial comparing the use of orlistat with metformin in overweight/obese PCOS women | Orlistat: 120 mg two times per day; Metformin was incremented stepwise to maximum 500 mg 3 times a day | 12             | 30/30 N/A                         | Normal protein, energy-restricted diet (1200-1800 kcal/day; 55% CHO, 30% FAT, 15% PTN) and exercise (1 h/day) |
| Moini et al., 2015 (41)   | Iranian            | Rotterdam    | Randomised double-blind placebo-controlled clinical trial comparing the use of orlistat with placebo in overweight/obese PCOS women | Orlistat: 120 mg three times per day                                    | 12             | 43/43 26.8 ± 5.2 vs. 27.4 ± 3.3 | Normal protein, energy-restricted diet (1200-1800 kcal/day; 55% CHO, 30% FAT, 15% PTN) and patients encouraged to walk for 30 min daily |
| Panidis et al., 2014 (35) | European (Greece)  | Rotterdam    | Prospective study comparing the use of orlistat in overweight/obese PCOS women and overweight/obese healthy controls | Orlistat: 120 mg three times per day                                    | 12/24          | 101/29 26.1 ± 6.4 vs. 31.5 ± 4.7 | Normal protein, energy-restricted diet (BMR – 600 kcal; 50% CHO, 30% FAT, 20% PTN) and instruction to exercise (moderate intensity aerobic exercise) at least 3 h/week |
| Spanos et al., 2012 (36)  | European (Greece)  | Rotterdam    | Prospective study comparing the use of orlistat in overweight/obese PCOS and healthy controls    | Orlistat: 120 mg three times per day                                    | 24             | 60/48 25.4 ± 6.2 vs. 30.6 ± 6.3 | Normal protein, energy-restricted diet (BMR – 600 kcal; 50% CHO, 30% FAT, 20% PTN) |

*Presence of hyperandrogenemia (free androgen index > 8) with a history of oligomenorrhoea (cycle length, < 21 days or > 35 days; < 8 cycles per year) or amenorrhoea and hirsutism (Ferriman–Gallwey score > 8). BMR, basal metabolic rate; CHO, carbohydrate; PTN, protein; BMI, body mass index; N/A, not available.
duration ranged from 12 to 24 weeks. Two 24-month studies also reported 12-week data.

The four RCTs included in the systematic review, comparing orlistat vs. metformin in PCOS women (37–39,42), lasted 12 weeks. Three studies used the same dosages for both drugs (37–39) and one used a lower dosage of orlistat (42). One of these studies also offered general dietary guidance (37), while another provided guidance on low-calorie diet and lifestyle modification (42). The sample size ranged from 10 to 40 women for both the PCOS group treated with orlistat and the PCOS group treated with metformin.

One study compared orlistat with sibutramine in overweight/obese women with PCOS (40). These women also received low-calorie diet guidance and instructions for performing moderate intensity aerobic exercise for at least 3 h/week. In that study, an additional group of lean women with PCOS received metformin for 6 months. Another study comparing orlistat vs. metformin was excluded, because baseline and final results were not available (42).

Only one RCT had a placebo control group (41). Participants were instructed to follow a diet (1200–1800 kcal) and were encouraged to walk for 30 min daily.

Three additional studies included in the systematic review compared the use of orlistat in overweight/obese PCOS women and overweight/obese healthy controls (34–36). All three studies offered an energy-restricted diet and one recommended moderate intensity aerobic exercise for at least 3 h/week (35).

The risk of bias of randomised trials included in the systematic review is shown in Figure 2.

**Qualitative data synthesis**

**Weight/BMI and waist circumference**

All studies reported significant reductions in BMI and/or weight in overweight/obese women with PCOS (34–42) (Table 2). Six studies evaluated waist circumference, and five showed significant reductions in waist or waist-to-hip ratio after orlistat treatment in women with PCOS (36,39–42). In addition, two studies comparing the effects of orlistat and metformin showed that both treatments equally reduced waist circumference in PCOS women (39,42).

**Insulin and HOMA**

While three studies found no changes in insulin resistance markers in PCOS women using orlistat (37,41,42), five studies did find significant decreases in HOMA and/or insulin levels (34–36,38,40) (Table 2).

**Testosterone levels**

All studies except one (40) reported a significant reduction in testosterone levels after orlistat treatment (Table 2).

**Menstrual cyclicity, ovulation rate and ovarian morphology at ultrasound**

The four studies assessing menstrual cycles and/or ovarian morphology found no improvements in oligo/amenorrheic cycles or ovarian morphology at ultrasound (35,36,40,41) with either orlistat or metformin. Two other studies have assessed ovulation rates (39,42). Ghandi et al. (39) compared ovulation rates only after (and not before) the intervention with orlistat or metformin, but did not observe differences between groups. Kumar and Arora (42) also assessed ovulation rates after the intervention and found improved ovulation rates in the orlistat and metformin groups in comparison with the control group, with no differences between orlistat and metformin users.

**Lipid profile**

Five studies assessed lipid profile after orlistat treatment (35,37,39,41,42) and four reported improvement in triglycerides and in LDL- and HDL-cholesterol (35,39,41,42). Jayagopal et al. (37) observed no changes in lipid profile after orlistat treatment.

Three studies compared the effects of orlistat and metformin in lipid profile. Two found similar effects with both treatments (37,42) and one reported that
| Study                                      | Length (weeks) | Baseline | After treatment | Delta (%) ± SEM | p     | Baseline | After treatment | Delta (%) ± SEM | p     | Unit        |
|--------------------------------------------|----------------|----------|----------------|----------------|-------|----------|----------------|----------------|-------|-------------|
| **BMI**                                   |                |          |                |                |       |          |                |                |       |             |
| Cho et al., 2009 (38)                      | 12             | 37.40 ± 2.70 | 35.20 ± 2.40  | (−5.70) ± 0.80 | < 0.05| 34.30 ± 1.80 | 33.20 ± 1.90  | (−3.40) ± 1.00 | < 0.05| kg/m²       |
| Diamanti-Kandarakis et al., 2007 (34)      | 12             | 35.43 ± 5.31 | 31.52 ± 4.80  | < 0.001        |       |          |                |                |       |             |
| Diamanti-Kandarakis et al., 2007 (34)      | 24             | 35.43 ± 5.31 | 29.70 ± 4.57  | < 0.001        |       |          |                |                |       |             |
| Ghandi et al., 2011 (39)                   | 12             | 34.88 ± 4.90 | 33.24 ± 4.19  | (−4.48) ± 0.47 | < 0.001| 34.30 ± 2.40 | 33.03 ± 3.43  | (−3.56) ± 0.70 | < 0.001| kg/m²       |
| Jayagopal et al., 2005 (37)                | 12             | 33.70 ± 6.60 | 29.90 ± 6.40  | < 0.001        |       |          |                |                |       |             |
| Koivu et al., 2013 (40)                    | 24             | 34.90 ± 5.90 | 30.40 ± 5.80  | < 0.001        |       |          |                |                |       | kg/m²      |
| Kumar and Arora, 2014 (42)                 | 12             | 34.90 ± 5.90 | 30.40 ± 5.80  | < 0.001        |       |          |                |                |       | kg/m²      |
| Moini et al., 2015 (41)                    | 12             | 29.10 ± 2.09 | 27.16 ± 1.93  | < 0.001        |       |          |                |                |       | kg/m²      |
| Spanos et al., 2012 (36)                   | 24             | 34.90 ± 5.90 | 30.40 ± 5.80  | < 0.001        |       |          |                |                |       | kg/m²      |
| **HOMA**                                  |                |          |                |                |       |          |                |                |       |             |
| Cho et al., 2009 (38)                      | 12             | 5.00 ± 0.80  | 3.70 ± 0.50   | (−19.70) ± 6.40| 0.013 | 3.60 ± 0.50 | 3.10 ± 0.60   | (−16.10) ± 6.80| 0.170| kg/m²      |
| Diamanti-Kandarakis et al., 2007 (34)      | 12             | 4.75 ± 2.48  | 3.10 ± 1.68   | 0.008          |       |          |                |                |       |             |
| Diamanti-Kandarakis et al., 2007 (34)      | 24             | 4.75 ± 2.48  | 2.67 ± 1.23   | 0.006          |       |          |                |                |       |             |
| Ghandi et al., 2011 (39)                   | 12             | 4.32 ± 1.20  | 3.58 ± 0.70   | (−10.80) ± 6.00| > 0.05| 4.27 ± 0.60 | 4.09 ± 0.70   | (−7.19) ± 8.40| > 0.05| kg/m²      |
| Jayagopal et al., 2005 (37)                | 12             | 4.39 ± 2.34  | 2.97 ± 2.74   | 0.002          |       |          |                |                |       |             |
| Koivu et al., 2013 (40)                    | 24             | 4.39 ± 2.34  | (10.56) ± 7.45| > 0.05         |       |          |                |                |       |             |
| Kumar and Arora, 2014 (42)                 | 12             | 3.46 ± 1.99  | 3.43 ± 1.11   | 0.430          |       |          |                |                |       |             |
| Moini et al., 2015 (41)                    | 12             | 4.78 ± 3.12  | 2.97 ± 1.59   | 0.001          |       |          |                |                |       |             |
| Pandis et al., 2014 (35)                   | 12             | 4.78 ± 3.12  | 2.97 ± 1.59   | 0.001          |       |          |                |                |       |             |
| Pandis et al., 2014 (35)                   | 24             | 4.78 ± 3.12  | 2.72 ± 1.85   | < 0.001        |       |          |                |                |       | kg/m²      |
| Spanos et al., 2012 (36)                   | 24             | 4.85 ± 3.48  | 2.82 ± 2.08   | < 0.001        |       |          |                |                |       | kg/m²      |
| **Insulin**                                |                |          |                |                |       |          |                |                |       |             |
| Cho et al., 2009 (38)                      | 12             | 23.60 ± 3.90 | 17.70 ± 2.30  | (−18.40) ± 5.60| < 0.05| 16.80 ± 2.30 | 15.10 ± 2.90  | (−12.80) ± 7.70| > 0.05| mUI/ml     |
| Diamanti-Kandarakis et al., 2007 (34)      | 12             | 127.37 ± 61.12 | 88.13 ± 47.36 | 0.014          |       |          |                |                |       | pmol/l     |
| Diamanti-Kandarakis et al., 2007 (34)      | 24             | 127.37 ± 61.12 | 76.40 ± 34.93 | 0.008          |       |          |                |                |       | pmol/l     |
| Ghandi et al., 2011 (39)                   | 12             | 19.00 ± 4.60 | 15.70 ± 8.00  | (−12.50) ± 5.80| 0.155 | 19.40 ± 2.50 | 18.20 ± 2.60  | (−1.20) ± 8.20| 0.527 | mUI/ml     |
| Jayagopal et al., 2005 (37)                | 12             | 17.30 ± 8.40 | 12.30 ± 10.60 | 0.004          |       |          |                |                |       | mUI/ml     |
| Koivu et al., 2013 (40)                    | 24             | 17.30 ± 8.40 | 8.35 ± 5.54   | > 0.05         |       |          |                |                |       | mUI/ml     |
| Kumar and Arora, 2014 (42)                 | 12             | 17.24 ± 6.49 | 17.20 ± 6.72  | 0.210          |       |          |                |                |       | mUI/ml     |
| Moini et al., 2015 (41)                    | 12             | 18.70 ± 10.80 | 12.40 ± 6.40  | < 0.001        |       |          |                |                |       | mUI/ml     |
| Pandis et al., 2014 (35)                   | 12             | 18.70 ± 10.80 | 11.30 ± 7.10  | < 0.001        |       |          |                |                |       | mUI/ml     |
| Pandis et al., 2014 (35)                   | 24             | 18.70 ± 11.70 | 11.50 ± 8.00  | < 0.001        |       |          |                |                |       | mUI/ml     |
| Spanos et al., 2012 (36)                   | 24             | 18.70 ± 11.70 | 11.50 ± 8.00  | < 0.001        |       |          |                |                |       | mUI/ml     |
orlistat was more effective in reducing total cholesterol than metformin (39).

Side effects
Four studies described side effects of orlistat. Cramping and oily stool were reported in 5%, 20% and 22% of participants respectively for Ghandi et al. (39), Jayagopal et al. (37) and Moini et al. (41). Jayagopal et al. (37) reported mild to moderate flatulence in 20% of participants. Occasional diarrhoea with faecal urgency was observed by Diamanti-Kandarakis (34) in 43% of participants and by Moini et al. (41) in 54%. Moini et al. (41) also observed headaches in 3% of the sample.

Quantitative data synthesis and meta-analysis
A meta-analysis was performed to compare the effects of orlistat vs. metformin on BMI, HOMA, testosterone and insulin levels (Figure 3). Fixed effects models were used because heterogeneity was not significant. The main results obtained in the three studies included in this meta-analysis (37–39) are presented in Table 2. One of the four RCTs comparing orlistat vs. metformin in PCOS women was excluded because data on baseline and final results were not available (42).

It was not possible to meta-analyse the effect of orlistat vs. placebo on clinical variables associated with weight loss because we found only one study comparing orlistat with placebo. Similarly, a meta-analysis of orlistat effects described in three prospective, non-controlled studies (before and after-treatment comparisons) (34–36) and three RCTs (40–42) was not performed because neither the measure of variability (% change) nor baseline and after-treatment values were available.

Weight/BMI
Data from two studies were available for BMI (38,39), totalising 100 women with PCOS. Orlistat and metformin produced similar BMI reduction (−0.65%, 95% CI: −2.03 to 0.73). Between-study heterogeneity was moderate ($I^2 = 58.1\%$, $p = 0.1222$).

HOMA
HOMA was analysed in two studies (37,38), totalising 41 women with PCOS. Orlistat and metformin produced similar reductions in HOMA (−3.60%, 95% CI: −16.99 to 9.78). Between-study heterogeneity was low ($I^2 = 0\%$, $p = 0.9994$).

Testosterone
Testosterone data were available from two studies (37,39), totalising 101 women with PCOS. A similar

| Study | Orlistat | Metformin | Length (weeks) | After treatment | Delta (%) | SEM | p | Baseline | After treatment | Delta (%) | SEM | p |
|-------|---------|-----------|---------------|---------------|-----------|-----|---|---------|---------------|-----------|-----|---|
| Cho et al., 2009 (38) | 12 | 3.01 ± 0.94 | 2.44 ± 0.91 | 0.57 | 0.001 | <0.001 | <0.001 | <0.001 |
| Diamanti-Kandarakis et al., 2007 (34) | 12 | 3.01 ± 0.94 | 2.28 ± 0.65 | 0.73 | 0.001 | <0.001 | <0.001 | <0.001 |
| Ghandi et al., 2011 (39) | 12 | 0.80 ± 0.26 | 0.63 ± 0.22 | 0.17 | 0.001 | <0.001 | <0.001 | <0.001 |
| Jayagopal et al., 2005 (37) | 12 | 1.14 ± 0.91 | 0.93 ± 1.10 | 0.21 | 0.001 | <0.001 | <0.001 | <0.001 |
| Koiou et al., 2013 (40) | 12 | 6.10 ± 2.92 | 0.63 ± 0.91 | 0.07 | 0.001 | <0.001 | <0.001 | <0.001 |
| Kumar and Arora, 2014 (42) | 12 | 0.28 ± 0.48 | 0.26 ± 0.42 | 0.02 | 0.001 | <0.001 | <0.001 | <0.001 |
| Moini et al., 2015 (41) | 12 | 0.63 ± 1.63 | 0.63 ± 1.63 | 0.00 | 0.001 | <0.001 | <0.001 | <0.001 |
| Panidis et al., 2014 (35) | 12 | 0.63 ± 2.40 | 0.63 ± 2.40 | 0.00 | 0.001 | <0.001 | <0.001 | <0.001 |
| Panidis et al., 2014 (35) | 24 | 0.63 ± 2.40 | 0.63 ± 2.40 | 0.00 | 0.001 | <0.001 | <0.001 | <0.001 |
| Spanos et al., 2012 (36) | 24 | 0.63 ± 2.40 | 0.63 ± 2.40 | 0.00 | 0.001 | <0.001 | <0.001 | <0.001 |
reduction in testosterone levels was achieved with orlistat and metformin (−2.08%, 95% CI: −13.08 to 8.93). Between-study heterogeneity was low ($I^2 = 0\%$, $p = 0.9976$).

**Insulin**

Two studies reported data for insulin (37,38), totalling 41 women with PCOS. A similar reduction in insulin levels was achieved with orlistat and metformin (−5.51%, 95% CI: −22.27 to 11.26). Between-study heterogeneity was low ($I^2 = 0\%$, $p = 0.982$).

**Discussion**

To the best of our knowledge, this is the first systematic review investigating the effects of orlistat in women with PCOS. Although only a few studies were identified, there is an agreement regarding the ability of orlistat to reduce BMI/weight in women with PCOS. In addition, most of the studies, but not all, found that orlistat treatment is associated with reduction in androgens and with improvement in insulin resistance (IR) markers and lipid profile. Our meta-analysis including three RCTs and 121 PCOS women showed that orlistat was comparable to metformin in reducing BMI, HOMA, testosterone and insulin in overweight/obese PCOS women.

**Systematic review**

Our systematic review revealed that orlistat was associated with BMI reduction after 12 (ranging from 4.48% to 8.10%) and 24 weeks (12.9%) in women with PCOS. The XENDOS study, a prospective clinical trial with obese patients from the general population, found that orlistat (120 mg three times daily) produced significantly higher weight loss as compared with placebo in 4 years (5.2% vs. 2.8%) (25).

Currently, guidelines for the treatment of obesity in the general population recommend an initial weight loss of 5–10% within 6 months (43). Moderate weight loss can produce health benefits, including improved glycaemic control and lipid profile and reduced risk of DM2 (44–47). Studies have shown improvement in menstrual cyclicity and a higher spontaneous ovulation rate and pregnancy in obese women with PCOS following a 5% decrease in body weight (48–54).

Regarding the effects of orlistat on markers of IR, five of eight studies showed a positive response, while three others found no significant improvement in these parameters (37,41,42). A difference in treatment duration may, however, help explain this discrepancy: the two studies that did not find significant changes in IR markers lasted only 12 weeks, whereas those with longer duration observed a significant effect of orlistat. In addition, the lack of statistical significance despite a marked reduction in fasting insulin (12.5%) and HOMA (10.8%) in the study of Jayagopal et al. (37) might have resulted from the small sample size, only 10 patients. In turn, Diamanti-Kandarakis et al. (34) showed that there were significant improvements in IR markers with orlistat regardless of weight loss only in the PCOS group.

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**Figure 3** Forrest plot showing the impact of orlistat and metformin on body mass index (BMI), homoeostasis model assessment (HOMA) estimates, testosterone and insulin levels in women with PCOS

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| Outcome | Study | Total | Mean | SD | Total | Mean | SD | Mean difference | MD | 95%–CI |
|---------|-------|-------|------|----|-------|------|----|-----------------|----|--------|
| BMI     | Cho 2009 (38) | 10 | −5.70 | 2.53 | 10 | −3.40 | 3.16 | −2.30 | −4.81; 0.21 |
|         | Ghandi 2011 (39) | 40 | −4.48 | 2.97 | 40 | −4.55 | 4.43 | 0.07 | −1.58; 1.72 |
|         | Fixed effect model | 50 | 0.00 | 50 | 0.00 | 50 | 0.00 | −0.65 | −2.03; 0.73 |
| Heterogeneity: $I^2$-squared = 58.2%, tau-squared = 1.634, $p = 0.1221$ |
| HOMA    | Cho 2009 (38) | 10 | −19.70 | 20.24 | 10 | −16.10 | 21.50 | −3.60 | −21.90; 14.70 |
|         | Jayagopal 2005 (37) | 10 | −10.80 | 18.97 | 11 | −7.19 | 26.56 | −3.61 | −23.22; 16.00 |
|         | Fixed effect model | 20 | 0.00 | 21 | 0.00 | 21 | 0.00 | −3.60 | −16.96; 9.78 |
| Heterogeneity: $I^2$-squared = 0%, tau-squared = 0, $p = 0.9994$ |
| INSULIN | Cho 2009 (38) | 10 | −18.40 | 17.71 | 10 | −12.80 | 24.35 | −5.60 | −24.26; 13.06 |
|         | Jayagopal 2005 (37) | 10 | −12.50 | 36.68 | 11 | −7.39 | 51.86 | −5.11 | −43.27; 33.05 |
|         | Fixed effect model | 20 | 0.00 | 21 | 0.00 | 21 | 0.00 | −5.51 | −22.27; 11.26 |
| Heterogeneity: $I^2$-squared = 0%, tau-squared = 0, $p = 0.982$ |
| TESTOSTERONE | Cho 2009 (38) | 10 | −19.37 | 22.26 | 10 | −17.30 | 33.52 | −2.07 | −14.54; 10.40 |
|         | Jayagopal 2005 (37) | 10 | −16.80 | 22.45 | 11 | −14.69 | 31.84 | −2.11 | −25.51; 21.29 |
|         | Fixed effect model | 50 | 0.00 | 51 | 0.00 | 51 | 0.00 | −2.08 | −13.08; 8.93 |
| Heterogeneity: $I^2$-squared = 0%, tau-squared = 0, $p = 0.9976$ |
In the present review, seven of eight studies (34–37,39,41,42) showed a decrease in testosterone levels in association with orlistat administration. Even though a reduction in BMI and IR markers was observed in these studies, the decrease in testosterone levels reported by Diamanti-Kandarakis et al. (34) cannot be attributed exclusively to weight reduction, because it persisted even after adjustment for changes in BMI.

None of the studies we analysed was able to demonstrate any improvement in menstrual regularity, ovarian volume or number of follicles with the use of orlistat. However, longer duration studies are needed to investigate the benefits of weight reduction, improved insulin resistance and androgen levels to restore or ameliorate menstrual cyclicity. Among the five studies describing the effect of intervention with orlistat on lipid profile (35,37,39,41,42), only one was unable to show a significant beneficial effect (37), possibly because of the small sample size. The prospective XENDOS study observed that orlistat led to significantly greater improvement than placebo in total cholesterol and LDL-cholesterol after 4 years of treatment in the general population (25).

The main side effects described for orlistat were related to the drug’s mechanism of action of decreasing fat absorption from the intestinal lumen – oily stool, flatulence and diarrhoea with faecal urgency occurring in around 5–40% of participants (34,37,39,41). In contrast, although not directly assessed in the present review, the side effects of metformin (nausea, mild abdominal pain and diarrhoea) are known to be dose-dependent (22,37,39).

**Meta-analysis**

Weight loss is considered the first-line treatment for obese PCOS women. Anti-obesity drugs have also been considered for these women. Orlistat promotes weight loss by partially preventing intestinal fat absorption (55,56). Metformin improves insulin action and has been considered a second-line treatment for obese and/or insulin-resistant PCOS women (19–24). Thus, the present meta-analysis was conducted to analyse the evidence for the differential effects of orlistat vs. metformin treatment on weight loss-associated clinical variables in overweight/obese women with PCOS.

The results of the present meta-analysis show that orlistat was comparable to metformin in reducing BMI. A recently published meta-analysis with more than 11,000 overweight/obese individuals from the general population showed that the use of metformin together with lifestyle change promoted a weight reduction of 1.92 kg (2.94–0.89; p = 0.11), while orlistat plus lifestyle change reduced weight by 3.05 kg (3.75–2.35; p = 0.0001); however, when the two drugs were compared, the difference was not statistically significant (p = 0.07) (57).

We did not observe a difference between metformin and orlistat in terms of insulin and HOMA reduction. Merlotti et al. (58) recently reported an effect of various interventions in reducing the risk of DM2 in obese individuals. All strategies assessed in that meta-analysis reduced the risk of developing DM2. Similar effectiveness was found for physical activity and diet (OR 0.44 (0.36–0.52)), antidiabetic drugs (metformin, glitazones, glinides, alpha-glucosidase inhibitors) [OR 0.53 (0.33–0.86)] and weight loss-promoting drugs (orlistat, bezafibrate, phentermine/topiramate controlled release) [OR 0.52 (0.35–0.78)].

Evidence indicates that weight reduction in PCOS improves hyperlipidaemia, reduces IR and increases SHBG concentration, thereby reducing biochemical hyperandrogenism and improving menstrual cyclicity (54,59,60). In the present meta-analysis, the lack of difference between the effect of metformin or orlistat on testosterone levels might be related to the lack of difference between these drugs in terms of their effect on weight loss.

We observed significant heterogeneity in the analysis of BMI. This heterogeneity limits the interpretation of data and suggests similar effects of orlistat and metformin. The analyses of HOMA, insulin and testosterone levels revealed very low heterogeneity between studies. In turn, as a result of the limited number of studies, we were not able to determine whether there was publication bias.

One strength of this systematic review and meta-analysis is that all studies considered the Rotterdam criteria to di- agnose PCOS, with the exception of one study, which employed NIH criteria. Therefore, the PCOS population was certainly homogeneous. Limitations of this meta-analysis are the reduced number of studies, the small sample sizes and the absence of studies with long-term interventions. However, similar analyses are not available in the literature, and this study represents the first evidence for orlistat effects in women with PCOS.

**Conclusion**

In conclusion, the present data suggest that orlistat leads to significant reduction in weight/BMI in overweight/obese PCOS women. Most studies also reported that orlistat significantly reduced testosterone and IR markers and improved lipid profile. Regarding our meta-analysis, the evidence produced is not entirely conclusive because only three RCTs with small samples were identified. Therefore, the observed similarity between orlistat and metformin
to improve BMI, HOMA, insulin and testosterone levels in PCOS should be considered with caution, and more studies are needed to confirm this data.

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**Author contributions**

Scheila K Graff: data collection, analysis/interpretation, drafting of article, critical revision of article. Fernanda M Mario: data collection, critical revision of article. Patrícia Ziegelmann: data analysis/interpretation, drafting of article, critical revision of article. Poli Mara Spritzer: concept/design, data analysis/interpretation, drafting of article, securing funding, critical revision of article. All authors read and approved the final manuscript.

**References**

1. Azziz R, Carmina E, Dewailly D et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril* 2009; 91(2): 456–88.

2. Wild RA, Carmina E, Diamanti-Kandarakis E et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab* 2010; 95(5): 2038–49.

3. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escober-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2008; 88(7): 2434–4.

4. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet* 2007; 370 (9588): 685–97.

5. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman’s long-term health using data linkage. *J Clin Endocrinol Metab* 2015; 100(3): 911–9.

6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004; 89(9): 2745–9.

7. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010; 25: 544–51.

8. Haqqi L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. *Endocr Connect* 2014; 3(1): 36–46.

9. Azziz R, Sanchez LA, Knochenhauer ES et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 2004; 89(2): 453–62.

10. Diamanti-Kandarakis E, Spritzer PM, Sir-Petermann T, Motta AB. Insulin resistance and polycystic ovary syndrome through life. *Curr Pharm Des* 2012; 18(34): 5569–76.

11. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2012; 18(6): 618–37.

12. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2011; (7): CD007506.

13. Toscani MK, Mario FM, Radavelli-Bagatini S, Wilgen D, Matos MC, Spritzer PM. Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. *Gynecol Endocrinol* 2011; 27(11): 925–30.

14. Carmina E, Buccheri S, Esposito A et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. *J Clin Endocrinol Metab* 2007; 92(7): 2500–5.

15. Wilgen D, Spritzer PM. Variation in metabolic and cardiovascular risk in women with different polycystic ovary syndrome phenotypes. *Fertil Steril* 2010; 94(6): 2493–5.

16. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* 2009; 92(6): 1966–82.

17. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. *Minerva Endocrinol* 2015; 40(3): 195–212.

18. Panidis D, Tzimolas K, Papadakis E, Vosnakis C, Chatzis P, Katsikis I. Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome. *Endocrine* 2013; 44(3): 583–90.

19. Chou KH, von Eye Corleta H, Capp E, Spritzer PM. Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: a randomized, double-blind and placebo-controlled trial. *Horm Metab Res* 2003; 35(2): 86–91.

20. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Hum Reprod Update* 2015; 21: 560–74.

21. De Sloover Koch Y, Ernst ME. Use of metformin in response to metformin in obese women with primary hyperlipidaemia. *Eur J Clin Pharmacol* 1994; 46(5): 405–10.

22. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; 327(7412): 951–3.

23. Nestler JE, Jakubowicz DJ, de Vargas AF, Bikri C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J Clin Endocrinol Metab* 1998; 83(6): 2001–5.

24. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, Rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 2003; 3: CD003053.

25. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27(1): 155–61.

26. Bucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 2007; 335 (7631): 1194–9.

27. Sjöström L, Rissanen A, Andersen T et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *European Multicentre Orlistat Study Group. Lancet* 1998; 352(9123): 167–72.

28. Davidson MH, Hauptman J, DiGirolamo M et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomised controlled trial. *JAMA* 1999; 281(3): 235–42.

29. Tonstad S, Pometta D, Erkelens DW et al. The effect of the gastrointestinal lipase inhibitor, orlistat, on serum lipids and lipoproteins in patients with primary hyperlipidaemia. *Eur J Clin Pharmacol* 1994; 46(5): 405–10.

30. Rissanen A. Pharmacological intervention: the antiobesity approach. *Eur J Clin Invest* 1998; 28 (Suppl 2): 27–30.

31. Group REA-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; 19(1): 41–7.

32. Zawadzki JF, Dunaf J. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaf JR, Givens FB, Haseltine GR, Merriam A, eds. *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific, 1992: 377–84.
43 Jensen MD, Ryan DH, Avoxian CM et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2013; 129(25 Suppl 2): S102–38.

44 Lindström J, Peltonen M, Eriksson JG et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia 2013; 56(2): 284–93.

45 Li G, Zhang P, Wang J et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008; 371(9622): 1783–9.

46 Unick JL, Beavers D, Bond DS et al. The long-term effectiveness of a lifestyle intervention for severely obese individuals. Am J Med 2013; 126(3): 236–42, 42.e1–2.

47 Gregg EW, Chen H, Wagenknecht LE et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012; 308(23): 2489–96.

48 Cossignani PG, Colombo M, Veggetti W, Somigliana E, Gesati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 2003; 18(9): 1928–32.

49 Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 2004; 10(5): 267–80.

50 Mahoney D. Lifestyle modifications in obesity change body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008; 93(9): 3373–80.

51 Clark AM, Ledger W, Gallyer C et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 1995; 10: 2705–12.

52 Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Hum Reprod 1996; 11(9): 1884–91.

53 Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and leuteinizing hormone. J Clin Endocrinol Metab 1999; 84(4): 1470–4.

54 Dixon JB. Weight loss medications—where do they fit in? Aust Fam Physician 2006; 35(8): 576–9.

55 Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet 2007; 369(9555): 71–7.

56 Peirson L, Douketis J, Ciliska D, Fitzpatrick-Lewis D, Ali MU, Raina P. Treatment for overweight and obesity in adult populations: a systematic review and meta-analysis. CMAJ Open 2014; 2(4): E306–17.

57 Merlotti C, Morabito A, Ceriani V, Pontiroli AE. Prevention of type 2 diabetes in obese at-risk subjects: a systematic review and meta-analysis. Acta Diabetol 2014; 51(5): 853–63.

58 Andersen P, Seljeflot I, Abdelnoor M et al. Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. Metabolism 1995; 44(5): 611–6.

59 Hamilton-Fairley D, Kidday D, Anyaoku V, Koistinen R, Seppälä M, Franks S. Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. Clin Endocrinol (Oxf) 1993; 39(3): 363–7.

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