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REVIEW

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Anti-obesity pharmacological agents for polycystic ovary syndrome: A systematic review and meta-analysis to inform the 2023 international evidence-based guideline

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Summary

This systematic review and meta-analysis evaluated the efficacy of anti-obesity agents for hormonal, reproductive, metabolic, and psychological outcomes in polycystic ovary syndrome (PCOS) to inform the 2023 update of the International Evidence-based Guideline on PCOS. We searched Medline, EMBASE, PsycInfo, and CINAHL until July 2022 with a 10-year limit to focus on newer agents. Eleven trials (545 and 451 participants in intervention and control arms respectively, 12 comparisons) were included. On descriptive analyses, most agents improved anthropometric outcomes; liraglutide, semaglutide and orlistat appeared superior to placebo for anthropometric outcomes. Meta-analyses were possible for two comparisons (exenatide vs. metformin and orlistat + combined oral contraceptive pill [COCP] vs. COCP alone). On meta-analysis, no differences were identified between exenatide versus metformin for anthropometric, biochemical hyperandrogenism, and metabolic outcomes, other than lower fasting blood glucose more with metformin than exenatide (MD: 0.10 mmol/L, CI 0.02–0.17, $I^2 = 18\%$, 2 trials). Orlistat + COCP did not improve metabolic outcomes compared with COCP alone (fasting insulin MD: −8.65 pmol/L, −33.55 to 16.26, $I^2 = 67\%$, 2 trials). Published data examining the effects of anti-obesity agents in women with PCOS are very limited. The role of these agents in PCOS should be a high priority for future research.

KEYWORDS
anti-obesity agents; GLP1 receptor agonists, meta-analysis; polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common metabolic and reproductive condition affecting females of reproductive age.[1] The complex interaction of altered hypothalamic–pituitary–ovarian function and

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concomitant hyperinsulinemia/insulin resistance with promotion of androgen excess underlie the pathophysiology of PCOS.[2] Characterized by heterogeneous features including reproductive, psychological, and metabolic sequelae, PCOS has been diagnosed applying the Rotterdam Criteria over the past two decades requiring two of three features (hyperandrogenism, ovulatory dysfunction, and/or polycystic ovarian morphology), after excluding other mimicking conditions.[3] Since this time in both 2018 and 2023, diagnosis has been upgraded from consensus-based Rotterdam criteria to International evidence-based Guideline PCOS criteria, endorsed by 40 Societies internationally. This differentiated adolescent and adult criteria defined each component of the criteria and included Anti-Mullerian Hormone as an alternative to ultrasonography for determining polycystic ovarian morphology.[4] Due to the increased risk for obesity, diabetes, metabolic pregnancy complications, cardiovascular disease,[5] and sleep apnea among individuals with PCOS, prevention of adverse metabolic consequences is crucial.[6]

The association between obesity and PCOS is complex and bidirectional.[7] Obesity genes are noted on genetic studies in PCOS, and cluster analyses, alongside epidemiological and longitudinal studies, show that obesity is increased in PCOS, is causal of PCOS, and exacerbates PCOS clinical features and as such is common in women with PCOS presenting to the clinic.[8,9] Weight loss is recommended as part of management in individuals with PCOS with higher body mass index (BMI), with weight reduction shown to improve reproductive and metabolic consequences of PCOS.[10–12] However, lifestyle modifications, including diet and exercise, are challenging to maintain and often insufficient to lead to meaningful weight loss.[13]

Pharmacotherapy is recommended in the general population, as an adjunct to lifestyle approaches to optimize weight loss success and efficacy in obesity. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) including liraglutide, exenatide, or semaglutide are indicated for both weight loss and type 2 diabetes treatment. Predominantly studied in individuals with BMI ≥ 30 kg/m^2, these agents have been shown to promote weight loss by a variety of mechanisms, including suppression of post prandial glucagon, inhibition of glucose production, slowed gastric emptying, and increased satiety to reduce food intake.[14] Orlistat is a long acting reversible pancreatic lipase inhibitor that is designed to reduce absorption of digestive fat, increasing fecal fat excretion.[15] Phentermine and topiramate are central acting medications that have been approved in some countries for management of obesity based on their appetite reducing properties, which occur through their effects on γ-Aminobutyric Acid (GABA) receptors and increasing norepinephrine in the hypothalamus.[16] Centrally acting anti-obesity agents, including naltrexone/bupropion and locarserin, target hypothalamic brain signaling as well as dopamine[17] and serotonin receptors,[18] respectively, to diminish food intake. In PCOS, metformin was recommended in the 2018 International Evidence-based Guidelines on PCOS as an adjunct to lifestyle management for treatment of weight, hormonal and metabolic outcomes,[3] with a focus on prevention of weight gain, noting limited efficacy for weight loss.[19–21] The need for alternative pharmacotherapies as adjunctive treatments to promote weight loss in PCOS is a key priority with weight gain a primary concern expressed by those with the condition. Although none of the anti-obesity agents outlined here have been approved for PCOS alone, their effects on weight loss and insulin resistance make them potentially important future PCOS therapies.

To clarify their potential utility in PCOS, and in the context of informing the 2023 update of the International evidence-based PCOS Guideline, the aim of this systematic review and meta-analysis was to evaluate the efficacy of anti-obesity pharmacological agents alone, or in combination, for the management of hormonal, reproductive, metabolic, and psychological outcomes in adolescents and adults with PCOS, with a focus on newer anti-obesity agents.

2 | METHODS

2.1 | Study design

This systematic review protocol was prospectively registered with PROSPERO (CRD42022347314) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] The review was intended to inform recommendations for the following clinical question: "Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?" This clinical question was prioritized by consumers, content experts within the guideline development group, and the expert evidence synthesis team, who devised eligibility criteria using the patient, intervention, comparison, and outcome (PICO) framework outlined below.

2.2 | Search strategy and selection criteria

The search strategy and selection criteria were developed by an international team of evidence synthesis experts and clinical leads (key contacts) including endocrinologists and a general practitioner (family physician). We searched Medline (OVID), EMBASE (OVID), PsycInfo (EBSCO), and CINAHL (EBSCO) on July 22, 2022 with a limit set for 10 years in order to focus the review on newer agents. We searched reference lists of relevant systematic reviews, and the key contact team reviewed the final list of included randomized controlled trials (RCTs) to ensure no important trials were missing. The search strategy included terms for PCOS, anti-obesity medications, and RCTs (see Appendix A). Citations were imported into Covidence,[23] wherein duplicates were removed. Two reviewers (AG, CE) independently screened titles and abstracts and then full-text manuscripts using Covidence web-based software, and disagreements were resolved by discussion, with a third reviewer to adjudicate if needed. Data were extracted on study characteristics, participant characteristics at baseline, intervention, and outcomes, using a data extraction template created by the guideline evidence team. Data were extracted by

independent reviewers (AG, CE, SG, VR, JL) in duplicate, with any disagreements resolved by discussion.

Inclusion criteria using the Participants-Interventions-Comparators-Outcomes (PICO) framework were as follows: (1) participants: individuals with PCOS diagnosed by Rotterdam, original National Institutes of Health (NIH) or Androgen Excess and Polycystic Ovary Syndrome society (AE-PCOS) criteria of any age, ethnicity or weight; (2) intervention: anti-obesity pharmacological agents (including, but not limited to, orlistat, GLP-1 RAs, phentermine/topiramate, lorcarserin, or naltrexone/bupropion), provided for a minimum of 3 months, alone or in combination with lifestyle, metformin, the combined oral contraceptive pill (COCP) or anti-androgens; (3) comparison: placebo or any other intervention listed in the intervention or combinations of those listed in the intervention; (4) outcomes: hormonal, metabolic, lipids, psychological, or anthropometric outcomes, and adverse effects (see Appendix B for full list of eligible outcomes). Only RCT designs were eligible for inclusion, and crossover trials were included only for the phase before the crossover. Quasi-randomized trials, conference abstracts, and any trials not published in English were excluded.

2.3 | Integrity assessment

Trial integrity was assessed by the Research Integrity Team following the "Research Integrity in Guideline Development (RIGID)" framework developed by Mousa et al. (2023; unpublished), as detailed in Section 6.7 of the guideline technical report.[24] Here, studies were assessed using the Trustworthiness in Randomised Controlled Trials (TRACT) checklist,[25] an integrity assessment tool based on the Cochrane Research Integrity Assessment tool,[26] which classifies studies on multiple domains related to integrity. Following this process, studies were classified as low, moderate, or high risk for integrity concerns. Low-risk studies were included, and authors for moderate- and high-risk studies were contacted to clarify integrity concerns. Where a satisfactory response was received, those studies were subsequently "included." Studies with no response were "not included," whereas studies requiring additional time to provide the necessary information (e.g., raw data and ethics protocols) are "awaiting classification" and have not been included in the review or analysis at this stage.

2.4 | Quality appraisal

Risk of bias was assessed at the study-level (i.e., for each trial) independently by two reviewers (AG, CE, SG, VR, JL), with disagreements resolved by discussion. We used the Cochrane Risk of Bias 1 tool to assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases.

The quality of the evidence at the outcome-level was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach by CE, as outlined in the GRADE handbook.[27] The evidence can be downgraded from "high certainty" by one or two levels for serious or very serious limitations, respectively, for each of four main domains: risk of bias, indirectness of evidence, inconsistency and imprecision of effect estimates, and for other biases including potential publication bias.

2.5 | Data analysis

The following outcomes were rated as critical: modified Ferriman-Gallwey (mFG) score, free androgen index (FAI), homeostatic model assessment of insulin resistance (HOMA-IR), 2-h glucose after 75-g oral glucose tolerance test (OGTT), and BMI. The remaining outcomes were judged as important but not critical. Outcome data were extracted from original intention-to-treat results wherever possible or from per-protocol results if these were the only outcomes available. For trials that used the same assessment method and provided continuous data, we reported mean difference (MD) and 95% confidence intervals (CIs), converting units of measurement to standardized units where required. Where trials did not use the same assessment methods, we reported standardized mean differences (SMD) and 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic. Outcomes from individual studies were pooled using random-effects models. All statistical analyses were performed using Review Manager.[28] We had planned subgroup analyses to separate those who were in the post-menopausal stage, adolescents versus adults, and by BMI category but were unable to conduct these due to the small number of included trials.

3 | RESULTS

3.1 | Study characteristics

The PRISMA flowchart of study selection is presented in Figure 1. A total of 782 citations were identified, with 675 remaining after duplicates were removed. After title and abstract screening, 647 were excluded, and 28 full-text manuscripts were screened for eligibility. Six were excluded, and five are awaiting classification (see Appendices C and D) leaving 17 manuscripts[29–46] representing 11 trials and 996 participants. Four trials were included in meta-analyses.[30,31,35,46] Table 1 summarizes the characteristics of included studies. Six trials were conducted in China,[30,31,35,40,41,46] two in the United States,[29,32] one in Slovenia,[47] one in Iran,[42] and one in Denmark.[43] Sample sizes for arms relevant for this study ranged from 25[47] to 240[31] with a mean sample size of 91 participants.

One study compared five arms[29] (exenatide, dapagliflozin, dapagliflozin + exenatide, dapagliflozin + metformin, and phentermine-topiramate). We included data from two arms—exenatide and phentermine-topiramate—and excluded the three arms

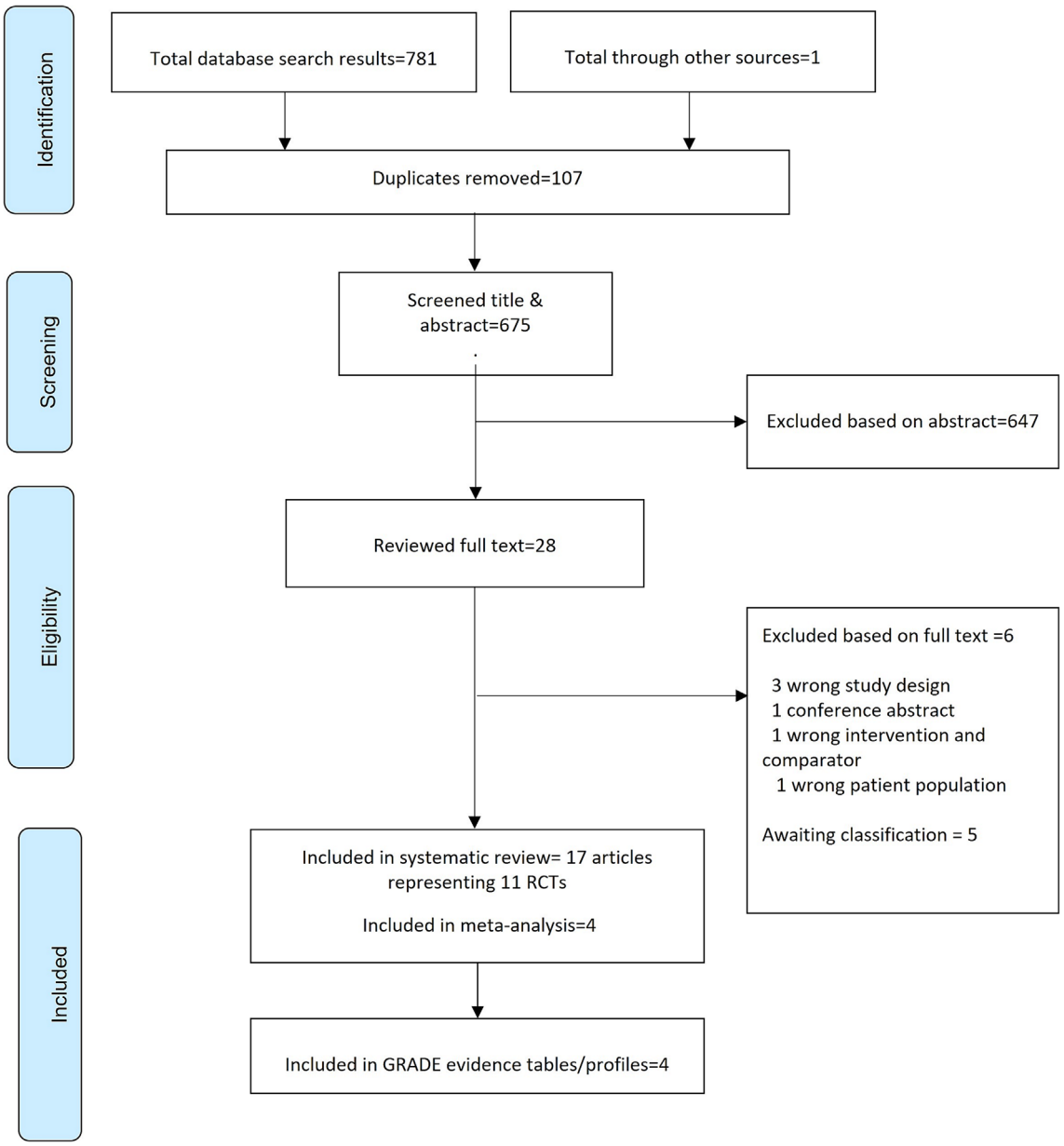


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study selection.

trialing dapagliflozin as dapagliflozin is classified as an oral hypoglycemic agent rather than anti-obesity drug. One study compared four arms[31] (orlistat + COCP + lifestyle, metformin + COCP + lifestyle, orlistat + metformin + COCP + lifestyle, and COCP + lifestyle), and another compared three arms[46] (exenatide, metformin, exenatide + metformin). All arms were included in these two studies.

3.2 | Participants

Eligibility criteria were adults with PCOS with a BMI in the overweight range or above with the exception of Nylander et al.,[43] who enrolled individuals who either had a BMI ≥ 25 kg/m^2 and/or insulin resistance (defined as fasting plasma C-peptide >0.6 nmol/L at screening). Overweight was generally classified as BMI ≥ 25 kg/m^2[41–43,46] or BMI ≥ 24 kg/m^2,[31,35,40] and one study did not define the BMI cut-off for overweight.[30] One study[31] required a concurrent diagnosis of insulin resistance, defined as fasting insulin >10 mIU/L, and another[46] required a diagnosis of prediabetes (defined as fasting plasma glucose 5.6–6.9 mmol/L and/or 2 h post glucose 7.8–11.0 mmol/L on OGTT).[46] One study[39,40] enrolled individuals who had also been diagnosed with infertility due to PCOS. We found no studies on adolescents.

Mean age ranged from 26.2 to 31.4 years and mean baseline BMI from 28.0 to 43.9 kg/m^2. Mean baseline BMI was in the overweight category (BMI ≥ 25 kg/m^2) in 5/11 studies,[30,31,35,40,42] Class I obesity category in 3/11 studies,[41,43,46] Class II obesity (BMI 35 to <40 kg/m^2) category in 2/11 studies,[29,47] and Class III obesity (BMI ≥ 40 kg/m^2) category in one study.[32]

TABLE 1 Characteristics of included studies.

Author, year, country, study design	Population/setting	Sample size per group	Intervention details	Comparison/control details	Co-interventions	Outcomes, follow-up duration
Elkind- Hirsch 2021, USA, single-blind five-arm RCT (data on two arms are provided)	Adult women with PCOS BMI 30–45 kg/m^2 Recruited from endocrine and weight loss clinic Mean/median BMI category: Obese Class II Mean age: EXE: 30y ± 1.1; PT: 30y ± 1.5	EXE 20 PT 16	Exenatide 2 mg weekly for 24 weeks	Phentermine 7.5 mg/topiramate 46-mg ER daily for 24 weeks	Lifestyle interventions: diet and exercise counseling, encouragement to increase daily exercise	Hormonal (FAI, TT, DHEAS) Metabolic (fasting glucose, HOMA-IR, Matsuda index: sensitivity index) Lipids (TC, LDL, HDL, TG) Anthropometric (weight, BMI, WHR, WC, body fat %, FM, FFM) AEs (GI, other) Follow-up: 24 weeks
Elkind-Hirsch 2022, USA, double-blind placebo-controlled RCT	Adult women with PCOS aged 18–45 BMI ≥ 30 kg/m^2 Recruited from outpatient Endocrinology and weight management clinic Mean/median BMI category: Obese Class III Mean age: NR	LIRA 44 Placebo 23	Liraglutide 3 mg daily for 32 weeks	Placebo (identical prefilled pen) for 32 weeks	Lifestyle interventions: diet of 500–800 kcal/day reduction made up of 50% carbohydrates, 20% proteins, and 30% of fat with increased consumption of fiber, whole grains, cereals, fruits, and vegetables; at least 30 min of moderate-intensity physical activity daily	Hormonal (FAI, TT, DHEA) Metabolic (fasting glucose, HOMA-IR, Matsuda) Lipids (TC, LDL, HDL, TG) Anthropometric (weight, BMI, WHR, WC, % 5% and 10% weight loss, FFM, FM, % body fat) Reproductive (menstrual cycles/year) AEs (GI, other) Follow-up: 32 weeks
Gu 2022, China, open-label RCT	Adult women with PCOS aged 18–40 BMI ≥ 24 kg/m^2 Recruited from department of gynecological endocrinology in a gynecological hospital Mean/median BMI category: Overweight Mean age: ORL: 29.67 y ± 2.53 OCP: 29.67 ± 2.36	ORL + lifestyle + COCP 33 Lifestyle + COCP alone 33	Orlistat 120 mg three times daily plus COCP and lifestyle for 12 weeks	COCP alone (DRSP 3 mg/EE 20 μg in a 24-active/4-inert pill regimen) and lifestyle for 12 weeks	Lifestyle interventions: personalized balanced nutrition diet based on the patient's resting energy expenditure	Hormonal (free/TT, SHBG) Metabolic (fasting glucose, FINS) Lipids (TC, HDL, LDL, TG) CRP Anthropometric (weight, BMI, WC, % body fat) Follow-up: 12 weeks

(Continues)

TABLE 1 (Continued)

Author, year, country, study design	Population/setting	Sample size per group	Intervention details	Comparison/control details	Co-interventions	Outcomes, follow-up duration
Jensterle 2021, Slovenia, single-blind placebo-controlled RCT	Adult women with PCOS BMI ≥ 30 kg/m^2 Recruited from an academic center Mean/median BMI category: Obese Class II Mean age: SEMA: 36.8 y ± 3.9 Placebo: 35.4 y ± 3.8	SEMA 13 Placebo 12	Semaglutide 1 mg weekly for 16 weeks	Placebo for 16 weeks	None	Metabolic (fasting glucose, FINS, HOMA-IR, 120-min glucose, and insulin) Lipids (TC, LDL, HDL, TG) Anthropometric (weight, BMI, WC, visceral body fat) AEs Follow-up: 16 weeks
Liu 2017/Li 2022, China, crossover open-label RCT	Adult women with PCOS aged 18–40 BMI ≥ 24 kg/m^2 Diagnosed with infertility Recruited from endocrinology department of hospital (outpatients) Mean/median BMI category: overweight Mean age: EXE: 27.93 y ± 2.7 MET: 27.69 y ± 3.8	EXE + COCP 78 MET + COCP 80 For reproductive outcomes: EXE 72 MET 75	Pregestational stage: Exenatide 5–10 μg twice daily for 12 weeks (5 μg twice daily for those who could not tolerate AEs) + lifestyle interventions + COCP Second stage: Metformin 1 g twice daily for 12 weeks or until pregnancy	Pregestational stage: Metformin 1 g twice daily for 12 weeks + lifestyle interventions + COCP Second stage: Metformin 1 g twice daily for 12 weeks or until pregnancy	Lifestyle interventions: diet and exercise were actively promoted in both groups according to international guidelines (ADA Standards of Medical Care 2018). COCP for first 12 weeks: low-dose hormonal contraceptive pill cyproterone and ethinyl estradiol ART as needed in second phase (ovulation induction for three cycles then IVF for one cycle)	Hormonal (FAI, TT, SHBG) Metabolic (fasting glucose, FINS, HOMA-IR, 120-min glucose, 120-min insulin) Lipids (TC, LDL-C, HDL-C, TG, hs-CRP) Anthropometric (weight, WC, BMI, WHR, % body fat) Reproductive (menstrual regularity, pregnancy rate, miscarriage rate, preterm delivery, live birth) Follow-up: 12 weeks (non-reproductive outcomes), 64 weeks (reproductive)
Ma 2021, China, open-label RCT	Adult women with PCOS BMI ≥ 25 kg/m^2 Recruited from department of gynecology and obstetrics Mean/median BMI category: Obese Class I Mean age: EXE + MET: 30.1 y ± 4.52 MET: 28.17 y ± 4.4	EXE + MET 19 MET 21	Exenatide 2 mg weekly + metformin 1.5 daily + COCP for 12 weeks	Metformin 1.5 g daily + COCP for 12 weeks	COCP: Diane-35 (ethinylestradiol 0.035 mg and cyproterone acetate 2 mg)	Hormonal (TT, DHEAS) Metabolic (fasting glucose, FINS, HOMA-IR, QUICKI, 120-min glucose, 120-min insulin, Matsuda index) Lipids (total cholesterol, LDL, HDL, TG) Hs-CRP Anthropometric (weight, BMI, WC) AEs (GI, other) Follow-up: 12 weeks

TABLE 1 (Continued)

Author, year, country, study design	Population/setting	Sample size per group	Intervention details	Comparison/control details	Co-interventions	Outcomes, follow-up duration
Moini 2015, Iran, double-blind placebo-controlled RCT	Adult women with PCOS BMI ≥ 25 kg/m^2 Recruited from university gynecology clinic Mean/median BMI category: Overweight Mean age: ORL: 26.8 y ± 5.16 Placebo: 27.42 y ± 3.31	ORL 43 Placebo 43	Orlistat 120 mg three times daily for 12 weeks	Placebo	Lifestyle interventions: hypocaloric diet, encouraged to walk 30 min/day	Hormonal (TT) Metabolic (fasting glucose, FINS, HOMA-IR) Lipids (LDL, HDL, TG) Anthropometric (weight, BMI, WHR) AEs Follow-up: 12 weeks
Nylander 2017/Nylander 2017/Frossing 2018/ Frossing 2018, Denmark, double-blind placebo-controlled RCT	Adult women with PCOS BMI ≥ 25 kg/m^2 and/or insulin resistance defined as fasting plasma C-peptide >0.6 nmol/L at screening Recruited from university hospital Mean/median BMI category: Obese Class I Mean age and range: LIRA: 31.4 y (24.6–35.6) Placebo 26.2 y (24.8–31.5)	LIRA 44 Placebo 21	Liraglutide 1.8 mg daily for 26 weeks	Placebo for 26 weeks	None	Hormonal (FAI, Free/TT, SHBG, A2) Metabolic (fasting glucose, Matsuda) Lipids (TC, LDL, HDL, TG) Hs-CRP Anthropometric (weight, BMI, WHR, WC, FFM, FM, % body fat) Reproductive (bleeding ratio) AEs (GI, other) Follow-up: 26 weeks
Song 2017, China, open-label four-armed RCT	Adult women with PCOS aged 18–40 BMI ≥ 24 kg/m^2 FINS > 10 mIU/L Recruited from gynecological endocrinology department in a university hospital Mean/median BMI category: overweight Mean age: ORL: 26.77 y ± 4.12 MET: 28.62 y ± 5.12 ORL + MET: 27.57 y ± 4.58 COCP alone 27.68 y ± 4.99	ORL 60 MET = 60 ORL + MET 60 COCP alone = 60	1. Orlistat 120 mg three times daily + COCP + lifestyle for 12 weeks 2. Orlistat 120 mg three times daily + metformin up to 1.5 daily + COCP + lifestyle for 12 weeks	1. Metformin up to 1.5 g daily + COCP + lifestyle for 12 weeks 2. Lifestyle + COCP alone for 12 weeks	Lifestyle interventions in all groups: based on each patient's basal energy requirements and on an estimation of the typical activity level, at baseline, a dietician prescribed an individualized low-fat diet, and moderate daily physical activity. COCP: Diane-35 (2-mg cyproterone acetate and 35-Ig ethinylestradiol) daily	Hormonal (FAI, free/TT, SHBG, DHEAS, A2) Metabolic (fasting glucose, FINS, HOMA-IR) Lipids (TC, HDL, LDL, TG) Anthropometric (weight, BMI, WC, FM, % body fat) AEs Follow-up: 12 weeks

(Continues)

TABLE 1 (Continued)

Author, year, country, study design	Population/setting	Sample size per group	Intervention details	Comparison/control details	Co-interventions	Outcomes, follow-up duration
Tao et al. 2021, China, three-arm open-label RCT	Adult women with PCOS BMI ≥ 25 kg/m^2 and diagnosed with prediabetes (fasting plasma glucose 5.6–6.9 mmol/L and/or 2 h post glucose 7.8–11.0 mmol/L on OGTT) Recruited from university teaching hospital Mean/median BMI category: Obese Class I Median (IQR) age: EXE: 28.0 y (25.00, 33.00) MET: 27.00 y (22.75, 31.00) EXE + MET: 28.00 y (21.75, 31.25)	EXE 50 MET 50 EXE + MET 50	Exenatide 10–20 μg daily for 12 weeks Exenatide 10–20 μg daily + metformin 1.5–2 g daily for 12 weeks	Metformin 1.5-2 g daily for 12 weeks	Guidance on diet and exercise	Hormonal (FAI, TT, SHBG, DHEAS, A2) Metabolic (fasting glucose, FINS, HOMA-IR, 120-min glucose) Lipids (TG, TC, HDL, LDL) Anthropometric (weight, BMI) AEs (GI, other)
Zheng 2017/Zheng 2019, China, open-label RCT	Adult women with PCOS aged 18–40 y Living with overweight/obesity (BMI not defined) Recruited from endocrinology department of hospital (outpatients) Mean/median BMI category: overweight Mean age: EXE: 27.7 y + 3.41 MET: 28.16 y ± 3.92	EXE 31 MET 32	Exenatide 10 μg twice daily for 12 weeks	Metformin 1 g twice daily for 12 weeks	Diet and exercise advice	Hormonal (mFG score, FAI, TT, SHBG, DHEAS) Metabolic (fasting glucose, FINS, HOMA-IR, 120-min glucose, 120-min insulin, AUC glucose, AUC insulin, Matsuda index [insulin secretion index (ISI)]) Lipids (TC, LDL-C, HDL-C, TG) Hs-CRP Anthropometric (weight, WC, BMI, WHR) Menstrual regularity (menstrual periods) AEs (GI, other) Follow-up: 12 weeks

Abbreviations: A2, androstenedione; AEs, adverse events; AUC, area under the curve; ART, assisted reproductive technology; BM, body mass; BMI, body mass index; COCP, combined oral contraceptive pill; CRP, C-reactive protein; DHEAS, dehydroepiandronate sulfate; ER, extended release; EXE, exenatide; FAI, free androgen index; FFM, fat-free mass; FINS, fasting insulin; FM, fat mass; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, hypersensitive C-reactive protein; IVF, in-vitro fertilization; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LIRA, liraglutide; MET, metformin; mFG, modified Ferriman–Gallwey; OGTT, oral glucose tolerance test; ORL, orlistat; PCOS, polycystic ovary syndrome; PT, phentermine/topiramate; QUICKI, quantitative insulin-sensitivity check index; RCT, randomized controlled trial; SEMA, semaglutide; SHBG, sex-hormone binding globulin; TC, total cholesterol; TG, triglycerides; TT, total testosterone; USA, United States of America; WC, weight circumference; WHR, waist-to-hip ratio.

3.3 | Interventions

Five studies trialed exenatide,[29,30,40,41,46] three trialed orlistat,[31,35,42] two trialed liraglutide,[32,43] one trialed semaglutide,[47] and one trialed phentermine-topiramate as well as exenatide.[29] Li et al. and Liu et al.[39,40] provided pre-gestational exenatide for 12 weeks followed by metformin for 12 weeks and assisted reproductive technology as needed in the second phase alongside metformin. Co-interventions were not provided in three studies.[29,43,47] Lifestyle interventions were provided in six studies[29–31,40,42,46] and the COCP in four studies.[31,35,40,41] All interventions were provided for at least 12 weeks.

3.4 | Comparisons

Four studies were placebo-controlled,[32,42,43,47] four used metformin as a comparator,[40,41,46,48] two trials used COCP and lifestyle[31,35] alone, and one trial used metformin and lifestyle[31] in combination. Li et al. and Liu et al.[39,40] provided pregestational metformin for 12 weeks and compared this with pregestational exenatide; metformin was then provided to both groups for a subsequent 12 weeks. Doses of metformin ranged from 1.5 to 2 g daily. The type of COCP used included cyproterone acetate 2 mg/ethinylestradiol 35 μg daily[31] and drospirenone 3 mg/ethinylestradiol 20 μg daily.[35]

3.5 | Outcomes

All studies collected data on anthropometric outcomes including weight and BMI,[29–32,35,40–43,46,47] waist circumference,[29–32,35,40,41,43,47] and percentage body fat.[29,31,32,35,40,43] All studies collected data on metabolic outcomes, with all reporting on fasting glucose, nine on HOMA-IR,[29–32,40–42,46,47] and eight on fasting insulin.[30,31,35,40–42,46,47] Four studies collected glucose 2 h post 75-g oral glucose.[30,40,41,47]

With the exception of a single study,[47] all studies collected data on biochemical hyperandrogenism. Only one study[30] collected data on clinical hyperandrogenism (hirsutism). The most frequently collected outcomes were total testosterone (TT),[29–32,35,40–43,46] FAI,[29–32,40,43,46] sex hormone binding globulin (SHBG),[30,31,35,40,43,46] and dehydroepiandrosterone sulfate (DHEAS).[29–32,41,46]

All studies collected data on lipid profile, three studies collected data on highly sensitive C-reactive protein (hsCRP),[30,40,41] and one study collected C-reactive protein (CRP) values.[35] No studies collected data on quality of life or psychological outcomes. Five studies collected reproductive outcomes, specifically menstrual regularity[30,32,40,43] and clinical pregnancy rate.[31,40] Liu et al. also collected data on pregnancy complications.[31,40] All but one study[35] reported on gastrointestinal (GI) adverse events (AEs), and seven reported on other AEs.[29–31,41–43,46] Duration of follow-up ranged from 12 to 32 weeks, and Liu et al.[40] followed up pregnancy outcomes for up to 64 weeks.

3.6 | Risk of bias

Figure 2A,B summarizes the assessed risk of bias of the included trials. The majority of trials were at unclear risk of selection bias, mainly due to failure to specify if or how allocation was concealed. More than half of the trials were at high risk of performance bias due to lack of blinding of participants and personnel. Three quarters of the trials were at unclear risk of detection bias, and more than half were at high or unclear risk for reporting bias. Greater than a quarter of trials were at high risk of other biases, mainly due to conflicts of interest.

3.7 | Effects of interventions

We report on a total of 12 comparisons. Meta-analyses were conducted for the following two comparisons: (1) exenatide v metformin (2 RCTs)[30,46] and (2) orlistat + lifestyle + COCP v lifestyle + COCP (2 RCTs).[31,35] For the remaining comparisons, a narrative synthesis was provided as a meta-analyses were not possible on any outcomes either due to the comparison only having one representative RCT or RCTs reporting non-parametric data (median and interquartile range/IQR) or change scores without any information on standard deviation or standard error.

3.8 | GLP-1 RAs

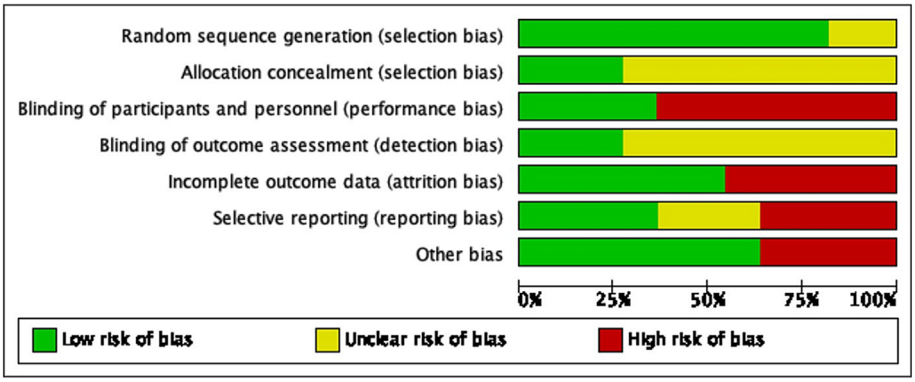
3.8.1 | Exenatide versus metformin

Exenatide 20 μg/day versus metformin 1.5–2 g/day

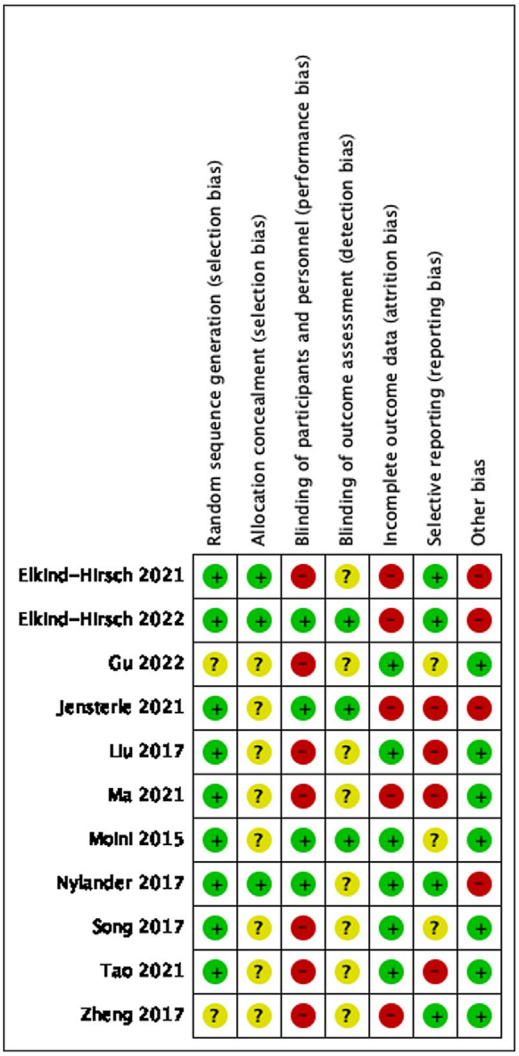
Two trials were included in this comparison.[30,46] Sample sizes were 100[46] and 63[30] per study for the two arms. Both trials enrolled individuals who were overweight/obese. Participants in the study by Tao et al.[46] also had a concurrent diagnosis of prediabetes. Both trials provided exenatide up to 20 μg daily for 12 weeks, together with diet and exercise guidance without active lifestyle interventions. The metformin dose was 1.5–2 g daily in one study[46] and 2 g daily in the other.[30] See Table 2 for a summary of GRADE assessments for this comparison.

Meta-analysis was conducted for four metabolic outcomes (HOMA-IR, fasting insulin/FINS, fasting blood glucose/FBG, and 2-h insulin). Metformin was superior to exenatide, showing higher fasting glucose with exenatide (MD 0.10 mmol/L, CI 0.02–0.17, $I^2 = 18\%$, 2 trials, very low certainty evidence, Figure 3A). No differences were identified between exenatide and metformin for fasting insulin (MD 1.52 pmol/L, CI −6.37 to 9.40, $I^2 = 83\%$, 2 trials, very low certainty evidence, see Figure 3B), HOMA-IR (MD 0.30, CI −0.67 to 1.28, $I^2 = 92\%$, 2 trials, very low certainty evidence, Figure 3C), and insulin 2 h post 75-g oral glucose (MD 80.11 pmol/L, CI −257.98 to 418.19, $I^2 = 99\%$, 2 trials, very low certainty evidence, Figure 3D).

From single study results, exenatide was superior to metformin for insulin area under the curve (AUC) (198.78 ± 113.39 vs. 233.66 ± 149.61 mU/L × h, $p < 0.001$) and the Matsuda index (0.017 ± 0.007



(A) *Risk of bias*



(B) *Risk of bias summary*

FIGURE 2 (A) Risk of bias. (B) Risk of bias summary.

vs. 0.016 ± 0.007, $p < 0.021$).[30] There were no differences between groups for AUC glucose or 2-h glucose.[30] Nausea was more frequent in the exenatide group,[30] and more participants in the exenatide group withdrew due to AEs which were mostly GI AEs.[30]

For the remaining outcomes, descriptive analysis showed no differences between groups for waist-to-hip ratio (WHR)[30] or for most androgen-related markers, including mFG score,[30] TT,[30,46] SHBG,[30,46] DHEAS,[30,46] and androstenedione.[46] Exenatide was superior to metformin for FAI (7.28 ± 6.46 vs. 7.66 ± 7.45, $p = 0.022$),[30] weight (66.64 ± 14.11 vs. 68.49 ± 12.23 kg, $p = 0.009$), BMI (26.12 ± 5.18 vs. 27.27 ± 4.13 kg/m^2, $p = 0.024$), and weight circumference (WC, 85.16 ± 13.21 vs. 90.52 ± 10.89 cm, $p = 0.017$) in one trial[30] but not in another.[46] These data could not be combined in meta-analyses due to the skewed data in Tao et al.'s study for these outcomes.[46] There was no difference between groups for menstrual regularity,[30] and other reproductive outcomes were not reported. Exenatide was

TABLE 2 GRADE assessment—Exenatide v metformin.

Comparison: exenatide v metformin												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	EXE	MET	Effect, random [95% CI]	Favors	Certainty	Importance
Outcome: HOMA-IR												
2	RCT	Serious[a]	Serious inconsistency[b]	No serious indirectness	Very serious imprecision[c]	None	81	82	MD 0.30 (−0.67, 1.28)	NS	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: fasting insulin (pmol/L)												
2	RCT	Serious[a]	Serious inconsistency[b]	No serious indirectness	Very serious imprecision[c]	None	81	82	MD 1.52 (−6.37, 9.40)	NS	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: fasting glucose (mmol/L)												
2	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	None	81	82	MD 0.10 (0.08, 0.14)	MET	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: 2-h OGTT insulin (pmol/L)												
2	RCT	Serious[a]	Serious inconsistency[b]	No serious indirectness	Very serious imprecision[c]	None	81	82	MD 80.11 (−257. 98, 418.19)	NS	⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations: EXE, exenatide; HOMA-IR, homeostasis model assessment of insulin resistance; MD, mean difference; MET, metformin; NS, not statistically significant; OGTT, oral glucose tolerance test; RCT, randomized controlled trial.

[a]Downgraded one level for unclear sequence generation and allocation concealment and lack of blinding.

[b]Downgraded one level for inconsistent direction of effect and high heterogeneity.

[c]Downgraded two levels for very small sample sizes and very small number of studies.

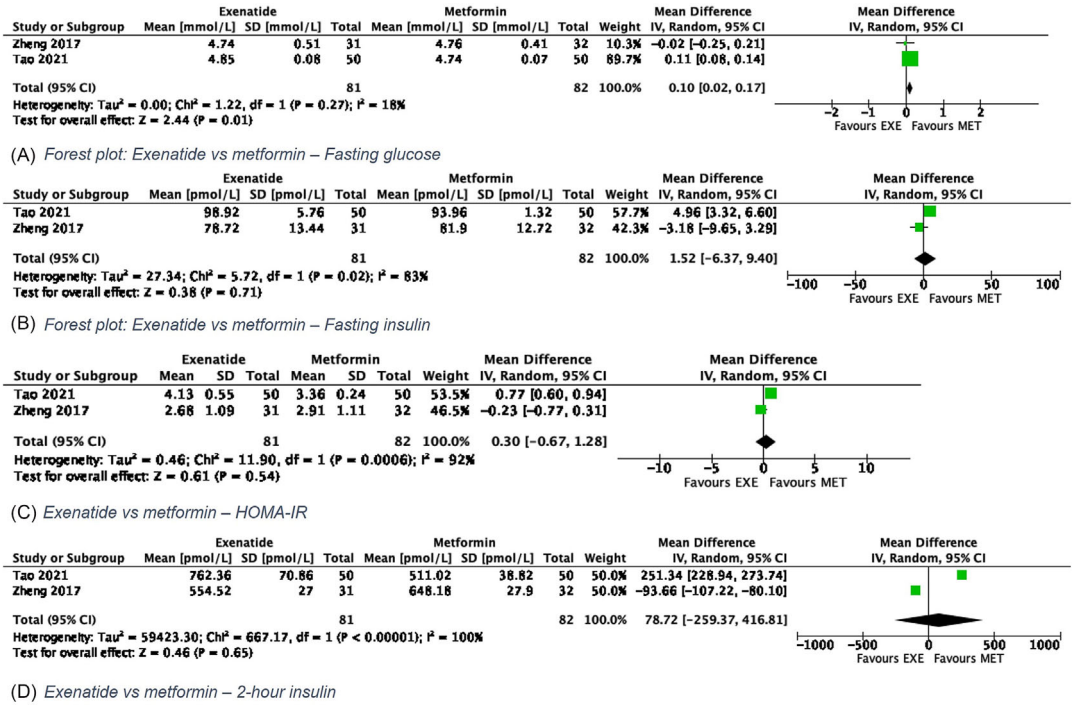


FIGURE 3 Forest plots of exenatide v metformin. (A) Fasting glucose, (B) fasting insulin, (C) homeostatic model assessment of insulin resistance (HOMA-IR), and (D) 2-h insulin.

superior to metformin for hsCRP (1.61 ± 1.47 vs. 1.93 ± 0.74 mg/L, $p = 0.016$).[30] For lipids, metformin was superior to exenatide for total cholesterol (TC, 4.49 ± 0.74 vs. 4.77 ± 0.68 mmol/L, $p < 0.001$),[30] but there were no differences in low-density lipoprotein (LDL)/high-density lipoprotein (HDL) cholesterol or triglycerides (TG).[30,46]

Pregestational exenatide 10 mg BID + COCP followed by metformin 1000 mg BID versus pregestational metformin 1000 mg BID + COCP followed by metformin 1000 mg BID

One trial reported on the comparison of 12 weeks of pregestational exenatide vs. metformin.[40] After 12 weeks, metformin was provided in both groups for a subsequent 12 weeks. Follow-up was conducted after the pregestational stage at 12 weeks for non-reproductive outcomes (androgens, metabolic, lipids, anthropometric) and after the pregestational stage (up to 64 weeks) for reproductive outcomes. The oral contraceptive pill (cyproterone acetate and ethinyl estradiol—dose not specified) was provided in both groups in the first 12 weeks.

In descriptive analysis of this trial,[40] mean body weight reduction (4.29 ± 1.29 vs. 2.28 ± 0.55 kg, $p < 0.05$), BMI (mean reduction 3.12 ± 1.36 vs. 0.98 ± 0.22 kg/m^2, $p < 0.001$), WC (9.04 ± 3.79 vs. 5.00 ± 4.66, $p < 0.05$), and body fat percentage were greater in the exenatide + COCP group compared with metformin + COCP, but there was no difference in WHR. For metabolic outcomes, exenatide + COCP was reported to be superior to metformin + COCP for FINS (12.12 ± 4.24 vs. 13.47 ± 4.24 mU/L, $p = 0.002$), HOMA-IR (2.92 ± 1.31 vs. 3.30 ± 1.00, $p = 0.013$), 2-h insulin (76.93 ± 67.03 vs. 104.39 ± 37.02 mU/L, $p = 0.003$), and 2-h glucose (7.12 ± 1.15 vs. 7.37 ± 1.04 mmol/L, $p = 0.002$). Mean post treatment hsCRP was lower in the exenatide + COCP group compared with the metformin + COCP group (2.30 ± 1.34 vs. 3.23 ± 1.49 mg/L, $p = 0.049$). There was no difference between groups for FBG or lipids (TC, low-density lipoprotein cholesterol/LDL-C, high-density lipoprotein cholesterol/HDL-C, TG) or for any biochemical hyperandrogenism outcomes including TT, FAI, or SHBG.

In relation to reproductive outcomes, the ratio of actual menses to expected menses was higher in the intervention group compared with control (0.90 ± 0.13 vs. 0.68 ± 0.03, $p < 0.001$) at 12 weeks post-treatment. After 12 weeks, the natural pregnancy rate was higher in the exenatide + COCP group (43% vs. 18.7% in metformin + COCP, $p < 0.05$), but there were no differences for total pregnancy or live birth rates at 64 weeks follow-up. There was no difference between groups for risks of miscarriage, preterm delivery, gestational diabetes mellitus, gestational hypertension, or fetal macrosomia. GI AEs were more frequent in the exenatide + COCP group compared with metformin + COCP.

3.8.2 | Exenatide + metformin versus metformin alone

Exenatide (10-20 μg/day) + metformin (1.5-2 g/day) versus metformin alone

Tao et al.[46] also reported on the comparison of a combination of exenatide (10–20 μg daily) and metformin (1.5–2 g daily) versus metformin alone (1.5–2 g daily). AEs were only reported in the context of reason for withdrawal. In this study, there were no between-group differences for weight, BMI, or any of the androgen levels collected (FAI, TT, SHBG, DHEAS, androstenedione). There were no differences in metabolic markers including FBG, FINS, HOMA-IR, or lipids (TC, HDL, TG), with the exception of metformin being superior to

exenatide + metformin for 2-h insulin (85.17 ± 6.47 vs. 120.85 ± 12.02 mIU/mL, $p = 0.01$) and LDL cholesterol (median of 2.52, IQR 2.21–2.59 vs. 2.81, IQR 2.51–3.21 mmol/L, $p < 0.05$).

Exenatide (2 mg weekly) + metformin (1.5 g/day) + COCP (Diane-35) versus metformin + COCP

One trial ($n = 40$) reported on the comparison of a combination of exenatide (2 mg weekly) and metformin (1.5 g daily) versus metformin; however, this trial also provided the COCP (cyproterone acetate 2 mg and ethinyl estradiol 35 μg, i.e., Diane-35) as a co-intervention in both groups.[41] There was more bloating in the exenatide + metformin + COCP group, but other GI AEs were comparable. There were injection site reactions in the exenatide + metformin + COCP group.

In this single study, exenatide + metformin was reported to be superior to metformin for change in body weight (mean weight loss 3.76 ± 2.4 vs. 2.05 ± 3.0 kg, $p = 0.045$), BMI (mean decrease 1.40 ± 0.87 vs. 0.77 ± 1.17 kg/m^2, $p = 0.041$), and WC (mean decrease 4.63 ± 4.42 vs. 1.72 ± 3.07 cm, $p = 0.023$). For metabolic outcomes, exenatide + metformin + COCP was superior to metformin + COCP for change in FBG (mean reduction 0.26 ± 0.45 vs. 0.01 ± 0.31 mmol/L, $p = 0.040$), 2-h glucose (mean reduction 0.85 ± 2.85 vs. 1.41 ± 1.64 mmol/L, $p < 0.001$), and 2-h insulin (mean reduction 67.96 ± 109.23 vs. 18.65 ± 85.03 μIU/mL, $p = 0.016$). There were no between-group differences for change in FINS, the Matsuda index, HOMA-IR, the quantitative insulin-sensitivity check index (QUICKI), lipids, or hsCRP. There were no differences between groups for TT or DHEAS.

3.8.3 | Exenatide versus phentermine/topiramate

Exenatide (2 mg weekly) versus phentermine 7.5 mg/topiramate 46-mg extended release (ER) daily

One trial[29] reported on exenatide 2 mg weekly versus phentermine 7.5 mg + topiramate 46-mg ER daily ($n = 36$ for these two arms). Nausea was more common with exenatide, whereas other AEs were more common in the phentermine/topiramate group such as insomnia, rapid heart rate, and dizziness. There were no between-group differences reported for any outcomes collected in this study, which included anthropometric (weight, BMI, WHR, WC, body fat %, fat mass, fat free mass-lean body mass), biochemical hyperandrogenism (FAI/TT/DHEAS), metabolic (FBG, HOMA-IR, Matsuda), or lipid (TC, LDL, HDL, TG) outcomes.

3.8.4 | Liraglutide versus placebo

Liraglutide (1.8 mg/day) versus placebo

One trial ($n = 65$)[44] reported on the comparison of liraglutide 1.8 mg daily versus placebo for 26 weeks in individuals with a BMI ≥ 25 kg/m^2 and/or insulin resistance. No co-interventions were provided. GI AEs were more common in the liraglutide group.

Liraglutide was reported to be superior to placebo for most anthropometric outcomes including weight (mean change −5.2 kg ± 0.7 vs. 0.2 ± 0.9 kg, $p < 0.001$), BMI (mean change −1.9 kg ± 0.3 vs. 0.1 ± 0.3 kg/m^2, $p < 0.001$), WHR (mean change 0.01 ± 0.01 vs. 0.04 ± 0.01, $p = 0.048$), WC (mean change −4.1 ± 1.1 vs. 1.1 ± 1.5 cm, $p = 0.01$), and fat mass (mean change −2.6 ± 0.5 vs. 0.3 ± 0.7 kg, $p = 0.02$) but also resulted in more lean body mass loss compared with placebo (mean change −2.4 ± 0.4 vs. 0.1 ± 0.4 kg, $p < 0.001$).[33] There was no difference between groups for percentage body fat. Liraglutide was superior to placebo for FBG (mean reduction of 0.24 mM, 95% CI 0.05–0.43, $p < 0.05$ in the liraglutide group compared with placebo) but not for the Matsuda index. There were no between-group differences for lipids including TC, TG, HDL, and LDL or hsCRP.

Liraglutide was superior to placebo for some hormonal outcomes including free testosterone (median change of −0.005, IQR −0.009 to −0.001 vs. 0.004, IQR −0.003 to 0.011 nmol/L, $p = 0.05$) and SHBG (median change of 7.4, IQR 4.1–10.7 vs. 2.0, IQR −2.9 to 7.0 nmol/L, $p < 0.05$) but not others (FAI, TT, and androstenedione). Participants in the liraglutide group reported a larger mean change in menstrual frequency compared with the placebo group at end of treatment (0.28, IQR 0.2–0.36 vs. 0.14, IQR 0.02–0.26, $p < 0.05$).

Liraglutide (3 mg/day) + lifestyle v placebo + lifestyle

One trial ($n = 67$)[32] reported on the comparison of liraglutide 3 mg/daily versus placebo for 32 weeks in individuals with a BMI ≥ 30 kg/m^2. All participants were prescribed a 500–800 kcal/day reduction diet and 30 min of moderate-intensity aerobic exercise daily. Participants in the liraglutide group complained of more nausea, vomiting, diarrhea, constipation, reflux, indigestion, prolonged menstrual bleeding, and injection site induration. The placebo group reported greater amenorrhea.

Liraglutide + lifestyle was superior to placebo + lifestyle for most anthropometric outcomes including weight (104.7 ± 2.9 vs. 117.9 ± 5 kg, $p = 0.002$), BMI (39.1 ± 1.1 vs. 43.4 ± 1.8 kg/m^2, $p = 0.001$), WHR (0.81 ± 0.01 vs. 0.83 ± 0.02, $p = 0.038$), WC (101 ± 2.0 vs. 110 ± 3.3 cm, $p = 0.011$), percentage with 5% weight loss (57% vs. 22%, $p = 0.09$), % with 10% weight loss (29.5% vs. 8.7%, $p = 0.046$), and percentage body fat (46.0 ± 0.9 vs. 47.9 ± 0.9%, $p = 0.028$) and for all metabolic outcomes including FBG (90.2 ± 1.3 vs. 94.3 ± 2.2 mg/dL, $p = 0.021$), HOMA-IR (4.1 ± 0.6 vs. 5.2 ± 1.1, $p = 0.05$), and the Matsuda index (3.7 ± 0.4 vs. 3 ± 0.5, $p = 0.028$). There were no differences between groups for fat free mass. Liraglutide + lifestyle was superior to placebo + lifestyle for FAI (5.98 ± 0.6 vs. 6.4 ± 0.75, $p = 0.006$), TG (109 ± 7.7 vs. 114 ± 11 mg/dL, $p = 0.016$), and number of menstrual cycles per year (8.65 ± 0.4 vs. 4.8 ± 0.65, $p = 0.0001$), but no between-group differences for TT, DHEAS, and other lipid parameters (TC, HDL, LDL cholesterol) were evident.

3.8.5 | Semaglutide versus placebo

Semaglutide (1 mg weekly) versus placebo

One trial ($n = 25$)[47] reported on the comparison of semaglutide 1 mg weekly versus placebo for 16 weeks. There was very serious

imprecision (single trial, very small sample size), and the study was rated at moderate risk of bias due to potential conflict of interest and selective outcome reporting. There was more nausea in the semaglutide group compared with placebo.

Semaglutide was superior to placebo for all anthropometric outcomes including body weight (95.6 ± 13.3 vs. 100.7 ± 14.8 kg, $p = 0.001$), BMI (34.8 ± 3.2 vs. 36.1 ± 4.2 kg/m^2, $p = 0.001$), waist circumference (99.7 ± 10.7 vs. 109.8 ± 14.6 cm, $p = 0.002$), and visceral body fat (632 ± 215 vs. 766 ± 237 g, $p < 0.001$). Semaglutide was superior to placebo for fasting insulin (14.57 ± 10.34 vs. 14.79 ± 8.13 mU/L), 2-h glucose (5.0 ± 0.8 vs. 5.9 ± 1.3 mmol/L, $p = 0.001$), and HDL cholesterol (1.28 ± 0.29 vs. 1.32 ± 0.24 mmol/L, $p = 0.026$), but there were no between-group differences for FBG, HOMA-IR, 2 hour insulin and other lipid parameters (TC, LDL, TG).

3.9 | Orlistat

3.9.1 | Orlistat versus placebo

Orlistat (120 mg three times/day) + lifestyle versus placebo + lifestyle

One trial ($n = 86$) reported on the comparison of orlistat 120 mg three times per day versus placebo for 3 months.[42] Both groups were prescribed a hypocaloric mono-unsaturated fatty-acid (MUFA) diet of 1200–1800 kcal/day and were encouraged to walk for 30 min daily. More than half of participants reported urgency to go to the bathroom, and 30% reported oily spotting in undergarments. About one in five participants reported oily or fatty stool.

Orlistat + lifestyle was reported to be superior to placebo + lifestyle for all anthropometric outcomes including weight (76.25 ± 4.3 vs. 79.15 ± 4.51 kg, $p < 0.01$), BMI (27.16 ± 1.93 vs. 28.57 ± 1.90 kg/m^2, $p < 0.01$), and WHR (0.76 ± 0.03 vs. 0.86 ± 0.03, $p < 0.01$) and for TT (63.95 ± 1.63 vs. 81.60 ± 4.64 ng/mL, $p = 0.01$) and all lipid parameters including LDL (71.18 ± 2.34 vs. 99.63 ± 5.8 mg/dL, $p < 0.01$), HDL (54.13 ± 2.32 vs. 49.23 ± 1.47 mg/dL, $p < 0.01$), and TG (128.34 ± 16.52 vs. 158.98 ± 11.93 mg/dL, $p < 0.01$). However, there were no between-group differences for any of the metabolic outcomes collected (FBG, FINS, HOMA-IR).

3.9.2 | Orlistat + lifestyle + COCP versus lifestyle + COCP alone

Orlistat (120 mg three times/day) + lifestyle + COCP versus lifestyle + COCP

Two trials reported on this comparison.[31,35] Both trials enrolled individuals with a BMI ≥ 24 kg/m^2, and Song et al. also required a diagnosis of insulin resistance.[31] Both trials provided all participants with lifestyle interventions (dietician-prescribed personalized balanced nutrition diet[31] or low-fat diet[35]) and the COCP (drospirenone/EE[35] and cyproterone acetate/EE[31]). The intervention groups received orlistat 120 mg three times/day in both trials. A small proportion of participants reported GI AEs with orlistat (flatulence and oily spotting).

Meta-analysis was conducted on six outcomes. Orlistat + lifestyle and the COCP were superior to lifestyle and the COCP alone for SHBG (MD 14.30 nmol/L, 2.94–25.66, $I^2 = 0\%$, 2 trials, low certainty evidence, Figure 4A). No between-group differences were evident for metabolic outcomes including FBG (MD −0.00 nmol/L, −0.17 to 0.17, $I^2 = 0\%$, 2 trials, low certainty evidence, Figure 4B), fasting insulin (MD −8.65 pmol/L, −33.55 to 16.26, $I^2 = 67\%$, 2 trials, very low certainty evidence, Figure 4C). Orlistat + lifestyle + the COCP was superior to lifestyle and the COCP for LDL cholesterol (MD −0.43 mmol/L, −0.84 to −0.02, $I^2 = 75\%$, 2 trials, low certainty evidence, Figure 4D) but not for HDL cholesterol (MD 0.22 mmol/L, −0.36 to 0.80, $I^2 = 92\%$, 2 trials, low certainty evidence, Figure 4E), or TG (MD 0.00 mmol/L, −0.22 to 0.21, $I^2 = 0\%$, 2 trials, low certainty evidence, Figure 4F).

In descriptive analyses from single trials, orlistat + lifestyle was superior to lifestyle and COCP alone for body weight (69.9 ± 7.86 vs. 72.52 ± 9.35 kg, $p = 0.001$),[35] BMI (26.26 ± 3.12 vs. 27.02 ± 3.31 kg/m^2, $p = 0.001$),[35] and % body fat (43.13 ± 8.89 vs. 43.3 ± 5.71%, $p < 0.001$).[35] There was no difference between groups for waist circumference.[35] Note that numerical data on endpoint weight and BMI were not available from the Song trial as only a figure lacking data labels was displayed. However, Song et al. reported between-group differences for weight and BMI favoring the intervention group.[31] See Table 3 for a summary of GRADE assessments for this comparison.

Orlistat + lifestyle was superior to lifestyle and COCP alone for CRP (4.43 ± 3.69 vs. 4.69 ± 3.84 mg/L, $p = 0.006$),[35] DHEAS (175.02 vs. 206.85 μg/dL), and FAI (2.15 vs. 4.59).[31] There were no differences between groups for TC,[31,35] free or TT,[31,35] androstenedione,[31] and HOMA-IR.[31]

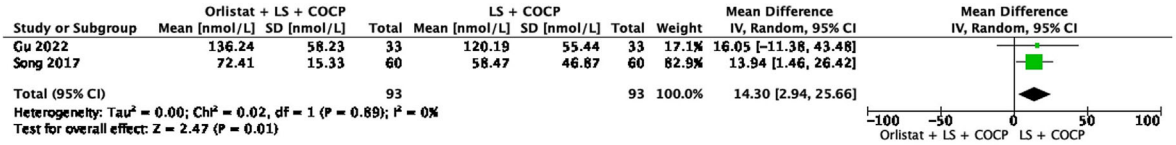
3.9.3 | Orlistat + metformin versus metformin

Orlistat (120 mg three times/day) + lifestyle + COCP v metformin (1.5 g/day) + lifestyle + COCP

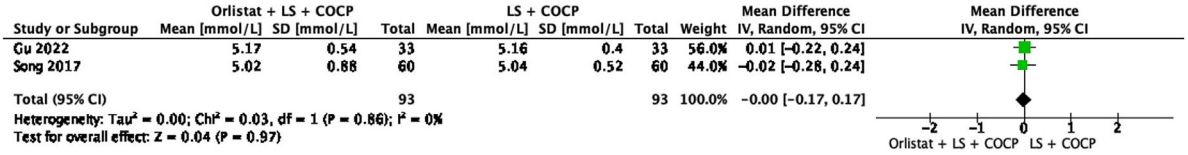
Song et al. also reported on the comparison of orlistat versus metformin, together with the co-interventions of lifestyle and COCP.[31] There were no between-group differences for any outcomes in this comparison that included biochemical hyperandrogenism (FAI, free/TT, SHBG, DHEAS, androstenedione), metabolic (fasting glucose, fasting insulin, HOMA-IR), lipids (TC, HDL, LDL, TG), and anthropometric (body weight, BMI, WC, fat mass, % body fat).

Orlistat + metformin + COCP + lifestyle v metformin + COCP + lifestyle

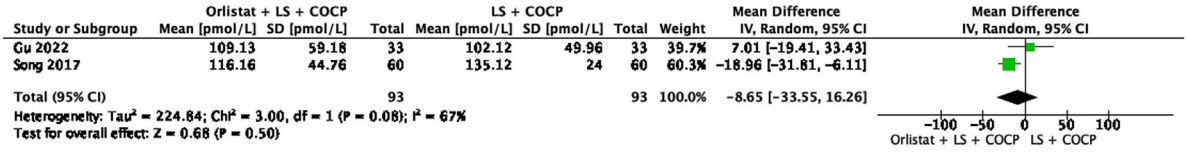
Song et al. also reported on the comparison of a combination of orlistat + metformin versus metformin alone (together with co-interventions of the COCP and lifestyle in both arms).[31] Orlistat + metformin was superior to metformin for body fat percent reduction. However, no between-group differences were noted for other outcomes of biochemical hyperandrogenism (FAI, free/TT, SHBG,



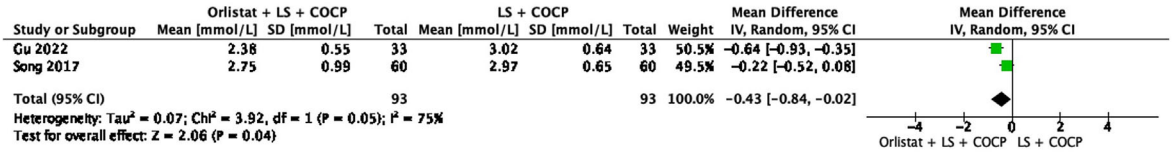
(A) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP - SHBG*



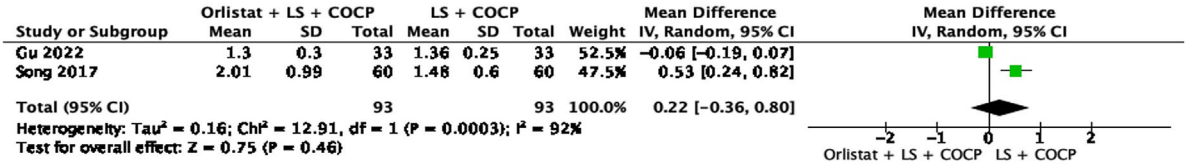
(B) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP – Fasting blood glucose*



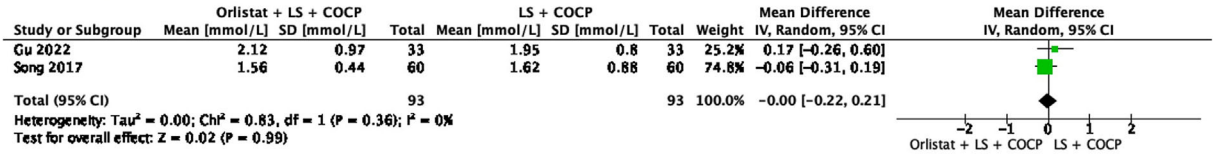
(C) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP – Fasting insulin*



(D) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP – LDL cholesterol*



(E) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP – HDL cholesterol*



(F) *Forest plot: Orlistat + lifestyle + COCP v lifestyle + COCP – Triglycerides*

FIGURE 4 Forest plots orlistat + lifestyle + combined oral contraceptive pill (COCP) v lifestyle + COCP. (A) Sex hormone binding globulin (SHBG), (B) fasting blood glucose, (C) fasting insulin, (D) low-density lipoprotein (LDL) cholesterol, (E) high-density lipoprotein (HDL) cholesterol, and (F) triglycerides.

DHEAS, androstenedione), metabolic (fasting glucose, fasting insulin, HOMA-IR), lipids (TC, HDL, LDL, TG), and anthropometric (body weight, BMI, WC, fat mass).

4 | DISCUSSION

This meta-analysis considered the effects of anti-obesity agents on hormonal, metabolic, anthropometric, and reproductive outcomes in individuals with PCOS. We found that GLP-1 RAs (exenatide, liraglutide, and semaglutide) have variable weight reduction efficacy within 12 weeks that appears to mostly correspond with metabolic and reproductive benefits in PCOS. Orlistat was superior to the COCP alone for some anthropometric outcomes but not for metabolic outcomes. No differences were observed between exenatide and phentermine/topiramate for anthropometric, biochemical hyperandrogenism, metabolic, and lipid outcomes. Evidence on fertility outcomes was limited to one trial that suggested increased pregnancy rates with pregestational exenatide compared with metformin; however, there was no difference between groups for live birth rate. Of note, all agents consistently resulted in greater AEs than controls, including metformin.

The interest in using GLP-1 RAs in women with PCOS has increased, due to general efficacy in weight reduction. Previous narrative reviews supporting the use of GLP-1 RAs in PCOS focused on single-center RCT and observational studies.[49] Two meta-analyses of GLP-1 RAs versus metformin in PCOS included six and eight RCT studies, respectively,[50,51] which concluded GLP-1 RAs were beneficial with or without metformin for metabolic, reproductive, and anthropometric parameters. However, these analyses combined exenatide and

TABLE 3 GRADE assessment: Orlistat + LS + COCP v LS + COCP.

Comparison: orlistat + LS + COCP v LS + COCP												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Orlistat + LS + COCP	LS + COCP	Effect, random [95% CI]	Favors	Certainty	Importance
Outcome: SHBG (nmol/L)												
2	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	93	93	MD 14.30 (2.94, 25.66)	Orlistat (for higher SHBG)	⨁⨁◯◯ LOW	IMPORTANT
Outcome: fasting glucose (mmol/L)												
2	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	93	93	MD −0.00 (−0.17, 0.17)	NS	⨁⨁◯◯ LOW	IMPORTANT
Outcome: fasting insulin (pmol/L)												
2	RCT	Serious[a]	Serious inconsistency[c]	No serious indirectness	Serious imprecision[b]	None	93	93	MD −8.65 (−33.55, 16.26)	NS	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL (mmol/L)												
2	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	93	93	MD −0.43 (−0.84, −0.02)	Orlistat	⨁⨁◯◯ LOW	IMPORTANT
Outcome: HDL cholesterol (mmol/L)												
2	RCT	Serious[a]	Serious inconsistency[c]	No serious indirectness	Serious imprecision[b]	None	93	93	MD 0.22 (−0.36, 0.80)	NS	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: triglycerides (mmol/L)												
2	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	93	93	MD −0.00 (−0.22, 0.21)	NS	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations: COCP, combined oral contraceptive pill; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; NS, not statistically significant; RCT, randomized controlled trial; SHBG, sex hormone binding globulin.

[a]Downgraded one level for lack of reporting of allocation concealment, no reporting of sequence generation in one study, and lack of blinding.

[b]Downgraded one level for small number of studies and small sample sizes.

[c]Downgraded one level for inconsistent direction of effect, limited overlap of confidence intervals, and high heterogeneity.

liraglutide in varying protocols and dosing regimens. Our conclusions are aligned, yet are more circumspect than previously, with several key differences in methodology. Wang and colleagues conducted a network meta-analysis on anti-obesity agents for PCOS and found that liraglutide was most effective for lowering BMI. Our results differed from these findings as we evaluated the effect of individual anti-obesity medications against a comparator, whereas Wang et al. combined medication classes and varying doses.[52] Furthermore, some studies in our review are awaiting classification after an integrity check aligned to Cochrane processes.[25] Overall, these agents show promise, based on general population data and emerging data in PCOS; however, inadequate quality trials have culminated in only low to very low certainty evidence with research now a major priority.

Our review found that exenatide used twice daily did not confer significant benefits over metformin and was associated with more AEs. Clinical outcomes in PCOS have been postulated to be correlated with degree of weight loss. Because our analysis failed to find clear differences in anthropometric outcomes, no differences in metabolic and biochemical parameters were anticipated or identified. This observation is consistent with studies in non-PCOS populations, where twice daily exenatide was compared with longer acting GLP1 RA. Exenatide twice daily induced modest changes in body weight ranging from +0.3 to −2.96 kg.[53] In contrast, liraglutide led to larger weight reduction, ranging from 0.3 to 3.38 kg, and semaglutide 1 mg led to greater weight loss again ranging from −3.47 to −6.5 kg. Concordantly, we have shown that clinical impacts were more likely to be observed with liraglutide and semaglutide, in PCOS.

We found that although liraglutide was superior to placebo for anthropometric outcomes, liraglutide alone (without lifestyle co-interventions) resulted in more lean body mass loss than placebo. When liraglutide was delivered with lifestyle co-interventions, there was no difference between groups for lean body mass. This finding supports that physical activity (specifically resistance training) should be part of a recommended approach to preserve lean body mass and promote weight maintenance alongside the use of GLP-1 RAs.[54]

Although metformin was superior to exenatide for lowering fasting glucose concentration, mean fasting glucose concentrations were less than 5.6 mmol/L for both interventions. Whether the minimal difference in fasting glucose between metformin and exenatide contributes to future metabolic co-morbidities is unknown. The associated glycated hemoglobin reduction noted with twice daily exenatide was less than that seen with long-acting agents. Longer acting GLP-1 RA medications have advantages with improved adherence, glycaemic effects, and tolerance.[53,55]

Limitations of these studies include the rapid evolution of the GLP-1 drug class with limited studies with each agent and with variable doses. As with many areas of PCOS, funding is limited and quality trials woefully inadequate given the prevalence and impact of the condition.[56] Many of the studies included suboptimal liraglutide doses; the 3-mg dose has been shown to optimize weight loss.[52] Many of the studies used a 12-week protocol that limits the ability to demonstrate changes in important clinical outcomes such as hirsutism and fertility. Longer studies allowing for effect of full dose GLP-1 RA medication may also lead to more substantial benefits in this population. Additionally, semaglutide is the most potent long acting GLP-1 RA[57] but has only been studied in one small pilot study in patients with PCOS showing benefits compared with placebo for anthropometric measures (including visceral body fat), with no reproductive outcomes and some but not all metabolic and lipid parameters showing only modest benefits that are unlikely to be clinically significant. More high quality, multicenter studies of semaglutide in PCOS are urgently needed, incorporating reproductive, metabolic, and psychological outcomes, in addition to anthropometric outcomes. Further, with the FDA approval of a new dual acting GLP1-RA along with gastric inhibitory polypeptide receptor activator (tirzepatide), and the prospect of additional newer agents on the horizon, medical weight management in those with PCOS will be continue to be an area of interest.

For other agents, a previous meta-analysis comparing orlistat and metformin in patients with PCOS, Graff et al.[58] reported benefits of orlistat for weight reduction and reduction in HOMA-IR, insulin, and testosterone (2 RCTs). Our review included two RCTs with orlistat, with or without lifestyle or the COCP, being superior to lifestyle or the COCP alone for some outcomes. Orlistat had high AEs as similarly reported by Graff et al.[58] Data regarding the efficacy of phentermine-topiramate in those with PCOS were limited with no superiority over exenatide for any reported outcomes and more AEs. No other evidence was found on other anti-obesity agents. However, their use is of interest, based on evidence from the general population with obesity, where naltrexone/bupropion and lorcaserin have each led to weight loss of up to 5% at 12 weeks.[59,60] Overall, those with PCOS and their healthcare professionals need to consider both evidence of potential benefits and AEs in shared decision making on the use of anti-obesity for weight loss in PCOS.

The strengths of this study include the rigorous design and conduct. Wherever possible, we have conducted meta-analyses on individual agents such as individual GLP-1 RAs rather than pooled agents. We excluded trials of uncertain integrity to reduce potential erroneous conclusions, and as such, the validity and trustworthiness of our results is strengthened. An extensive global prioritization exercise identified the need for this review, which was conducted by a multidisciplinary team. Limitations are that only published studies, available in English, were included, and due to resource and time limitations, grey literature was not searched. Despite little to no integrity concerns identified in the included studies, the quality of these studies (in terms of risk of bias) and small sample sizes decreased the level of certainty of the evidence presented. Data on adolescents were not available, and due to time limitations, we did not include searches of grey literature or clinical trial registries.

5 | CONCLUSION

Our findings support the need for further investigations of anti-obesity agents in PCOS. On the basis of our analyses, we cannot provide definitive recommendations at this time due to the small number of trials, short follow-up periods, and overall high or unclear risk of bias in the majority of trials. Given the association of metabolic and reproductive benefits that appear to have a dose response with

degree of weight loss, anti-obesity medications including liraglutide, semaglutide, GLP-1 RAs, and orlistat could be considered, in addition to active lifestyle intervention, for the management of higher weight in adult women with PCOS as per general population guidelines. Weight management is an important outcome for those with PCOS, and further studies in this area need to be prioritized. In particular, the need for placebo-controlled trials is urgent. With increasing popularity but limited initial data, more trials to assess the efficacy of these agents are needed, particularly for GLP-1 RAs given their promising benefits and minor AEs. Future research should also examine weight regain in PCOS following cessation of anti-obesity agents and evaluate the impact of anti-obesity agents on quality of life and clinical hyperandrogenism. Longer follow-up periods are also required to demonstrate meaningful clinical benefits. With PCOS currently impacting approximately 10% of reproductive-aged women, this research should be designated as high priority.

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CONFLICT OF INTEREST STATEMENT

SFW declares that she has received royalties from UpToDate for authorship of an article and an honorarium from the Canadian Society of Endocrinology and Metabolism for a talk and that she is a Member of the Board of Directors of the Pediatric Endocrine Society. CT declares that she received support for registration for the 2023 AEPCOS and ASPIRE conferences and is the Chair of the Early Career Researcher Network, CRE WHIRL (unpaid). All other authors declare that they have no conflicts of interest.

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APPENDIX A: SEARCH STRATEGY

Search strings used in OVID or other database/s –
OVID and EMBASE Medline
1 exp Polycystic Ovary Syndrome/49396
2 poly?cystic ovar*.mp.50776
3 PCO#.mp.71172
4 (stein?leventhal or leventhal).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]1525
5 anovulat*.mp.16658
6 oligo?ovulat*.mp.179
7 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.60215
8 1 or 2 or 3 or 4 or 5 or 6 or 7107933
9 exp Anti-Obesity Agents/26934
10 Obesity/dt, th [Drug Therapy, Therapy]62364
11 ((anti?obesity or obesity or weight loss) and (agent* or drug* or therap*)).mp.497216
12 orlistat.mp. or exp Orlistat/9517
13 sibutramine.mp.6130
14 exp Appetite Depressants/94233
15 exp Appetite Depressants/94233
16 appetite suppressant*.mp.1487
17 exp Glucagon-Like Peptide 1/ or Glucagon-Like Peptide 1 agonist.mp.32498
18 (GLP-1 adj2 agonist*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]10048
19 semaglutide.mp.3397
20 tirzepatide.mp.310
21 liraglutide.mp.15050
22 dulaglutide.mp.2796
23 exenatide.mp. or exp Exenatide/15334
24 lixisenatide.mp.2560
25 albiglutide.mp.1485
26 Lorcaserin.mp.1842
27 phentermine.mp. or exp Phentermine/5217
28 topiramate.mp. or Topiramate/31119
29 naltrexone.mp. or exp Naltrexone/28800
30 exp Bupropion/ or buproprion.mp.23012
31 incretin.mp.15542
32 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31688891
33 8 and 329353
34 randomized controlled trial.pt.575128
35 controlled clinical trial.pt.94983
36 randomi*ed.ab.1665228
37 placebo.ab.565580
38 drug therapy.fs.6697085
39 randomly.ab.901041
40 trial.ab.1500989
41 groups.ab.5706526
42 34 or 35 or 36 or 37 or 38 or 39 or 40 or 4113488139
43 33 and 425456
44 exp animals/ not humans.sh.33866843

(Continues)

Search strings used in OVID or other database/s –
45 43 not 441276
46 limit 45 to last 10 years643
47 limit 46 to english language627
48 remove duplicates from 47613

APPENDIX B: FULL LIST OF ELIGIBLE OUTCOMES

- Androgenicity: hirsutism-FG score (ethnicities), FAI, testosterone (free/total), SHBG, DHEAS, androstenedione, irregular cycles
- Metabolic: fasting glucose, fasting insulin, HOMA-IR, QUICKI, OGTT: 120-min glucose and insulin, 30/60/90-min glucose and insulin where available, AUC glucose, AUC insulin, Matsuda index, euglycemic hyperinsulinemic clamp.
- Lipids and other biomarkers: total Chol, LDL, HDL TG, CRP
- Psychological: Qol, depression
- Anthropometric: weight BMI, WHR, waist circumference, % with >5% or >10% weight loss, fat mass, fat free mass, % body fat
- Fertility: menstrual regularity, live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, adverse events (including preterm delivery, growth restriction, low birth weight, stillbirth. Pregnancy complications, preeclampsia, hyperglycemia, hypertension in pregnancy, gestational diabetes, perinatal morbidity, fetal macrosomia, cesarean)
- Adverse events: gastrointestinal effects, other adverse events

APPENDIX C: STUDIES AWAITING CLASSIFICATION

Reference

1. Jensterle, M., Kravos, N. A., Pfeifer, M., Kocjan, T., & Janez, A. (2015). A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones (Athens, Greece)*, *14*(1), 81–90. doi: https://doi.org/10.1007/BF03401383
2. Jensterle, M., Salamun, V., Kocjan, T., Vrtacnik Bokal, E., & Janez, A. (2015). Short term monotherapy with GLP-1 receptor agonist liraglutide or PDE 4 inhibitor roflumilast is superior to metformin in weight loss in obese PCOS women: a pilot randomized study. *Journal of ovarian research*, *8*(101474849), 32. doi:https://doi.org/10.1186/s13048-015-0161-3
3. Jensterle Sever, M., Kocjan, T., Pfeifer, M., Kravos, N. A., & Janez, A. (2014). Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. *European journal of endocrinology*, *170*(3), 451–459. doi:https://doi.org/10.1530/EJE-13-0797
4. Kumar, P., & Arora, S. (2014). Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. *Journal of Human Reproductive Sciences*, *7*(4), 255–261. doi:https://doi.org/10.4103/0974-1208.147492
5. Salamun, V., Jensterle, M., Janez, A., & Vrtacnik Bokal, E. (2018). Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. *European journal of endocrinology*, *179*(1), 1–11. doi:https://doi.org/10.1530/EJE-18-0175

APPENDIX D: STUDIES EXCLUDED ON FULL TEXT ASSESSMENT

Reference	Reason
1. Jensterle, M., Kravos, N. A., Goricar, K., & Janez, A. (2017). Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial. *BMC Endocrine Disorders*, *17*(1), 5. doi:https://doi.org/10.1186/s12902-017-0155-9	Wrong intervention and comparator—liraglutide + metformin v liraglutide
2. Min, Min; Ruan, Xiangyan; Wang, Husheng; Cheng, Jiaojiao; Luo, Suiyu; Xu, Zhongting; Li, Meng; Mueck, Alfred Otto. Effect of orlistat during individualized comprehensive life-style intervention on visceral fat in overweight or obese PCOS patients. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology* / 2022;(8,807,913):1–5, England 2022 / https://doi.org/10.1080/09513590.2022.2089108	Wrong study design—described as a clinical cohort study, no randomization applied.
3. Salamun V.; Jensterle M.; Janez A.; Vrtacnik Bokal E. Short term intervention with liraglutide and metformin increased fertility potential in a subset of obese PCOS proceeding IVF. *Human Reproduction* / *2017;32(Supplement 1)*:i291-i292. Netherlands Oxford University Press 2017	Conference abstract
4. Salehpour, Saghar; Hosseini, Sedighe; Nazari, Leila; Saharkhiz, Nasrin; Zademodarres, Shahrzad. Effects of orlistat on serum androgen levels among iranian obese women with polycystic ovarian syndrome. *JBRA assisted reproduction* / 2018;22(3):180–184 Brazil 2018. https://doi.org/10.5935/1518-0557.20180033	Wrong study design—pre-post single arm study
5. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study. Jensterle, Mojca; Pirs, Bostjan; Goricar, Katja; Dolzan, Vita; Janez, Andrej/ *European journal of clinical pharmacology* / 2015;71(7):817–24, Germany 2015 / https://doi.org/10.1007/s00228-015-1868-1	Wrong study design—pre-post single arm study
6. Jensterle, Mojca; Kocjan, Tomaz; Kravos, Nika Aleksandra; Pfeifer, Marija; Janez, Andrej Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocrine research* / 2015;40(3):133–8. England 2015 https://doi.org/10.3109/07435800.2014.966385	Wrong study design—pre-post single arm study