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EDITORIAL

What's new on the horizon for polycystic ovarian syndrome? Exploring emerging drugs in phase II

Giuseppe D'Angelo[a], Mario Ascione[a], Ilaria Morra[a], Paolo Verrazzo[b], Giuseppe Bifulco[a], Pierluigi Giampaolino[a] and Luigi Della Corte[c]

[a]Department of Public Health, University of Naples Federico II, Naples, Italy; [b]Hospital Santa Maria delle Grazie of Pozzuoli - ASL Napoli 2 Nord, Naples, Italy; [c]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

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1. Introduction

Polycystic Ovarian Syndrome (PCOS) affects millions of women globally, and, depending on the diagnostic criteria used, PCOS has an estimated prevalence of between 7% to 17% of reproductive-aged women causing a range of symptoms such as irregular menstrual cycles, excessive hair growth, weight gain, and infertility [1].

PCOS is characterized by a complex interplay of hormonal, metabolic, and reproductive disturbances. The syndrome's underlying changes impact multiple systems, leading to several and complex clinical manifestations. One of the hallmark features of PCOS is hyperandrogenism which brings on symptoms like excessive hair growth, acne and alopecia. Anovulation and irregular menstrual cycles stem from the imbalance in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) triggered by androgen fluctuations. PCOS often involves both hyperandrogenism and insulin resistance, due to reduced sensitivity of target cells. These metabolic conditions over time lead to increased risk of type 2 diabetes, obesity, and dyslipidemia development. The interplay between insulin resistance and hyperandrogenism intensifies the syndrome's clinical symptoms. Abnormal gonadotropin-releasing hormone (GnRH) secretion has consequences of ovarian anovulation and cyst formation, resulting in unbalanced FSH and LH production.

The current pharmacological approaches for PCOS management primarily include hormonal contraceptives, antiandrogens, and insulin-sensitizing agents such as metformin. These pharmacological agents play a central role in managing PCOS. Despite targeting specific symptoms, these treatments often fail to tackle the underlying hormone imbalances holistically [2,3]. The urgent requirement for novel advanced drugs stems from the limitations in managing PCOS and the quest for a more comprehensive, personalized treatment strategy. To achieve optimal outcomes, medications should aim to rectify the delicate hormonal, insulin resistance, and ovulatory imbalances, alleviating symptoms while restoring ovulation and improving metabolic health.

Several promising medications are presently undergoing phase II clinical studies, providing hope for more successful management of PCOS. This article focuses on three chosen phase II clinical studies that have produced notable outcomes out of many phase II clinical trials undertaken on the therapy of PCOS. These studies were prudently selected for the innovative contribution that they could bring to therapeutic options in the treatment of PCOS. Moreover, these studies have explored innovative pathways that could lead to a deeper understanding of the underlying pathological mechanisms of PCOS. Consequently, studies that did not achieve statistical significance for any endpoint or did not present published results were excluded.

These studies were selected from a total of 10 phase II completed trials (Table 1).

This article explores these novel medications, their mechanism of action, and their possible effects on PCOS-affected women's lives, in order to gain a deeper understanding of the ongoing efforts to develop improved management strategies for PCOS.

2. GnRH antagonists

GnRH antagonists are a different family of drugs being investigated for the treatment of PCOS. They prevent the release of FSH and LH, which are frequently high in PCOS patients. Phase II trials on Elagolix, an oral GnRH antagonist, have been conducted for PCOS. Normalization of the ovulatory cycle was not observed in this phase 2 trial examining its effectiveness and safety for the treatment of PCOS, indicating that elagolix alone may not be an effective treatment for PCOS [1]. Out of 114 participants, only 3 (2.6%) met the primary endpoint of menstrual cycle regulation: 2 in the placebo group and 1 in the elagolix 300-mg group. However, adverse events associated with the treatment were infrequent and consistent with previous studies [4–6]. The study aimed to identify an optimal dose of Elagolix that would reduce LH levels while maintaining FSH levels without suppressing the hypothalamic-pituitary-ovarian axis. Unfortunately, the current scientific evidence highlighted in the clinical trial shows that there was no

CONTACT Luigi Della Corte dellacorte.luigi25@gmail.com; luigi.dellacorte@unina.it Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Table 1. Completed phase II clinical trials on PCOS.

Trial Number	Interventions	Brief Summary	Primary Outcome Measures	Results	Phases
NCT03981861	Metformin and Spironolactone	To assess the effect of a combination of low dose Metformin and Spironolactone on menstrual regulation and metabolism in adolescents.	Glucose and Insulin, Total Testosterone (TT) ng/dL, Free Testosterone ng/dL, DHEAS mcg/dL, BMI kg/m2.	Unpublished results	PHASE2/ PHASE3
NCT02865915	MLE4901 vs Placebo	To assess the effect of a selective neurokinin-3receptor antagonist vs placebo.	Menstrual Cycle Duration.	Unpublished results	PHASE2
NCT00151411	Metformin vs Placebo BEHAVIORAL: Lifestyle Intervention	To assess if the combination therapy of lifestyle intervention and use of Metformin together improves ovulation induction and hyperandrogenemia.	TT (ng/dL).	Testosterone levels were only significantly less at 3 months in MET compared to baseline.	PHASE2
NCT02729545	Tung's acupuncture vs Cyproterone acetate/ ethinylestradiol	To evaluate if Tung's acupuncture therapy vs Diane (CPA/EE) as a control group improves ovarian function.	Change in LH/FSH Ratio.	Both groups showed a significant decline in LH/FSH ratio at the end of treatment (acupuncture group: −0.66, $P = 0.001$; CPA/EE group: −0.96, $P < 0.001$).	PHASE2
NCT00704912	Orlistat/Meal Replacement/ Lifestyle Modification vs Loestrin 1/20 Combination of treatments	To establish the relative roles of treatment of hyperandrogenism versus obesity (as the largest modifiable factor contributing to insulin resistance) in treating infertility and improving pregnancy outcomes among obese PCOS women.	Live Birth Rate.	Live birth rates were after preconceptional OCP 12%, lifestyle changes 26%, and combined 24% ($P = .13$).	PHASE2
NCT00529542	Lipitor vs Placebo	To determine the efficacy of Lipitor (Atorvastatin) for the treatment of PCOS with elevated LDL cholesterol.	Brachial Artery Flow-mediated Dilation (FMD) to evaluate percent change in brachial artery diameter following release of transient occlusion.	Atorvastatin appeared to worsen FMD by reducing it by 1.5% whereas in the placebo group FMD increased by 0.4%. These differences were not statistically significant in the within or between-group comparisons.	PHASE2
EudraCT 2014–004409–34	ESN364 vs Placebo	To evaluate efficacy of two doses of Fezolinetant (ESN364) vs placebo when administered for 12 weeks to decrease TT levels in women with PCOS.	Total Testosterone (nmol/L)	In patients receiving ESN364 180 mg/day a reduction of 33% (95% [CI], $P \leq .0001$) in TT concentration was observed relative to placebo.	PHASE2
NCT00907153	Vitamin D vs Placebo	To determine if vitamin D improves insulin resistance, inflammation, and overall well-being in women with PCOS.	Quantitative Insulin Sensitivity Check Index (QUICKI).	No significant differences in QUICKI and other measures of insulin sensitivity were observed.	PHASE1| PHASE2
NCT03152591	LIK066 vs Placebo	To evaluate whether LIK066 can be developed for the treatment of PCOS in overweight and obese women.	Free Testosterone (ng/dL)	Comparing the treatment groups, there was a non-significant 12% lower ratio for licogliflozin (TR LIK066:TR PCB [FT]: 0.88; 90% CI: 0.70–1.11; $P = .353$).	PHASE2
NCT03951077	Elagolix vs Placebo	To assess the potential impact of elagolix on disordered pituitary and ovarian hormones in women with PCOS.	Percentage of Menstrual Cycle Responders.	There were no statistical differences observed between the placebo group and any of the elagolix treatment groups for the primary endpoint.	PHASE2

observed increase in FSH levels or reinitiation of follicular development, suggesting that Elagolix alone may not be sufficient to promote follicular development in PCOS [1]. Analysis of FSH concentrations demonstrated that FSH levels were generally maintained through 16 weeks of elagolix treatment. FSH AUCs were also not significantly affected by elagolix treatment compared with placebo treatment ($P \geq .321$ at week 1 and $P \geq .123$at week 4 for all elagolix groups). To make progress in the field, future research should explore alternative dosing regimens and combinations with other medications to effectively induce ovulation in PCOS patients. In conclusion, while the research on Elagolix did not yield the desired outcomes, it has shed light on the challenges and potential directions in PCOS management [2].

3. Neurokinin B receptor antagonism

PCOS is characterized by altered signaling in the neuroendocrine circuits that regulate fertility [5]. The hypothalamic network involving kisspeptin, neurokinin B, and dynorphin A (KNDy) neurons has been identified as the pulse generator for GnRH. This network controls the secretion pattern of LH and FSH throughout the ovarian cycle [6]. In PCOS patients, there are high-frequency LH pulses, elevated serum LH levels,

and a high LH-to-FSH ratio [7]. According to recent research, the kisspeptin-neurokinin B (NKB)-GnRH pathway is essential for controlling LH secretion [8].

Premenopausal women's NK3 receptor antagonism in the KNDy neuron decreases GnRH pulse frequency as observed by reduced basal LH secretion, lower LH-to-FSH ratio, and suppressed follicle development, as well as the modulation of ovarian sex hormone production patterns throughout the menstrual cycle [9]. In order to target the primary pathophysiology of LH hypersecretion and hyperandrogenism in PCOS, pharmacological NKB inhibition may be an effective strategy. Phase 2 studies examining the effects of the NK3 receptor antagonist Fezolinetant (ESN364) on PCOS were conducted. The findings demonstrated that in PCOS-affected women, Fezolinetant decreased serum LH and testosterone levels as well as the LH-to-FSH ratio ($P < .001$). In the Fezolinetant 180 mg/d group, there was a baseline-adjusted mean (SE) reduction in LH of − 10.17 (1.28) IU/L (95% confidence interval [CI], $P = < .0001$) and there was a baseline-adjusted reduction in total Testosterone concentration of 33% (95% [CI], $P = < .0001$) relative to placebo at weeks 12 of treatment. The results indicate that by addressing the underlying neuroendocrine dysfunction of PCOS, NKB antagonism may be a potential treatment strategy. To assess the clinical results and possible advantages of Fezolinetant, more and longer investigations are required also to extend the findings to various PCOS subtypes. Overall, the study shows promise for NKB antagonism as a new PCOS therapy option, although additional study is needed to validate its effectiveness, investigate its mechanisms, and explore its clinical implications [10].

4. Sodium-glucose co-transporter type 1 and 2 (SGLT1/2)

Currently, treatments for insulin resistance, such metformin, have shown some promise in easing PCOS symptoms [11]. Sodium-glucose co-transporter type 1 and 2 inhibitors (SGLT1/2is), which are frequently used to treat type 2 diabetes, have recently showed promise in decreasing insulin resistance and glucose control [12]. Phase II trial examining the effects of licogliflozin, a dual SGLT1/2 inhibitor, on glucose, insulin, and androgen levels in PCOS patients have been conducted. The studies emphasize the possibility of the dual SGLT1/2 inhibitor licogliflozin as a unique treatment choice for PCOS patients. The findings show that licogliflozin therapy lowers the levels of glucose, insulin, A4 and DHEAS in PCOS patients. Licogliflozin showed a statistically significant reduction of A4 and DHEAS after 2 weeks of treatment, with an effect size of 19% for A4 (TR_{LIK066}:TR_{PCB} [A4]: 0.81; 90% CI: 0.68–0.99; $P = .089$) and 24% for DHEAS levels (TR_{LIK066}:TR_{PCB} [DHEAS]: 0.76; 90% CI: 0.65–0.89; $P = .008$;). In the licogliflozin group, 9/10 patients had a decrease in FT concentration compared with 5/10 in the placebo group ($P = .07$). This shows that treating hyperinsulinemia and focusing on glucose management may help alleviate PCOS symptoms in general, and ovarian hyperandrogenism in particular [13–15]. To validate these results, investigate the effects of SGLT1/2 inhibitors in various PCOS groups, and evaluate their effect on ovulation rates and clinical outcomes, additional study is nonetheless required. Overall, these preliminary results offer encouraging new information about the possible application of SGLT1/2 inhibitors in the treatment of PCOS.

5. Conclusion

In conclusion, although managing PCOS continues to be difficult, recent developments in medical science have opened the possibility of novel therapeutic alternatives. Phase II clinical trials have shed light on the effects and limitations of various drugs. Although some therapies, such as elagolix, did not adequately regulate the menstrual cycle, there is promise in developing new delivery systems and combination therapies. This emphasizes the necessity of additional studies to investigate alternative dose schedules and combination medications to successfully address the hormonal abnormalities related to PCOS. Coupling the kisspeptin-neurokinin B-GnRH pathway through the neurokinin B receptor inhibition may reduce LH secretion and hyperandrogenism in PCOS. Sodium-glucose cotransporter type 1 and 2 inhibitors (SGLT1/2is) show potential to improve insulin resistance and glucose tolerance. However, further research is needed to validate these findings, assess their impact in different PCOS populations, and assess long-term outcomes. Collaborative efforts and ongoing research are critical for refining PCOS management strategies to improve the lives of affected women.

6. Expert opinion

Research in the field of PCOS has yielded several key findings, as well as a number of weaknesses that need to be addressed. One important finding has been the discovery of new treatment options through phase II clinical trials. These studies have shed light on the potential benefits and limitations of various agents used in the management of PCOS.

The ultimate goal is to develop effective personalized treatments that underlying hormonal abnormalities and symptoms associated with PCOS. By analyzing different drugs and understanding how they work, researchers are trying to find new treatments that reverse hormone imbalances, promote ovulation, manage insulin resistance, and other PCOS symptoms.

To achieve this goal, further research and knowledge are needed. Firstly, alternative dosing regimens and combination therapies should be explored to enhance the effectiveness of medications like Elagolix in promoting ovulation and regulating menstrual cycles. Additionally, more in-depth studies are required to understand the mechanisms of action and clinical implications of neurokinin B receptor antagonism and sodium-glucose co-transporter type 1 and 2 inhibitors. It is essential to investigate the effects of these treatments in diverse PCOS

subtypes and evaluate their long-term outcomes, including ovulation rates and overall clinical improvements.

The biggest challenge in achieving these goals is the complexity and heterogeneity of PCOS itself. PCOS is a multifaceted disorder with a variety of presentations and underlying pathology. This requires a comprehensive understanding of the disease and individual approaches to diagnosis and treatment. There are also significant challenges in conducting large clinical trials, managing long-term outcomes, and ensuring the safety and efficacy of emerging therapies.

Collaborative efforts between physicians, researchers, and pharmaceutical companies may lead to the development of targeted therapies targeting specific subtypes and symptoms of PCOS.

One current study of particular interest is the modulation of the kisspeptin-neurokinin B-GnRH pathway. Targeting this pathway through neurokinin B receptor antagonism shows promise in regulating LH secretion and hyperandrogenism. Conversely, despite observed changes in hormone levels, this 12-week study failed to yield enhanced clinical outcomes. The data indicate that targeted therapy on the hypothalamic KNDy-HPG axis leads to positive changes in biochemical biomarkers, yet the expected changes in neuroendocrine circuit plasticity and ovarian physiology are gradual; therefore, prolonged therapy may be required to demonstrate clinical benefit.

Overall, the research to date has provided valuable insights into the management of PCOS. However, highlighting limitations include the short duration of clinical trials, small sample sizes, and extensive sample heterogeneity which could all be confounding factors in the studies. Furthermore, the different phenotypes of PCOS are often underestimated in the targeting of PCOS therapies, often leaving this aspect in the background which has now become essential in the treatment of the pathology. The ultimate target remains to increase the understanding, appreciation and treatment of PCOS, and ultimately improve the quality of life for affected women.

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ORCID

Mario Ascione http://orcid.org/0000-0002-7845-1149
Luigi Della Corte http://orcid.org/0000-0002-0584-2181

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