

# Considerations in the Treatment of Depression and Anxiety in Women with PCOS

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## Abstract

Women with polycystic ovary syndrome (PCOS) are known to be at a greater risk of depression and anxiety. What is less clear is whether existing treatments for PCOS are effective in managing this increased risk and what the optimal approach to treatment is. In this review, currently available interventions are explored including lifestyle modifications, oral contraceptives, insulin sensitizing agents, psychosocial interventions and psychiatric medications. While data are often conflicting, lifestyle interventions, and cognitive behavioral therapy (CBT) appear most promising in reducing depression and anxiety symptoms in this population. There is an urgent need for large prospective studies to fill gaps in the literature.

## Keywords

- ▶ PCOS
- ▶ depression
- ▶ anxiety
- ▶ treatment

Polycystic ovary syndrome (PCOS) is a multi-faceted endocrine disorder. It is associated with a multitude of medical comorbidities, namely, mental health conditions including depression and anxiety. A meta-analysis of 18 studies found that in women with PCOS, the median prevalence of depressive symptoms was 36.6% (interquartile range [IQR]: 22.3–50.0%) and women with PCOS had increased odds of depressive symptoms, even after matching for body mass index (BMI) (odds ratio [OR]: 3.25, 95% confidence interval [CI]: 1.73–6.09) compared to those without PCOS.<sup>1</sup> The same meta-analysis also found women with PCOS to be at increased risk for anxiety compared to controls (OR: 5.62, 95% CI: 3.22–9.80). The odds of moderate and severe anxiety symptoms were also high in this group (OR: 6.55, 95% CI: 2.87–14.93). These findings have been confirmed with more recent reviews and meta-analyses as well.<sup>2–4</sup>

In addition, the risk persists across ages, with significantly higher depression prevalence noted in adolescent<sup>5</sup> and young adult PCOS women,<sup>6</sup> as well as increased depression noted in longitudinal studies stretching into the fourth and fifth decades of life.<sup>7,8</sup> Similarly, social anxiety disorder was the second most common psychiatric disorder in a cross-sectional study of adolescents with PCOS,<sup>5</sup> and higher anxiety scores persisted in a 15-year follow-up study of a Finnish

PCOS cohort extending up to age 46 years.<sup>8</sup> A recent systematic review and meta-analysis of observational studies evaluating depression and anxiety symptoms in adolescent and young adult women with PCOS found that those with PCOS had significantly more depressive (standard mean difference [SMD]: 0.72; 95% CI: 0.09–1.34) and anxiety symptoms (SMD: 0.59; 95% CI: 0.13–1.05) compared to those without PCOS.<sup>9</sup>

Yet despite the known increased associations, several studies have demonstrated limited assessment for mental health issues in women with PCOS amongst gynecologists and primary care providers.<sup>10,11</sup> Per the 2023 International Guidelines, healthcare professionals should not only be aware of the increased prevalence of moderate to severe depression and anxiety in this population, but should also be screening all adults with PCOS for these using regionally validated tools.<sup>12</sup> While the optimal interval for screening is unknown, an option discussed by the guidelines is at diagnosis, the perinatal period, and then using clinical judgment based on comorbidities and life events. In addition to decreased evaluation by healthcare providers, patients with depression and anxiety are less likely to comply with medical treatment recommendations in general.<sup>13</sup> Patients with depression are less likely to implement and adhere to several

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of the behaviors known to improve symptoms of PCOS, such as lifestyle interventions.<sup>14</sup> Taken together, these findings highlight the importance of understanding depression and anxiety treatment options in order to better serve this population.

### Potential Etiologies

The proposed mechanisms for this increased prevalence include both intrinsic factors such as insulin resistance, chronic inflammation, and hyperandrogenism, as well as extrinsic factors such as obesity and body image distress. A secondary analysis of a multi-center trial including women with PCOS found that elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was associated with increased odds of depression even after accounting for age and BMI (OR: 2.23, 95% CI: 1.11–4.46).<sup>15</sup> Inflammatory cytokines are thought to affect the availability of serotonin, resulting in decreased serotonin levels which consequently manifest in depression symptoms. Depression in turn is thought to increase inflammation.<sup>16</sup> Others have found that serum androstenedione levels and testosterone levels were associated with depressive symptoms or scores.<sup>17,18</sup> However, a meta-regression of 9 studies in women with PCOS failed to demonstrate an association between depression and total or free testosterone.<sup>1</sup> These intrinsic components can then manifest as extrinsic factors associated with depression risk. For example, in a meta-regression of 14 studies evaluating the pooled SMDs, women with PCOS and concurrent depression had higher BMIs and Ferriman Galleway (FG) scores compared to those without concurrent depression, although effect sizes were small.<sup>1</sup> However, several studies have shown that depression risk in those with PCOS is independent of BMI.<sup>19</sup>

Similar to depression, several underlying risk factors may contribute to the increased risk of anxiety observed in those with PCOS. In a meta-regression of pooled SMDs, women with PCOS and concurrent anxiety had a higher mean BMI, FG scores, and free testosterone/free androgen index, but not HOMA-IR, compared to those who did not have anxiety.<sup>1</sup> Supporting the role of hyperandrogenism and subsequent hirsutism on mental health, a randomized controlled trial (RCT) of laser treatment over 6 months in 88 hirsute women with PCOS found that mean depression scores and anxiety scores as measured by the Hospital Anxiety and Depression Scale (HADS) fell significantly in the intervention group ( $3.6 \pm 3.5$  vs.  $6.7 \pm 4.5$  for depression;  $8.2 \pm 3.8$  vs.  $11.1 \pm 3.5$  for anxiety,  $p < 0.05$  for both).<sup>20</sup> In contrast, other studies have found that those with anxiety did not have increased odds of hirsutism.<sup>1</sup> Body image distress, potentially stemming from extrinsic factors such as hirsutism, may also correlate with both anxiety and depression. In a cross-sectional study of 189 women with PCOS and 225 controls, anxiety in PCOS was predicted by negative body image and lower appearance evaluation on body image surveys was associated with depression independent of BMI.<sup>21</sup>

Interestingly, daughters of mothers with PCOS are at increased risk of developing anxiety disorders, with one Swedish registry study of 8,864 children of mothers with

PCOS finding a hazard ratio [HR] of 1.78 (95% CI 1.19–2.67) in daughters of mothers with PCOS being diagnosed with anxiety.<sup>22</sup> Another prospective birth cohort study of 1,915 mother–child dyads had similar findings for increased risk of anxiety with children of mothers with PCOS (adjusted risk ratio [aRR]: 1.62; 96% CI: 1.02–2.57) as well as increased risk of borderline emotional symptoms (aRR: 1.66; 95% CI: 1.18–2.33).<sup>23</sup> Mice studies exploring this association have found prenatal androgen exposure as a proposed mechanism. In a PCOS-like mouse model, first-generation female offspring (F1 generation) had anxiety-like behaviors that were transmitted through the female germline to the third generation. Research targeting the amygdala suggests that differential gene expression in androgenized mice may contribute to this association.<sup>22</sup> Taken together, these findings suggest that therapeutic interventions targeting the metabolic and androgenic features of PCOS or those improving body image may help decrease depression and anxiety symptoms.

## Impact of Current PCOS Treatments on Depression

### Lifestyle Intervention

Lifestyle interventions are some of the first-line treatments for symptoms of PCOS. A RCT of 104 overweight/obese PCOS women found that lifestyle interventions in 3 arms including diet restriction, diet and aerobic exercise, or diet and a combined aerobic-resistance exercise all resulted in improvements in depression scores over the course of 20 weeks.<sup>24</sup> A clinical trial of 87 women with PCOS randomized to 16 weeks of continuous aerobic training, intermittent aerobic training or control, found that those in the intervention arms had significant improvements in both depression and anxiety scores for HADS ( $p < 0.02$ ).<sup>25</sup> In contrast, a secondary analysis of the oral contraceptive pill (OCP) versus weight loss (OWL-PCOS) study which utilized a 16-week lifestyle intervention program showed that while the lifestyle and combination OCP/lifestyle intervention groups had significant improvements in quality of life as measured by the Polycystic Ovarian Syndrome Questionnaire (PCOSQ), the prevalence of depression as screened by positive screens on the Prime-MD and/or use of medications did not significantly change (OR: 0.64; 95% CI: 0.34–1.22 for lifestyle group), although small sample size may have contributed to these findings.<sup>26</sup> A separate trial of 72 women with PCOS randomized to 16 weeks of acupuncture, exercise, or no interventions also found that those in the exercise group did not have significant changes in depression or anxiety scores at weeks 16 or 32.<sup>27</sup> In a systematic review of exercise interventions on mental health in women with PCOS, eight studies measured the effect of exercise interventions, with five reporting significant improvements in depression scores, including the studies described earlier.<sup>24,25,28</sup> Exercise characteristics varied with each study from resistance training to aerobic exercises as did measures of depression; therefore, conclusions could not be made about individual regimens. They do note, however, that a large proportion of exercise interventions resulted in improvements across

multiple domains of quality of life surveys, including emotions and infertility domains, suggesting that exercise can improve several aspects of mental health and quality of life in women with PCOS outside of weight loss. This parallels what is known in the general population, where exercise can positively impact mood independent of weight through several immunologic and physiologic pathways such as endorphin release.<sup>29,30</sup>

### Bariatric Surgery

Bariatric surgery is considered a highly effective weight loss option particularly for those unable to lose weight with exercise or dietary modification.<sup>31</sup> Prior meta-analyses in the general population have demonstrated improvements in depressive symptom severity following bariatric surgery,<sup>32</sup> although some of this benefit may attenuate 2 to 3 years following surgery.<sup>33</sup> Further studies are needed, however, in the PCOS population. While several studies have shown improvements in PCOS symptomatology with bariatric surgery,<sup>34</sup> to date none have evaluated depression and anxiety as primary outcomes.

### Oral Contraceptive Pills

Given OCPs' anti-androgenic effects, OCPs have been evaluated for their effect on mental health parameters in women with PCOS. In the general population, they can improve premenstrual dysphoric disorder and are generally beneficial for affect but may worsen mood in some individuals dependent on their psychiatric history.<sup>35</sup> In a prospective observational study of 36 patients with PCOS, 6 months of treatment with oral contraceptives did not result in significant changes in mean depression scores.<sup>36</sup> However, in data from the OWL-PCOS study in 2016, OCP use was associated with a significant reduction in abnormal depression score prevalence (4.4 vs. 13.3%, OR: 0.30; 95% CI: 0.09–0.99).<sup>26</sup> There are, however, no subsequent studies evaluating OCPs' direct effect on depression as a primary outcome in the PCOS population; therefore, more studies are necessary to draw conclusions.

### Insulin Sensitizing Agents

As previously mentioned, women with PCOS and depression had higher HOMA-IRs compared to those without depression.<sup>15</sup> Therefore, the role of insulin-sensitizing agents on mood has been explored. In the general population of diabetic patients, there is no clear consensus on whether anti-diabetic agents reduce depression, with some supporting metformin or pioglitazone use but others not finding consistent associations, and positive findings not correlating with HOMA-IR.<sup>37,38</sup> A pilot trial of 19 adolescents and 25 adults with PCOS found that after 3 months of metformin 1,500 mg/day, the severity of depression symptoms as measured by the Beck Depression Inventory-II (BDI-II) decreased significantly in both the adolescent and adult groups, with 70.5% of patients having a decrease of 2 points or more ( $p < 0.001$ ).<sup>39</sup> However, prior meta-analyses have not shown improvements in PCOS quality of life with the addition of metformin to lifestyle interventions.<sup>40</sup> A 6-week double-

blind study of 50 patients with PCOS and major depressive disorder found that those randomly assigned to pioglitazone for 6 weeks had superior reductions in Hamilton depression rating scale (HDRS) depression scores compared to metformin (38.3 vs. 8.3% reduction,  $p < 0.001$ ), although interestingly this appeared to be independent of any effect on HOMA-IR.<sup>41</sup> In a prospective study in China of 75 patients with PCOS and psychological distress as measured by the Symptom Checklist 90-R (SCL 90-R), patients on a pioglitazone-metformin complex had significantly decreased depression symptom severity (mean:  $2.08 \pm 0.74$  to  $1.61 \pm 0.46$ ,  $p = 0.010$ ) at week 12 of therapy, whereas those on metformin alone or placebo showed no change in scores. The authors here postulated its mechanism of action to be via improvement in inflammatory markers and total testosterone levels that were concomitantly noted in biochemical assessments, although correlation analyses were not performed within the study to confirm this theory.<sup>42</sup> In contrast, a cross-sectional study of 19 obese women with PCOS and 17 age- and weight-matched controls, after 6 months of treatment with 1.8 mg daily of liraglutide, did not show significant differences in the prevalence of those with elevated Centre for Epidemiologic Studies Depression (CES-D) scores; however, drop-out rate was high resulting in only 25 total participants analyzed at the end.<sup>43</sup> Larger prospective studies are needed to evaluate effects of individual agents on mood, but as with the general population, limited evidence does not support a consistent association.

### Psychosocial Interventions

Cognitive behavioral therapy (CBT) is a form of psychotherapy that focuses on changing the dysfunctional thoughts that lead to negative mood and is currently one of the first-line treatments for major depressive disorder.<sup>44,45</sup> In a RCT of 84 women with PCOS, participants were randomized to 8 weekly group sessions of CBT. Those in the intervention group were noted to have significantly lower depression scores on the BDI (mean:  $6.7 \pm 4.3$  vs.  $24.4 \pm 5.0$ ,  $p < 0.001$ ) and higher quality of life scores as measured by the PCOSQ (mean:  $89.0 \pm 12.9$  vs.  $71.4 \pm 4.1$ ,  $p < 0.001$ ) compared to the control group after intervention (BDI mean:  $24.5 \pm 2.8$  vs.  $23.3 \pm 3.2$ ).<sup>46</sup> Another randomized trial of 33 overweight/obese women with PCOS and depressive symptoms noted that 8 weeks of weekly CBT plus lifestyle interventions resulted in a 0.24 points/week reduction in CES-D scores; however, this was not significantly different from the lifestyle intervention alone arm ( $-0.34$  points/week,  $p = 0.68$ ).<sup>47</sup> A systematic review and meta-analysis of the impact of CBT for depression in women with PCOS found that of four included studies with low risk of bias, CBT resulted in moderate improvements in depression compared to care as usual (Cohen's  $d$  of 0.66 [95% CI: 0.26–1.06]). When excluding studies with lifestyle intervention, the results were more favorable (Cohen's  $d$  of 2.11 [95% CI: 1.64–2.59]), though this sensitivity analysis included a study with high risk of bias and results were notable for greater heterogeneity ( $I^2$  statistic of 85%).<sup>48</sup>

Mind-body interventions such as yoga and mindful meditation are a group of various techniques focusing on

mindfulness and paying attention to one's thoughts and physical sensations with the aim of reducing stress and increasing acceptance.<sup>49</sup> A RCT in Greece explored the impact of an 8-week mindfulness stress management program on measures of depression and anxiety in women with PCOS. The 23 women randomized to the intervention group were noted to have significant reductions in depressive symptoms as measured by the Depression Anxiety and Stress Scale (DASS21) compared to the 15 women in the control group (mean:  $17.2 \pm 10.0$  vs.  $4.3 \pm 3.3$ ,  $p = 0.011$ ) along with reductions in salivary cortisol levels ( $p = 0.001$ ), with no significant changes observed between intervention and control groups for anxiety.<sup>50</sup> A separate randomized clinical trial of 37 obese women with PCOS randomized to either 6 months of motivational interviewing or standard advice did not find differences in weight loss, quality of life, or depression as measured by the Major Depression Index (MDI) between groups. Of note, drop-out rates were high at approximately 20% for each group.<sup>51</sup> Another systematic review of five RCTs utilizing multiple forms of psychosocial interventions such as CBT, stress management, and hypnosis on depressive symptoms in women with PCOS found CBT significantly improved depression scores in several studies, although studies were conflicting on the benefit of concurrent lifestyle interventions with CBT.<sup>52</sup> Due to significant heterogeneity between studies, a meta-analysis could not be completed, and the authors emphasized the need for larger, higher quality studies that utilize such techniques as multiphase optimization strategy to evaluate varying impacts of recommended treatments such as medication and lifestyle interventions.

It is likely that given the various etiologies for depression, combinations of treatments may be necessary. A secondary analysis of a randomized study compared changes in depression scores in a CBT lifestyle intervention trial including 140 women with PCOS over the course of 12 months. Depression scores as measured by the BDI-II were found to be significantly reduced in the lifestyle intervention arms compared to controls ( $p = 0.045$ ). Interestingly, however, androgen levels and HOMA-IR did not appear to mediate this effect.<sup>53</sup>

### Psychiatric Medications

The 2023 International Guidelines for the management of PCOS noted only one RCT evaluating use of antidepressants specifically in women with PCOS.<sup>12</sup> The RCT was conducted in Iran on 64 women with PCOS evaluating effect of sertraline on HDRS scores and prolactin levels. The authors noted that both in the normal and high baseline prolactin groups, those who received sertraline had significantly lower HDRS scores after treatment compared to placebo ( $p < 0.001$ ); however, sample sizes were small and mean scores were not reported.<sup>54</sup> The guidelines recommended considering antidepressants if psychotherapeutic strategies are unsuccessful or symptoms are persistent. When looking in the general population, the 2019 American Psychological Association guidelines recommend clinicians offer either psychotherapy or second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors for the initial treatment of

depression in adults. Psychotherapy includes CBT, behavioral therapy, interpersonal psychotherapy, and supportive therapy. There was insufficient evidence to recommend one pharmacotherapy over another, but in general switching agents is considered if no response is noted within 4 to 8 weeks of initiating treatment.<sup>55</sup> While they are first line, common side effects to SSRIs to be aware of include headache, nausea, and insomnia, which can be mitigated by adjusting the timing or dose of medication.<sup>56</sup> Weight gain is also a potential side effect of antidepressants<sup>57</sup> which could be antagonistic to other comorbidities associated with PCOS. However, SSRIs are less likely to cause weight gain compared to other antidepressants with the exception of paroxetine. Moreover, when using certain antipsychotics, this side effect may be counteracted through concomitant use of metformin, though this finding needs further evaluation with antidepressants.<sup>58</sup>

### Complimentary Medicine Treatments

Acupuncture has often been used in the treatment of depression in the general population.<sup>59,60</sup> A randomized clinical trial of 72 women with PCOS assigned to 16 weeks of acupuncture, exercise, or control groups found reductions in Montgomery Asberg Depression Rating Scale ( $-1.00 \pm 8.07$ ) and Brief Scale for Anxiety ( $-1.74 \pm 7.88$ ) in the acupuncture group at week 32.<sup>27</sup> A secondary analysis of a pilot randomized trial in China conducted over 16 weeks in 54 women with PCOS found that those in the electroacupuncture arm had significantly decreased depression scores as measured by the Zung-SDS (median: 33 [IQR: 31–40] vs. 42 [IQR: 37–50],  $p = 0.004$ ) and significantly improved total Chinese Quality of Life scores (median: 198 [IQR: 175–210] vs. 176 [IQR: 173–187],  $p = 0.023$ ).<sup>61</sup>

Dietary modifications targeting insulin-sensitizing and inflammatory pathways have also been evaluated. A trial of 84 women with PCOS allocated to vitamin K2 supplements, which is proposed to have insulin-sensitizing effects, or placebo found significant reductions in BDI-II scores in the intervention arm (mean  $15.0 \pm 8.3$  vs.  $16.9 \pm 7.9$ ,  $p = 0.013$ ).<sup>62</sup> However, vitamin K's glycemic effects in the general population are controversial.<sup>63</sup> A randomized placebo-controlled trial of the effect of 12 weeks of 100 mg/day of coenzyme Q10 (CoQ10) in 55 women with PCOS found significant reductions in BDI scores ( $p = 0.03$ ) and high-sensitivity C-reactive protein ( $p = 0.005$ ) as well as biochemical androgen levels compared to placebo.<sup>64</sup> However, several published studies on supplements have suffered from a lack of data transparency and validity, resulting in expression of concern or retractions and difficulty in drawing reliable conclusions.<sup>65–67</sup>

## Impact of Current PCOS Treatments on Anxiety Treatments

### Lifestyle Interventions

Studies exploring treatment options for anxiety in women with PCOS have in general been more limited compared to depression. In the secondary analysis of the OWL-PCOS study, the prevalence of anxiety, as screened by positive

screens on the Prime-MD and/or use of medications, decreased significantly in the group with 16 weeks of lifestyle intervention (OR: 0.30; 95% CI: 0.10–0.85).<sup>26</sup> In contrast, the previously discussed trial comparing acupuncture to lifestyle intervention did not find improvements in anxiety scores in the lifestyle group.<sup>27</sup> In the systematic review of exercise interventions on mental health in women with PCOS, six studies measured the effect of exercise interventions which ranged in length from 12 to 16 weeks, with half reporting significant improvements in anxiety symptoms.<sup>28</sup> Evidence is therefore conflicting and due to the variety in types of interventions (such as aerobic or resistance training of varying frequency per week), conclusions could not be made regarding impacts of specific types of regimens.

### Bariatric Surgery

In the general population, data are more mixed as to the benefit of bariatric surgery on anxiety, with some showing no benefit or slight worsening of symptoms.<sup>33</sup> As mentioned previously, further data are needed to evaluate this in the PCOS population.

### Oral Contraceptive Pills

There are few studies exploring the impact of oral contraception on anxiety in the general population; however, some studies suggest that as with depression, effect on mood may be influenced by prior or current psychiatric history with others finding that OCPs may be detrimental to exposure therapy for specific anxieties.<sup>68–70</sup> Similarly, limited evidence exists as to OCP's role in alleviating anxiety symptoms in women with PCOS. In the prospective observational study of 36 patients with PCOS conducted in 2012, six months of treatment with oral contraceptives did not result in significant changes in mean anxiety rates as measured by the HADS.<sup>36</sup> The secondary analysis of OWL-PCOS also did not show significant changes in anxiety related to OCPs (OR: 0.32, 95% CI: 0.06–1.64).<sup>26</sup>

### Insulin-Sensitizing Agents

In the general population, data on association of insulin-sensitizing agents with anxiety are limited, with some studies suggesting that use of GLP-1 agonists improves depression and anxiety while data on metformin reducing anxiety are generally limited to rodent studies.<sup>71–73</sup> In the pilot trial of 19 adolescents and 25 adults with PCOS taking daily metformin for 3 months, significant reductions in anxiety symptoms as measured by the Beck Anxiety Inventory (BAI) were also noted, with 77.5% of patients noting improvement in anxiety ( $p < 0.001$ ).<sup>39</sup> In the prospective study in China of 75 patients with PCOS and psychological distress as defined by SCL 90-R scores, patients on a pioglitazone–metformin complex medication had significantly decreased anxiety symptom severity, as defined by any SCL 90-R factor scores  $> 2$ , after 12 weeks of therapy (mean:  $2.31 \pm 0.75$  to  $1.65 \pm 0.38$ ,  $p < 0.001$ ), whereas those on metformin alone or placebo showed no change in scores.<sup>42</sup> However, conclusions are difficult to draw given the limited number and small sample sizes of existing studies.

### Psychosocial Interventions

CBT is also considered one of the first-line treatments for anxiety disorders in the general population.<sup>74</sup> In the randomized trial of 33 overweight/obese women with PCOS, authors noted that 8 weeks of weekly CBT plus lifestyle interventions resulted in a 0.16-point reduction in State Trait Anxiety Inventory (STAI-S) scores per week (95% CI:  $-0.50$  to  $-0.18$ ), although no differences were noted when compared to the lifestyle intervention alone arm ( $p = 0.49$ ).<sup>47</sup> In the RCT of 84 women with PCOS randomized to CBT, significantly lower anxiety scores as measured by the STAI were also noted compared to controls (state anxiety mean:  $29.0 \pm 3.9$  vs.  $42.3 \pm 2.8$ ; trait anxiety mean:  $29.3 \pm 4.3$  vs.  $41.3 \pm 2.9$ ,  $p < 0.001$ ).<sup>46</sup> In contrast, a 4-month RCT of 56 women with PCOS and BMI  $> 27$  kg/m<sup>2</sup> found that those in the behavioral modification program did not have significantly different levels of anxiety on the Psychological General Well-being Index Questionnaire compared to the control group ( $p = 0.06$ ).<sup>75</sup> An exploratory study of 42 women in PCOS in Slovenia who were randomized to a 2-month Mindfulness-Based Stress Reduction (MBSR) program found that the severity of anxiety symptoms as assessed by the BAI was significantly decreased post-intervention ( $p = 0.009$ ) and persisted at 6-month follow-up.<sup>76</sup> A randomized control trial of 90 adolescents with PCOS found that after a 12-week holistic yoga module, STAI trait anxiety scores were significantly different between groups ( $p = 0.002$ ), but not state anxiety ( $p = 0.243$ ).<sup>77</sup> However, a recent systematic review of three RCTs evaluating psychosocial interventions on anxiety symptoms in women with PCOS found that anxiety post-behavioral interventions was not significantly different when compared to controls.<sup>52</sup>

### Psychiatric Medications

There are no studies evaluating the efficacy of different anxiolytics in treating women with PCOS. As with depression, the 2023 International Guidelines suggest considering antidepressant medications if first-line management with psychological therapy fails to achieve symptom control or if suicidal symptoms are present.<sup>12</sup> The choice of antidepressants may be guided by general population guidelines and can be SSRIs, noradrenergic reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, or melatonin agonists, taking into consideration to limit use of agents that exacerbate PCOS symptoms, including weight gain. Within the general population, in addition to SSRIs and benzodiazepines, beta-blockers such as propranolol have also been used to manage symptoms of anxiety. However, its use may be dependent on the type of disorder, showing promise for posttraumatic stress disorder but limited controversial evidence for long-term management of anxiety.<sup>78,79</sup>

### Complimentary Medicine Treatments

In the secondary analysis of Chinese randomized trial of 16 weeks of electroacupuncture in women with PCOS, those in the intervention arm had significant reductions in anxiety symptoms as measured by the Zang-SAS compared to the control group (median: 35 [IQR: 32–38] vs. 43 [IQR: 38–48],  $p = 0.003$ ).<sup>61</sup> The randomized placebo-controlled trial of 55 women with PCOS receiving CoQ10 or placebo also found

significant reductions in the Beck Anxiety Inventory (BAI) compared to the placebo group ( $p = 0.01$ ).<sup>64</sup> A scoping review of 57 studies evaluating Ayurvedic interventions in women with PCOS found only three studies exploring psychosocial outcomes,<sup>80</sup> with one study demonstrating improvements in anxiety and depression scores on hospital anxiety depression inventory among 60 women doing a 3-month course of Ayurveda or Ayurveda plus yoga.<sup>81</sup>

## Summary

PCOS is a complex and multifactorial endocrine disease; therefore, it should not be surprising that treating its sequelae may require a multifactorial approach. Women with PCOS are known to be at a greater risk for anxiety and depression, with several proposed pathophysiologic mechanisms. What is less clear is the optimal strategy to take when addressing mental health concerns. Currently, data on the impact of first-line medications and interventions used to manage PCOS symptoms such as lifestyle interventions or insulin-sensitizing agents are promising but limited. Therapeutic options that have been explored include OCPs, insulin-sensitizing agents, and psychosocial interventions. Lifestyle interventions appear to decrease depression and anxiety scores in women with PCOS. OCPs and insulin-sensitizing agents have inconclusive data as to their benefit. CBT appears to be beneficial in treating both depression and anxiety, consistent with findings in the general population. There is very limited evidence when looking at potential psychiatric medications. Larger observational or RCT studies with longer follow-up time are urgently needed to determine which strategies are effective. Strategies currently used in the general population should be further explored in women with PCOS as well, such as bariatric surgery. In addition, as with the multipronged treatment options that are likely needed, a collaborative approach with obstetrician-gynecologists, primary care providers, and mental health providers is vital to providing comprehensive care to this population. For this to occur, there should be increased awareness among these groups as to the negative impact of PCOS on depression and anxiety so that patient education and compliance with recommended treatments can also be improved.

### Conflict of Interest

None declared.

## References

- Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2017;32(05):1075–1091
- Wang Y, Ni Z, Li K. The prevalence of anxiety and depression of different severity in women with polycystic ovary syndrome: a meta-analysis. *Gynecol Endocrinol* 2021;37(12):1072–1078
- Yin X, Ji Y, Chan CLW, Chan CHY. The mental health of women with polycystic ovary syndrome: a systematic review and meta-analysis. *Arch Women Ment Health* 2021;24(01):11–27
- Brutocao C, Zaiem F, Alsawas M, Morrow AS, Murad MH, Javed A. Psychiatric disorders in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Endocrine* 2018;62(02):318–325
- Çoban ÖG, Tulacı ÖD, Adanır AS, Önder A. Psychiatric disorders, self-esteem, and quality of life in adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2019;32(06):600–604
- Rowlands IJ, Teede H, Lucke J, Dobson AJ, Mishra GD. Young women's psychological distress after a diagnosis of polycystic ovary syndrome or endometriosis. *Hum Reprod* 2016;31(09):2072–2081
- Greenwood EA, Yaffe K, Wellons MF, Cedars MI, Huddlestone HG. Depression over the lifespan in a population-based cohort of women with polycystic ovary syndrome: longitudinal analysis. *J Clin Endocrinol Metab* 2019;104(07):2809–2819
- Karjula S, Morin-Papunen L, Auvinen J, et al. Psychological distress is more prevalent in fertile age and premenopausal women with PCOS symptoms: 15-year follow-up. *J Clin Endocrinol Metab* 2017;102(06):1861–1869
- Nasiri-Amiri F, Faramarzi M, Omidvar S, Alizadeh-Navaei R. Depression and anxiety in adolescents and young women with polycystic ovary syndrome: a systematic review and meta-analysis. *Int J Adolesc Med Health* 2023;35(03):233–242
- Lee IT, Sansone S, Irfan M, Copp T, Beidas R, Dokras A. Implementation of international guidelines for polycystic ovary syndrome: barriers and facilitators among gynecologists and primary care providers. *F S Rep* 2022;3(02):94–101
- Ismayilova M, Yaya S. "I felt like she didn't take me seriously": a multi-methods study examining patient satisfaction and experiences with polycystic ovary syndrome (PCOS) in Canada. *BMC Womens Health* 2022;22(01):47
- Teede HJ, Tay CT, Laven J, et al; International PCOS Network. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Fertil Steril* 2023;120(04):767–793
- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000;160(14):2101–2107
- Castro A, Roca M, Ricci-Cabello I, et al. Adherence to lifestyle interventions for treatment of adults with depression: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2021;18(24):13268
- Greenwood EA, Pasch LA, Cedars MI, Legro RS, Eisenberg E, Huddlestone HGEunice Kennedy Shriver National Institute of Child Health and Human Development Reproductive Medicine Network. Insulin resistance is associated with depression risk in polycystic ovary syndrome. *Fertil Steril* 2018;110(01):27–34
- Xing L, Xu J, Wei Y, et al. Depression in polycystic ovary syndrome: Focusing on pathogenesis and treatment. *Front Psychiatry* 2022;13:1001484
- Milman LW, Sammel MD, Barnhart KT, Freeman EW, Dokras A. Higher serum total testosterone levels correlate with increased risk of depressive symptoms in Caucasian women through the entire menopausal transition. *Psychoneuroendocrinology* 2015;62:107–113
- Yoshida T, Saito K, Kawamura T, et al. Circulating steroids and mood disorders in patients with polycystic ovary syndrome. *Steroids* 2021;165:108748
- Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Obstet Gynecol* 2011;117(01):145–152
- Clayton WJ, Lipton M, Elford J, Rustin M, Sherr L. A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. *Br J Dermatol* 2005;152(05):986–992
- Alur-Gupta S, Chemerinski A, Liu C, et al. Body-image distress is increased in women with polycystic ovary syndrome and mediates depression and anxiety. *Fertil Steril* 2019;112(05):930–938.e1

- 22 Risal S, Manti M, Lu H, et al. Prenatal androgen exposure causes a sexually dimorphic transgenerational increase in offspring susceptibility to anxiety disorders. *Transl Psychiatry* 2021;11(01):45
- 23 Robinson SL, Ghassabian A, Sundaram R, et al. The associations of maternal polycystic ovary syndrome and hirsutism with behavioral problems in offspring. *Fertil Steril* 2020;113(02):435–443
- 24 Thomson RL, Buckley JD, Lim SS, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. *Fertil Steril* 2010;94(05):1812–1816
- 25 Kogure GS, Lopes IP, Ribeiro VB, et al. The effects of aerobic physical exercises on body image among women with polycystic ovary syndrome. *J Affect Disord* 2020;262:350–358
- 26 Dokras A, Sarwer DB, Allison KC, et al. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J Clin Endocrinol Metab* 2016;101(08):2966–2974
- 27 Stener-Victorin E, Holm G, Janson PO, Gustafson D, Waern M. Acupuncture and physical exercise for affective symptoms and health-related quality of life in polycystic ovary syndrome: secondary analysis from a randomized controlled trial. *BMC Complement Altern Med* 2013;13:131
- 28 Patten RK, Pascoe MC, Moreno-Asso A, Boyle RA, Stepto NK, Parker AG. Effectiveness of exercise interventions on mental health and health-related quality of life in women with polycystic ovary syndrome: a systematic review. *BMC Public Health* 2021;21(01):2310
- 29 Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. *Maturitas* 2017;106:48–56. Doi: 10.1016/j.maturitas.2017.09.003
- 30 Smith PJ, Merwin RM. The role of exercise in management of mental health disorders: an integrative review. *Annu Rev Med* 2021;72:45–62
- 31 Kang JH, Le QA. Effectiveness of bariatric surgical procedures: a systematic review and network meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017;96(46):e8632
- 32 Dawes AJ, Maggard-Gibbons M, Maher AR, et al. Mental health conditions among patients seeking and undergoing bariatric surgery: a meta-analysis. *JAMA* 2016;315(02):150–163
- 33 Gill H, Kang S, Lee Y, et al. The long-term effect of bariatric surgery on depression and anxiety. *J Affect Disord* 2019;246:886–894
- 34 Skubleny D, Switzer NJ, Gill RS, et al. The impact of bariatric surgery on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Surg* 2016;26(01):169–176
- 35 Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002;70(03):229–240
- 36 Cinar N, Harmanci A, Demir B, Yildiz BO. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study. *Hum Reprod* 2012;27(06):1840–1845
- 37 Hamal C, Velugoti LSDR, Tabowei G, et al. Metformin for the improvement of comorbid depression symptoms in diabetic patients: a systematic review. *Cureus* 2022;14(08):e28609
- 38 Moulton CD, Hopkins CWP, Ismail K, Stahl D. Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials. *Psychoneuroendocrinology* 2018;94:91–103
- 39 Erensoy H, Niafar M, Ghafarzadeh S, Aghamohammadzadeh N, Nader ND. A pilot trial of metformin for insulin resistance and mood disturbances in adolescent and adult women with polycystic ovary syndrome. *Gynecol Endocrinol* 2019;35(01):72–75
- 40 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(05):560–574
- 41 Kashani L, Omidvar T, Farazmand B, et al. Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression. *Psychoneuroendocrinology* 2013;38(06):767–776
- 42 Guo QJ, Shan J, Xu YF, et al. Pioglitazone metformin complex improves polycystic ovary syndrome comorbid psychological distress via inhibiting NLRP3 inflammasome activation: a prospective clinical study. *Mediators Inflamm* 2020;2020:3050487
- 43 Kahal H, Kilpatrick E, Rigby A, Coady A, Atkin S. The effects of treatment with liraglutide on quality of life and depression in young obese women with PCOS and controls. *Gynecol Endocrinol* 2019;35(02):142–145
- 44 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000;157(4, Suppl):1–45
- 45 Gautam M, Tripathi A, Deshmukh D, Gaur M. Cognitive behavioral therapy for depression. *Indian J Psychiatry* 2020;62(Suppl 2):S223–S229
- 46 Majidzadeh S, Mirghafourvand M, Farvareshi M, Yavarikia P. The effect of cognitive behavioral therapy on depression and anxiety of women with polycystic ovary syndrome: a randomized controlled trial. *BMC Psychiatry* 2023;23(01):332
- 47 Cooney LG, Milman LW, Hantsoo L, et al. Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: a pilot randomized clinical trial. *Fertil Steril* 2018;110(01):161–171.e1
- 48 Jiskoot G, van der Kooi AL, Busschbach J, Laven J, Beerthuisen A. Cognitive behavioural therapy for depression in women with PCOS: systematic review and meta-analysis. *Reprod Biomed Online* 2022;45(03):599–607
- 49 Bandyaly SS, Sheth NC, Matuella SK, et al. Mind-body interventions for anxiety disorders: a review of the evidence base for mental health practitioners. *Focus Am Psychiatr Publ* 2021;19(02):173–183
- 50 Stefanaki C, Bacopoulou F, Livadas S, et al. Impact of a mindfulness stress management program on stress, anxiety, depression and quality of life in women with polycystic ovary syndrome: a randomized controlled trial. *Stress* 2015;18(01):57–66
- 51 Moeller LV, Lindhardt CL, Andersen MS, Glintborg D, Ravn P. Motivational interviewing in obese women with polycystic ovary syndrome - a pilot study. *Gynecol Endocrinol* 2019;35(01):76–80
- 52 Phimpasone-Brady P, Palmer B, Vela A, et al. Psychosocial interventions for women with polycystic ovary syndrome: a systematic review of randomized controlled trials. *F&S Reviews* 2022;3(01):42–56
- 53 Jiskoot G, Dietz de Loos A, Beerthuisen A, Timman R, Busschbach J, Laven J. Long-term effects of a three-component lifestyle intervention on emotional well-being in women with polycystic ovary syndrome (PCOS): a secondary analysis of a randomized controlled trial. *PLoS One* 2020;15(06):e0233876
- 54 Masoudi M, Ansari S, Kashani L, et al. Effect of sertraline on depression severity and prolactin levels in women with polycystic ovary syndrome: a placebo-controlled randomized trial. *Int Clin Psychopharmacol* 2021;36(05):238–243
- 55 Guideline Development Panel for the Treatment of Depressive Disorders. Summary of the clinical practice guideline for the treatment of depression across three age cohorts. *Am Psychol* 2022;77(06):770–780
- 56 Permanente K Adult and Adolescent Depression Screening, Diagnosis, and Treatment Guideline 2021. Accessed September 7, 2023 at: <https://wa.kaiserpermanente.org/static/pdf/public/guidelines/depression.pdf>
- 57 Fava M. Weight gain and antidepressants. *J Clin Psychiatry* 2000;61(Suppl 11):37–41
- 58 de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry* 2016;16(01):341

- 59 Zhichao H, Ching LW, Huijuan L, et al. A network meta-analysis on the effectiveness and safety of acupuncture in treating patients with major depressive disorder. *Sci Rep* 2021;11(01):10384
- 60 Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. *Cochrane Database Syst Rev* 2018;3(03):CD004046
- 61 Wang Z, Dong H, Wang Q, et al. Effects of electroacupuncture on anxiety and depression in unmarried patients with polycystic ovarian syndrome: secondary analysis of a pilot randomised controlled trial. *Acupunct Med* 2019;37(01):40–46
- 62 Tarkesh F, Namavar Jahromi B, Hejazi N, Hoseini G. Effect of vitamin K2 administration on depression status in patients with polycystic ovary syndrome: a randomized clinical trial. *BMC Womens Health* 2022;22(01):315
- 63 Shahdadian F, Mohammadi H, Rouhani MH. Effect of vitamin K supplementation on glycemic control: a systematic review and meta-analysis of clinical trials. *Horm Metab Res* 2018;50(03):227–235
- 64 Karamali M, Gholizadeh M. The effects of coenzyme Q10 supplementation on metabolic profiles and parameters of mental health in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2022;38(01):45–49
- 65 Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Clin Endocrinol (Oxf)* 2023;98(05):745
- 66 Expression of concern: “Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial”. *Clin Endocrinol (Oxf)* 2023;98(05):746
- 67 Expression of concern: “Comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in polycystic ovary syndrome: a randomized controlled clinical trial”. *Clin Endocrinol (Oxf)* 2023;98(05):748
- 68 Bengtsdotter H, Lundin C, Gemzell Danielsson K, et al. Ongoing or previous mental disorders predispose to adverse mood reporting during combined oral contraceptive use. *Eur J Contracept Reprod Health Care* 2018;23(01):45–51
- 69 Raeder F, Merz CJ, Tegenthoff M, et al. Do oral contraceptives modulate the effects of stress induction on one-session exposure efficacy and generalization in women? *Psychopharmacology (Berl)* 2023;240(05):1075–1089
- 70 Raeder F, Heidemann F, Schedlowski M, Margraf J, Zlomuzica A. No pills, more skills: the adverse effect of hormonal contraceptive use on exposure therapy benefit. *J Psychiatr Res* 2019;119:95–101
- 71 Zemdeg J, Martin H, Pintana H, et al. Metformin promotes anxiolytic and antidepressant-like responses in insulin-resistant mice by decreasing circulating branched-chain amino acids. *J Neurosci* 2019;39(30):5935–5948
- 72 Tsai WH, Sung FC, Chiu LT, Shih YH, Tsai MC, Wu SI. Decreased risk of anxiety in diabetic patients receiving glucagon-like peptide-1 receptor agonist: a nationwide, population-based cohort study. *Front Pharmacol* 2022;13:765446
- 73 Pozzi M, Mazhar F, Peeters GGAM, et al. A systematic review of the antidepressant effects of glucagon-like peptide 1 (GLP-1) functional agonists: Further link between metabolism and psychopathology: Special Section on “Translational and Neuroscience Studies in Affective Disorders”. Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summarize relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. *J Affect Disord* 2019;257:S0165-0327(19)30593-2
- 74 Kaczurkin AN, Foa EB. Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. *Dialogues Clin Neurosci* 2015;17(03):337–346
- 75 Oberg E, Lundell C, Blomberg L, Gidlöf SB, Egnell PT, Hirschberg AL. Psychological well-being and personality in relation to weight loss following behavioral modification intervention in obese women with polycystic ovary syndrome: a randomized controlled trial. *Eur J Endocrinol* 2020;183(01):1–11
- 76 Dema H, Videtič Paska A, Kouter K, et al. Effects of mindfulness-based therapy on clinical symptoms and DNA methylation in patients with polycystic ovary syndrome and high metabolic risk. *Curr Issues Mol Biol* 2023;45(04):2717–2737
- 77 Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Effect of holistic yoga program on anxiety symptoms in adolescent girls with polycystic ovarian syndrome: a randomized control trial. *Int J Yoga* 2012;5(02):112–117
- 78 Steenen SA, van Wijk AJ, van der Heijden GJ, van Westrhenen R, de Lange J, de Jongh A. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. *J Psychopharmacol* 2016;30(02):128–139
- 79 Szeleszczuk Ł, Frączkowski D. Propranolol versus other selected drugs in the treatment of various types of anxiety or stress, with particular reference to stage fright and post-traumatic stress disorder. *Int J Mol Sci* 2022;23(17):10099
- 80 Rao VS, Armour M, Patwardhan K, et al. A scoping review of Ayurveda studies in women with polycystic ovary syndrome. *J Integr Complement Med* 2023;29(09):550–561
- 81 Rao V, Metri K, Rao S, Nagarathna R. Improvement in biochemical and psychopathologies in women having PCOS through yoga combined with herbal detoxification. *J Stem Cells* 2018;13(04):213–222