Management of Mental Health in Polycystic Ovarian Syndrome: A Review

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Abstract

Polycystic Ovarian Syndrome (PCOS) is the most prevalent endocrine condition in women of reproductive age. Due to physiological changes, worries about their aesthetics, and societal pressure brought on by infertility, women with PCOS may experience psychological distress. It has been estimated that up to 40% of women with PCOS experience depression and 34% showed clinically relevant anxiety. So far, only a few pharmaceutical drugs have been investigated for their psychological impact on PCOS patients. Apart from drug treatment, supplementation with various nutrients has been gaining interest due to their lesser side effects. Furthermore, lifestyle changes, particularly in the areas of diet and exercise, as well as psychological therapies such as cognitive behavioral therapy and stress management therapy, are advised to improve mental health conditions in PCOS women. The current study is focused on effective interventions for treating psychological symptoms in women affected with PCOS

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Keywords: *PCOS, mental health, psychological symptoms, depression, anxiety, supplements.*

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most prevalent endocrine condition in women of reproductive age, which results in anovulation, infertility, hirsutism, and hyperandrogenism. In PCOS, physical and metabolic abnormalities often lead to psychological issues such as sadness, anxiety, and sleep disorders. It has been estimated that up to 40% of women with PCOS experience depression. Numerous studies have revealed that women with PCOS experience psychological issues more frequently than women without the condition (Adali *et al.,* 2008). Additionally, social disengagement, eating disorders, and anxiety symptoms are all more prevalent in women having PCOS than in women without the condition. According to research, it is important to investigate the women's quality of life (QoL) and psychological health, 34% of women with PCOS show clinically relevant anxiety, and women with PCOS are at increased risk of acquiring anxious and depressive disorders (Benson *et al.,* 2009; Stapinska-Syniec *et al.,* 2018). The treatment of PCOS involves psychological wellness, which is crucial for self-efficacy and leading a healthy lifestyle. The current study offers good knowledge and evidence on the strategies for enhancing the psychological well-being of women affected with PCOS.

Risk factors

Infertility, subfertility, acne, hirsutism, and obesity are PCOS-related issues that may significantly lower a woman's quality of life (QoL) and her self-esteem of physical appearance, thus, experiencing anxiety and depression for a variety of causes, including high body mass index (BMI) and social stigma (Figure 1). Together with poor metabolic and hormonal characteristics, depression and anxiety are high-risk factors for patients with PCOS, if these issues are severe, individuals with PCOS might disengage from society. Hollinrake *et al*. found other factors that contributed to PCOS patients' higher incidence of depression compared to the control group, these include the genetic history of fertility problems, depression, a high BMI, sleeplessness, fatigue, a reduction in enthusiasm for everyday tasks, and appetite fluctuations (Hollinrake *et al.,* 2007). Pastore *et al* have reported that depression and anxiety in a patient with PCOS are because by the physical manifestations of hyperandrogenism, such as obesity, cystic acne, hirsutism, and hair loss (alopecia) (Pastore *et al.,* 2011). As women with PCOS seem to experience obesity more than women without PCOS and there is substantial evidence linking obesity and depression in the regular populace (Stunkard *et al.,* 2003), it is possible to theorize that obesity may contribute to psychological symptoms in women with PCOS and negatively affect their QoL (Bishop *et al.,* 2009). Additionally, the condition may make it difficult for individuals to engage in their regular jobs and social activities, significantly lowering their health-related quality of life (HRQoL). Another major complication of PCOS is a miscarriage, which may leave people in a great deal of physical and emotional pain (Kersting *et al.,* 2012).

ANIMAL MODELS FOR PCOS-INDUCED PSYCHOLOGICAL SYMPTOMS

The investigation of the psychological aspects of PCOS in animal models is still a novel and current endeavor. Since mental disorders may be experienced uniquely by humans and whose cognitive aspects are challenging to represent in animals, it might be difficult to

construct an actual animal model for PCOS-associated anxiety or depression. Nevertheless, a few studies have been conducted to examine the psychology of PCOS-induced animal models using depression- and anxiety-like behavioral tests. According to Ressler *et al.,* animals treated with dihydrotestosterone (DHT) exhibit increased anxiety-like conduct as seen by a reduction in the amount of time they spend in an EZM's open arms. Similarly, rats given a high-fat diet (HFD) showed more depressive-like behavior and higher immobility (Ressler *et al.,* 2015). Another similar study used a rat prenatal model and injected DHT to investigate anxiety-like behavior in the neonate (Hu *et al.,* 2015). According to data, dehydroepiandrosterone (DHEA) therapy caused depression-like behavior in PCOS mice, perhaps through lowering brain monoamine levels and/or its derivatives. This suggests that hyperandrogenism contributes to the mental conditions in PCOS (Yu *et al.,* 2016). PCOS rats that have been treated with letrozole exhibit anxiety, poor working memory, and substantial depressive-like behavior (Mohammadi *et al.,* 2021). Modified insulin production and insulin sensitivity, adiposity, decreased levels of serotonin as well as other neurotransmitters, disturbances of the hypothalamic-pituitary-adrenal (HPA) axis, and female hormones may contribute to its pathophysiology. However, the actual pathophysiology of the development of psychological symptoms in PCOS is not yet comprehended.

MANAGEMENT OF PSYCHOLOGICAL SYMPTOMS IN PCOS

Pharmacological treatment

So far, only a few drugs have been investigated for their psychological impact on patients with PCOS. In metabolic disorders, anti-depressant activities of both metformin and pioglitazone have already been confirmed. However, their effect on the mental status of PCOS women has received little attention. AlHussain *et al.* studied the impact of metformin in combination with lifestyle intervention on psychological parameters of PCOS women (AlHussain *et al.,* 2020). The findings revealed that metformin-treated PCOS women were at a lower risk of developing depression. However, women who were given metformin combined with lifestyle modifications did not show any improvement in anxiety scores. In another study, Metformin was found to improve the psychosocial aspects of HRQoL among patients with PCOS after six months of treatment (Hahn *et al.,* 2006) After six weeks of treatment with pioglitazone, PCOS women with moderate depression reported a considerable improvement in their depression scores (Kashani *et al.,* 2013). Pioglitazone likely reduces inflammation to produce its antidepressant effects. Importantly, it can suppress cyclooxygenase-2 and nuclear factor kappa B (NF-KB), limit TNF-α expression, and reduce quinolinic acid-mediated neurotoxicity, which has all been associated with depression (Kalonia *et al.,* 2010). An intracellular protein complex called the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome recognizes damaging stimuli and triggers caspase-1 activation, which causes the cytokines to be released. As a result, the NLRP3 inflammasome and inflammation are key factors in mental distress. Treatment with Pioglitazone-Metformin complex, for 12 weeks in PCOS women with comorbid psychological distress, lessened the severity of anxiety and depression symptoms (Guo *et al.,* 2020). The mechanism behind this action is believed to be blocking the activation of NLRP3 inflammasome and the production of inflammatory cytokines. Histone deacetylase-2 (HDAC2) is expressed more often and the prefrontal cortex (PFC) and hippocampal DNA are

hypermethylated in PCOS-related depression. Acetate has been shown to reduce the expression of HDAC2 in PFC, and DNA methyltransferase in both PFC and hippocampus, thereby alleviating depression in PCOS patients. (Wolugbom *et al.*, 2022).

Nutritional supplementation

Apart from drug treatment, supplementation with various nutrients has been gaining interest due to their lesser side effects and beneficial effects in improving the mental health outcomes of PCOS patients. Carnitine has positive benefits in reducing depressive symptoms and treating mild cognitive impairment. Women with PCOS who took a 12-week dose of 250 mg carnitine exhibited improvements in oxidative stress as well as psychological symptoms. Consuming carnitine may promote cholinergic neurotransmission, stabilize membranes, regulate protein and gene expression, or boost mitochondrial activity, all of which are indicators of better mental health. Additionally, the impacts of carnitine on behavioral activities may result from modifications in brain metabolism that affect cognitive flexibility, the restoration of attention/concentration-related cognitive skills, linguistic short-term memory, attentiveness, and computational ability (Jamilian *et al.,* 2017). In another study, twelve weeks of administration of carnitine plus chromium to PCOS patients enhanced mental health measures. Carnitine has been suggested as having anti-oxidant properties, improving the equilibrium of energy processes, boosting dopamine and glutamate levels, and reducing brain-derived neurotrophic factor (BDNF) levels. Chromium's anti-depressive benefits might be attributed to its ability to improve glucose uptake and tolerance in the hypothalamic region, which then causes an increase in the production of serotonin, noradrenaline, and melatonin (Jamilian *et al.,* 2019). In individuals with vitamin D insufficiency, there is mounting evidence that probiotics and vitamin D therapy together have a synergistic effect on metabolic diseases, which may improve mental health indices, metabolic syndrome, and associated illnesses. The 12-week co-supplementation of probiotics and vitamin D to PCOS patients improved parameters of psychological health. Through increased expression of tyrosine hydroxylase genes and increased neurotransmitter accessibility, particularly dopamine and norepinephrine, vitamin D may help treat psychological symptoms. The interaction of vitamin D and probiotic supplements' antioxidant, immunomodulatory, and anti-inflammatory capabilities may increase their effect on mental health indicators (Ostadmohammadi *et al.,* 2019).

It has been established that sleep disorders are related to low melatonin production (Xie *et al.,* 2017). Additionally, noradrenaline regulates the pineal gland's melatonin synthesis, raising the possibility that there is a connection between melatonin and psychological conditions (Huang *et al.,* 2015). According to research, PCOS people who received melatonin for 12 weeks reported a marked improvement in their mental conditions and the restoration of their circadian rhythms, which had been disturbed due to depression (Shabani *et al.,* 2019). Studies have shown that *myo*-inositol possesses psychotropic activity, with initial studies proving efficiency in the treatment of depression, anxiety, panic disorder, and obsessive-compulsive disorder (Chiappelli *et al.,* 2015; Kofman *et al.,* 2000; Benjamin *et al.,* 1995; Fux *et al.,* 1996). In a study by Jamilian et al., psychological indicators improved when *myo*-inositol and folate were consumed for 12 weeks in women with PCOS (Jamilian *et al.,* 2018a). Inositol may enhance aspects of mental health via regulating serotonin function and

intracellular ca^{+2} concentration. Additionally, S-adenosylmethionine and the formation of healthy red blood cells through folate consumption may help alleviate the signs of depression.

Reduced levels of omega-3 fatty acid have been reported in plasma and serum phospholipids, red blood cell membranes, and adipose tissue of depressed patients, and hence its supplementation improves depression and other psychological symptoms. Individuals with PCOS who took omega-3 fatty acids for 12 weeks reported better mental health as well as the quality of life (Amini *et al.,* 2020). Depressive illness patients have higher peripheral and cerebral inflammation markers, and omega-3 fatty acids and their active compounds are inflammatory mediators (Mori *et al.,* 2004; Calder *et al.,* 2017). It is not entirely clear how precisely omega-3 fatty acids affect certain mental health metrics. But, according to Haag M, alterations in membrane structure, inflammatory responses, and neurotransmitter activity are how omega-3 fatty acids enhance mental health metrics (Haag M, 2003). The co-supplementation of vitamin E and omega-3 fatty acids for 12 weeks with PCOS individuals also demonstrated positive impacts on mental health metrics. These nutrients may function more effectively when taken together than when taken alone and have a powerful synergistic impact (Jamilian *et al.,* 2018b). Probiotics and selenium co-supplementation for 12 weeks exhibited positive impacts on mental health indicators in PCOS patients (Jamilian *et al.,* 2018c).

According to another study, administering vitamin D and omega-3 fatty acids together in people with PCOS for 12 weeks enhanced their overall and mental health. The mechanism of vitamin D on brain activity has been explained by several pathways, such as its direct influence on the brain and serotonin absorption via vitamin D receptors scattered throughout the nervous system, and its indirect action on enhancing muscle strength, which intensifies physical activity and overall health, and its activity on reducing parathyroid hormone (PTH) level, which has been linked to a rise in mental activity. Additionally, brain phospholipids, the primary constituent of the neuron's cellular membranes, contain unsaturated fatty acids like omega-3. Dopaminergic and serotonergic systems that are necessary for healthy brain activity, may be regulated by omega-3 fatty acids. Omega-3 fatty acids and vitamin D may improve the production, secretion, and activity of serotonin in the brain (Jamilian *et al.,* 2018d). Menaquinone-7, a vitamin K2 homolog, is proposed as a promising approach to preserving cognitive functions (Elkattawy *et al.,* 2022). When compared to placebo capsules, Menaquinone-7 dramatically reduced depressive state in women with PCOS, however, it is unknown what causes its actions (Tarkesh *et al.,* 2022). There exists proof that serious depression is associated with a decreased antioxidant state, and coenzyme Q10 has strong antioxidant (Sharafi *et al.,* 2020) and neuroprotective properties (Okudan *et al.,* 2022). 100 mg/day of Coenzyme Q10 supplementation for 12 weeks also had a positive effect on the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) scores in women with PCOS (Karamali *et al.,* 2021).

Lifestyle and psychological I\interventions

There is emerging evidence to suggest that many of the psychological symptoms of PCOS can be improved by lifestyle interventions, such as diet and regular participation in physical activity along with psychological interventions. Due to sensations of restriction, there is almost certainly a rise in irritation and depression when attempting to lose weight in patients

with PCOS-associated obesity. Since these detrimental psychological impacts may lead to high levels of dietary noncompliance, it is crucial to understand if any given diet composition is psychologically favorable. A 16-week high-protein, low-carbohydrate (HPLC) diet was linked to a substantial reduction in self-esteem and depression scores in obese individuals with PCOS. It is unclear if the greater protein content, reduced carbohydrate content, the mixture of both or other variables are responsible for this. It is feasible that the HPLC diet will make participants feel more satisfied, reducing their sense of deprivation (Galletly *et al.*, 2007). In a randomized controlled trial (RCT), the impact of a comprehensive yoga program and physical activity on state and trait anxiety in PCOS-affected teenagers was compared. A yoga program that lasted 12 weeks dramatically reduced anxiety symptoms compared to a program that only involved physical activity. The outcomes seen in this study might be attributed to the peace of mind attained following a yoga session (Nidhi *et al.*, 2012). Other psychological and lifestyle interventions that have been studied in women with PCOS are tabulated in Table 1.

Table 1- Lifestyle and Psychological interventions for improvement of mental health in PCOS patients

Intervention	**Population**	**Duration of treatment**	**Outcome**	**References**
CBT	Overweight/obese women with PCOS	12 months	Enhanced QoL	Jiskoot et al., 2017
	Women with PCOS (18-35 years)	8 weeks	Improved QoL, lessened tiredness, and eventually improved health	Abdollahi et al., 2019
Energy-restricted diet	Overweight/obese women with PCOS	20 weeks	Reduction of depression and improvement of health-related quality of life (HRQOL) scores	Thomson et al., 2010
Acupuncture	Swedish women with PCOS	16 weeks	Improvement in depression and anxiety scores	Stener-Victorin et al., 2013
	Unmarried women with PCOS	16-week	Improved psychological symptoms and QoL	Wang et al., 2019
CBT and lifestyle modification	Overweight/obese women with PCOS and depressive symptoms	8 weeks	Improved mental health regulated the stress response	Cooney et al., 2018

Continuous oral contraceptive pill (20 μg ethinyl estradiol/1 mg norethindrone acetate) or intensive LS or the combination	Women 18 – 40 years and BMI 27– 42kg/m2 with PCOS	16 weeks	Improved QoL, depressive and anxiety symptoms	Dokras et al., 2016
Mindfulness stress management program	Pre-menopausal women aged 15–40 years	8 weeks	Significant reduction in anxiety, depression, and stress scores	Stefanaki et al., 2015
Lifestyle changes + Oral contraceptive (ethinyl estradiol + drospirenone)	PCOS adolescent (12–18 years)	24 weeks	Improvement in QoL	Harris-Glocker et al., 2009
Exercise	Women with PCOS (18-50 years)	-	Decreased the intensity of depression	Banting et al., 2014
PRT	Women with PCOS (18-42 years)	12 weeks	Noteworthy reduction in depression and anxiety	Vizza et al., 2016
Aerobics	Women with PCOS	-	Remarkable reductions in depression and anxiety scores	Kogure et al., 2020

CBT Cognitive-behavioural therapy; PCOS Polycystic ovarian syndrome; QoL Quality of life; LS Lifestyle; BMI Body mass index; PRT Progressive resistance training.

FUTURE PROSPECTS

An essential concern for future research in this area is conducting high-quality studies comparing the relative outcomes of various interventions on the psychological health of PCOS women, throughout the BMI range, and including varied ethnicities. Research is necessary to determine the most appropriate approach for patients with PCOS who want to achieve better physical and mental results. How to enrol these women most effectively in physical exercise programs is one of the major research concerns. To compare studies and provide information for efficient management of mental co-morbidities in PCOS, we should preferably employ consistent mental health evaluation techniques in future research. To

tackle these concerns, a variety of research methodologies must be considered. Qualitative and quantitative methodologies are required to better comprehend how these therapies affect the mental health of women with PCOS.

CONCLUSION

The current review offers a comprehensive overview of the literature on the treatment of psychological symptoms in patients with PCOS. Despite being a medical problem, PCOS requires a multidisciplinary approach to treatment. For women with PCOS, nutritional support, lifestyle modifications, and psychological therapies may have favorable therapeutic potential. It is crucial to use tactics that can both lessen depressive and anxious symptoms and boost adherence to therapies. Consequently, it would be possible to improve psychological health with multi-component therapies that address complicated physical and mental health issues and sustain patient compliance.

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