

General Psychiatry **Nutritional and herbal supplements in the treatment of obsessive compulsive disorder**

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder that is characterised by obsessions and compulsions. The recommended treatments for OCD are cognitive–behavioural therapy using exposure and response prevention and/or pharmacotherapy. On the other hand, some nutritional and herbal supplements may be effective in the treatment of OCD. Nutritional and herbal supplements in OCD treatment will be reviewed in this paper. PubMed (Medline), Cochrane Library and Google Scholar databases were reviewed for the topic. There are some supplements that have been researched in OCD treatment studies such as vitamin D, vitamin B₁₂, folic acid, homocysteine, trace elements, N-acetyl cysteine, glycine, myoinositol, St John's wort, milk thistle, valerian root, curcumin and borage. The effectiveness of herbal and nutritional supplements in the treatment of OCD should be supported with more conclusive evidence.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder that is characterised by obsessions and compulsions. OCD usually begins in childhood or adolescence and comorbid disorders such as mood, anxiety, psychotic and somatoform disorders are common in patients with OCD.¹

Structural, neurochemical, genetic and immunological factors play a role in the aetiology and pathophysiology of OCD.² Alterations in certain neurotransmitters are involved in OCD symptoms. Serotonin deficiency and the dysfunction in the availability of serotonin transporter (5-HTT) have been implicated in OCD symptomatology.³ In addition, elevated glutamate, glutamine and gamma aminobutyric acid (GABA) levels in the caudate nucleus⁴ and increased glutamate levels in the cerebrospinal fluid have been found in patients with OCD.⁵ Also, the glutamatergic ionotropic N-methyl D-aspartate (NMDA) receptor has been associated with OCD.⁶

The recommended treatments for OCD are cognitive–behavioural therapy using exposure and response prevention⁷ and/or

pharmacotherapy with selective serotonin reuptake inhibitors (SSRI), the tricyclic antidepressant clomipramine, or serotonin noradrenaline reuptake inhibitors such as venlafaxine or duloxetine.^{8,9}

Limited effectiveness and possible side effects of present treatments have led to the search for alternative strategies. It is known that various nutritional deficiencies can be detected in patients with mental disorders. Therefore, nutritional supplements are thought to be effective in treatment. In this paper, use of nutritional and herbal supplements in the treatment of OCD will be reviewed.

METHODS

This review is focused on herbal and nutritional treatments for OCD. Therefore, PubMed (Medline), Cochrane and Google Scholar databases were searched using the terms ‘Obsessive-Compulsive Disorder’ OR ‘OCD’ in combination with ‘herbal’ OR ‘plant’ OR ‘nutrition’ OR ‘nutraceuticals’ OR ‘supplement’ OR ‘minerals’ OR ‘vitamin’. Papers written in English and conducted with humans were reviewed.

RESULTS

Vitamin D

Vitamin D has important functions in immunity modulation, inflammatory response and antioxidant processes.¹⁰ It is also essential for normal brain development and functioning, and plays key roles nervous system processes such as neurotransmission, neuroprotection, proliferation and differentiation.^{11,12}

Vitamin D is synthesised in the epidermis as vitamin D₃ (cholecalciferol) and then it is converted to 25-OH D₃ in the liver by hydroxylation. After rehydroxylation in the kidney, 25-OH D₃ becomes 1,25-dihydroxy-vitamin D₃, the active form of vitamin D.¹¹



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Previous studies have demonstrated that vitamin D deficiency is associated with numerous neuropsychiatric diseases that include autism, major depressive disorder, schizophrenia and OCD.^{13–15} There are several possible relationships between vitamin D and OCD pathophysiology. One of these is the association between the active form of vitamin D₃ (1,25-dihydroxy-vitamin D₃) and tyrosine/tryptophan hydroxylase. While tyrosine hydroxylase is the rate-limiting enzyme in dopamine, epinephrine and norepinephrine synthesis, tryptophan hydroxylase is the rate-limiting enzyme in serotonin synthesis. Levels of these two enzymes are regulated by 1,25-dihydroxy-vitamin D₃.^{16,17} Therefore, vitamin D deficiency may contribute to OCD aetiology by affecting the pathway of serotonin and catecholamines synthesis.

The other relationship between vitamin D and OCD has to do with the neuroprotective effect of vitamin D. In some studies, the role of free radicals, especially increased levels of nitric oxide, is shown in OCD.¹⁸ Vitamin D has antioxidant effects and inhibits an essential enzyme (inducible nitric oxide synthase) for nitric oxide synthesis.¹⁹ Thus, vitamin D deficiency may play a role in OCD by causing the deterioration of neuroprotection.

In the literature, all available papers on OCD and vitamin D are studied with child and adolescent patients. There is no adult study on this topic. Esnafoğlu and Yaman have compared vitamin D, vitamin B₁₂, homocysteine and folic acid levels between 52 patients with OCD and 30 healthy controls. They found that there was a negative correlation between severity of OCD and the level of vitamin D and also vitamin D levels were lower in patients with OCD.²⁰ On the other hand, Yazici *et al* showed no significant difference in vitamin D, calcium, phosphate and alkaline phosphatase levels between patients with OCD and healthy controls. But the level of vitamin D was negatively correlated with symptom severity in patients with OCD.²¹ This study has compared 60 patients with OCD and 60 healthy controls. Similarly, Celik *et al* found lower vitamin D levels in paediatric autoimmune neuropsychiatric disorders were associated with streptococcal infection (PANDAS)- in patients with OCD (n=33) compared to healthy controls (n=20), but the difference was not statistically significant.²² PANDAS is a neuropsychiatric disorder that OCD symptoms manifest in following streptococcal infections. There may be a relationship between vitamin D levels and increasing oxidative stress due to recurrent infections in patients with PANDAS.²²

Vitamin D levels can be influenced by latitude and season, due to sunlight. Celik *et al* and Yazici *et al* have stated the time interval of blood samples taken. But in the study of Esnafoğlu and Yaman, it is not clear.

Vitamin B₁₂, folic acid and homocysteine

Vitamin B₁₂, folic acid and homocysteine play an important role in carbon transfer metabolism that maintains the methylation of proteins, neural membrane phospholipids and neurotransmitters such as serotonin and other monoamines. Thus, neurotransmitter levels may

decrease due to deficiency of vitamin B₁₂ and folic acid.²³ Increased plasma homocysteine levels are accepted as a sensitive marker of folic acid and vitamin B₁₂ deficiency.²⁴ Increased homocysteine levels may cause DNA damage, mitochondrial dysfunction, activation of apoptotic signals and increased oxidative stress.²⁵ All these findings suggest that vitamin B₁₂, folic acid and homocysteine may be related with the aetiology of OCD.

In the literature, there are case reports of patients with OCD having vitamin B₁₂ deficiency.^{26,27} Also, some studies have investigated the association between OCD and vitamin B₁₂, folic acid, and homocysteine levels both in adult and child-adolescent patients. Hermesh *et al* have compared 30 patients with OCD, 30 patients with chronic schizophrenia and 30 healthy controls. They have reported that vitamin B₁₂ deficiency was more frequent in patients with OCD compared with controls, but there was no significant difference between vitamin B₁₂ and folate levels among the three groups.²⁸ Atmaca *et al* found lower folate and higher homocysteine levels in patients with OCD (n=23) compared with controls (n=23) and those levels were significantly correlated with the symptom severity of OCD.²⁹ Türksoy *et al* showed that vitamin B₁₂ deficiency was significantly higher in patients with OCD (n=35) compared with control (n=22).³⁰ But folate deficiency was not found in either group. Additionally, homocysteine levels were significantly higher in the OCD group, and highest in the OCD group with major depressive disorder. Similarly, Esnafoğlu and Yaman found lower vitamin B₁₂ and higher homocysteine levels in the group of children and adolescents with OCD compared with healthy controls. However there was no significant difference in the folic acid levels of both groups.²⁰ A double-blind, 12-weeks study was conducted in 36 patients with OCD who were randomly assigned to folic acid+fluoxetine or placebo+fluoxetine group. They have reported no significant difference in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores between folic acid and placebo groups. Also, all baseline folate levels of patients with OCD were not lower than the normal range.³¹

Folate and vitamin B₁₂ levels might be influenced by dietary habits. So the results of studies can vary in samples from different societies.

Trace elements

Imbalances in trace elements may be associated with the pathophysiology of OCD. Selenium is an essential trace element that plays a role in the antioxidant properties of glutathione peroxidase.³² Ozdemir *et al* found that serum selenium level was lower in patients with OCD (n=28). They reported a positive correlation between plasma glutathione peroxidase activity and selenium concentration.³³ In another study, 48 patients with OCD were compared with 48 healthy controls and found that serum zinc, iron and magnesium levels decreased in patients with OCD; however, manganese and calcium levels were increased. Also, they reported an imbalance in the trace elemental homeostasis and element-to-element inter-relationship

pattern.³⁴ In a pilot, randomised, double-blind, placebo-controlled study, patients with OCD (n=30) who had taken an SSRI for at least 3 months were divided into two groups. While one group took 400 mg selenium capsules plus SSRI, the other group took placebo plus SSRI. At the end of the 6 weeks, it was reported that there was a significant difference in Y-BOCS scores between the two groups.³⁵ Selenium is a dietary element, so results of these studies could be affected by dietary habits.

Zinc is an antioxidant trace element that is required for many processes such as gene expression, protein synthesis and enzymatic catalysis.³⁶ Zinc presents in the central nervous system, cerebral cortex, pineal gland and hippocampus, and modulates inhibitory and excitatory transmissions such as GABA and NMDA.³⁷ In a randomised placebo-controlled clinical trial, one group received fluoxetine plus zinc, other group received fluoxetine plus placebo for 8 weeks. This study showed that the zinc group had a greater improvement compared with the placebo group.³⁸

Because of the possible role of oxidation mechanisms in OCD pathogenesis, trace elements associated with antioxidant processes are thought to be useful in OCD treatment.

N-acetyl cysteine

N-acetyl cysteine (NAC) is a better source of cysteine rather than parenteral cysteine due to being less reactive, less toxic, more resistant to oxidation and more soluble in water.³⁹ Some high-protein foods may be the source of cysteine but NAC should be taken as a supplement. NAC is well tolerated thus an oral dose of it can be increased up to 8000 mg/d without significant adverse effect.⁴⁰

NAC, which is orally taken, is converted to cysteine in the liver and used for glutathione synthesis.⁴⁰ Cysteine may cross the blood–brain barrier. So, cysteine prodrugs such as NAC inhibit the synaptic glutamate release by cysteine-glutamate exchange and may contribute to the treatment of psychiatric disorders.⁴¹ When the role of oxidative stress in the pathogenesis of OCD is considered, NAC that reduces oxidative stress and inflammation may be beneficial for OCD.⁴²

In a case study of a patient with SSRI-refractory OCD, Lafleur *et al* showed that there was a significant improvement in OCD symptoms due to the NAC (3000 mg/d) augmentation of fluvoxamine.⁴³ In contrast, a series of six case reports of patients with treatment-resistant severe OCD observed little efficacy of NAC (3000 mg/d) treatment.⁴⁴ A randomised clinical trial assessing NAC treatment in OCD showed a significant improvement of symptoms in the SSRI plus NAC group (2400 mg/d) compared with SSRI plus placebo group. But patients' comorbidities have not been included in evaluations.⁴⁵ Sarris *et al*⁴⁶ have conducted a randomised, double-blind, placebo-controlled clinical trial of NAC augmentation in patients with OCD who have been taking psychotropic drugs or adjunctive therapies. The NAC-treated group had more reduction in Y-BOCS score compared

with the placebo group. The same authors have made a further analysis and reported that NAC is more effective in younger patients with a shorter diagnosis period of OCD.⁴⁷ The other randomised double-blind placebo-controlled trial did not demonstrate a significant benefit of NAC in reducing OCD symptoms in patients with treatment-resistant OCD but NAC might have effects on reducing anxiety symptoms in these patients.⁴⁸ In this study, patients were taking at least an SSRI. Payday *et al*⁴⁹ have compared NAC augmentation plus fluvoxamine treatment with placebo. There was no significant difference in Y-BOCS scores between the two groups, however NAC-treated patients accomplished remission more than the control group. Ghanizadeh *et al*⁵⁰ performed a randomised, double-blind, placebo-controlled study that searched NAC augmentation of citalopram treatment in children and adolescents. Y-BOCS scores were significantly decreased in the NAC group.

Glycine

Glycine is an amino acid that is associated with cortical glutamatergic function. Glycine has potential to ameliorate OCD symptoms due to its agonist effect on NMDA receptors.⁵¹ High-protein foods such as meat, fish, beans and dairy products include glycine. A case report showed benefit of glycine in patients with OCD and body dysmorphic disorder but large amounts of glycine (60 g/d) are required and unfortunately the large daily dose of glycine had side effects such as significant nausea.⁵² There is only a placebo-controlled, double-blind study on glycine augmentation in patients with OCD (n=24). Dropout rates in this study were high due to adverse effects of glycine. Evaluable patients have showed near significant improvements in Y-BOCS scores.⁵³

Myoinositol

Myoinositol (MI) is an endogenous isomer of glucose and has been used in the treatment of psychiatric disorders for a long time. High amounts of MI have been found in fruits, grains, nuts and beans. Also, MI is synthesised de novo from glucose-6-phosphate in the brain. A sustained supply of MI is essential for the synthesis of membrane phospholipids and for intracellular secondary messenger cycle.⁵⁴

It is suggested that MI may modulate the reuptake of serotonin and increase 5-HT₂ receptor density. Its therapeutic effects may be due to these mechanisms.⁵⁵ There are few studies with small samples that investigate the efficacy of high-dose MI (18 g/d) in OCD treatment. Fux *et al* and Carey *et al* reported positive data of MI supplementation in OCD treatment.^{56 57} The participants of these studies were not receiving concurrent SSRI treatment. In contrast, Fux *et al* and Seedat and Stein failed to find evidence for efficacy of MI in OCD treatment.^{58 59} In these studies, MI has been used as augmentation for concurrent SSRI treatment. The existing clinical evidence suggests that MI may potentially be effective as monotherapy for OCD.

St John's wort (*Hypericum perforatum*)

St John's wort (SJW) is derived from a plant and has been used for centuries as a traditional medicine to treat a wide range of disorders. The effectiveness of SJW has been mostly studied in depression and found to be equivalent to antidepressants.^{60,61} SJW contains flavonoid that has some anxiolytic effects. The neurobiological effects of SJW include monoamine reuptake inhibition, neuroendocrine modulation, increased sensitisation and binding to receptors (eg, 5-HT).⁶¹ These monoaminergic effects may have potential benefits on OCD symptoms.

Evidence for efficacy of SJW in OCD is based on only two studies. A 12-week open-label trial showed significant improvements with the treatment of SJW (900 mg/d) in patients with OCD (n=12).⁶² A placebo-controlled trial with a much larger sample size (n=60) failed to show a significant difference between SJW (600–1800 mg/d) treatment group and placebo group.⁶³

Milk thistle (*Silybum marianum*)

Silybum marianum (milk thistle) is a medicinal plant, which is grown in Mediterranean and Persian regions.⁶⁴ It contains flavonoid complex silymarin, which has anti-inflammatory, antioxidant, immune modulator, sedative and antidepressant effects.⁶⁵ Also silymarin has been found to increase serotonin in the cortex and acts as a monoamine oxidase inhibitor.⁶⁶

Results of the only randomised controlled trial (n=35) of milk thistle for OCD treatment revealed no significant difference in treatment effects between milk thistle (600 mg/d) and fluoxetine. It is indicated that milk thistle has similar effects with fluoxetine in OCD symptoms and its positive effect starts in the fifth week without severe side effects.⁶⁴

Valerian root (*Valeriana officinalis* L)

Valerian is a perennial plant, which was used as a perfume in the 16th century. Valerian roots have aleuronic acid that is associated with the modulation of GABA_A receptors.⁶⁷ The other content of valerian roots is valepotriates, which is effective in treating the psychotic symptoms of severe anxiety.⁶⁸ Valerian is most commonly used in insomnia and migraine treatment due to its sedative, pain reliever effects. There is only one double-blind placebo-controlled trial of valerian extract in OCD treatment (n=31). They found that valerian extract was more effective in OCD treatment compared with placebo. Also, they observed the rapid onset of the effects of extract (28, 42, 56 days). Low incidence of impairment of libido with valerian extract was an important advantage of this treatment.⁶⁹

Curcumin

Curcumin is an active constituent of turmeric. Both turmeric and curcumin are thought to strengthen the overall energy of the body, relieving gas, dispelling worms, improving digestion, regulating menstruation, dissolving gallstones and relieving arthritis. Curcumin

is most commonly used to ameliorate pain associated with arthritis and other musculoskeletal disorders due to its anti-inflammatory effect.⁷⁰ Potential pharmacodynamic benefits of curcumin in neuropsychiatric disorders are associated with the monoaminergic imbalances, hypothalamus-pituitary-adrenal axis disturbances, oxidative stress, mitochondrial disturbances and dysregulated inflammation.⁷¹

Although there are no human studies that examine benefits of curcumin in OCD treatment, in an OCD animal model, rats were injected with the dopamine-agonist quinpirole and compulsive checking was induced. After the oral curcumin administration for 35 days, compulsive checking and ritualistic behaviours were significantly reduced, and quinpirole-induced deteriorations were reversed. These effects of curcumin were comparable with paroxetine.⁷²

Borage (*Echium amoenum*)

Borage is a traditional Persian plant, which has anxiolytic and sedative effects comparable to diazepam and also antidepressant effects. In only one study, borage extract (n=24) has been compared with placebo (n=20) in OCD treatment. While no significant difference was observed between the groups in the first week, a significant difference occurred at week 4 and week 6. In addition, anxiety symptoms were significantly improved with the borage treatment over placebo.⁷³

CONCLUSION

There are limited studies about herbal and nutritional supplements for OCD treatment in the literature. OCD and vitamin D association has been studied only in children and adolescents. Limited data show a negative correlation between OCD symptom severity and vitamin D. But these studies have been conducted in small samples and have some controversial points in methodology.

Vitamin B₁₂ and folate are thought to be effective in OCD treatment due to their associations with neurotransmitters. Depending on their antioxidant effect, zinc and selenium can be used in augmentation therapy for OCD. However, both trace elements and vitamin B₁₂/folate can be affected by diet. Therefore, dietary habits of participants have to be considered when designing studies on OCD treatment.

There are some studies and case reports that have shown improvement with NAC in OCD. However, these studies had small samples and participants who use SSRI or any psychotropic drug or psychotherapy. Data on the effect of glycine in OCD treatment are quietly restricted. On the other hand, maintaining treatment with glycine is very difficult due to its adverse effects. The existing limited clinical data suggest that MI may potentially be effective as monotherapy for OCD.

Some herbal medicines may provide a synergistic effect with pharmaceuticals. On the other hand, it should be noted that some herbal supplements should not

be used with some drugs, for example, SJW with SSRIs due to potential serotonin syndrome. SJW, milk thistle, curcumin, valerian root and borage are herbal supplements that have been researched in OCD treatment. Despite the few studies on herbal supplements for OCD treatment, double-blind randomised controlled studies with standardised preparations of these herbals are needed. Although previous studies showed that some herbal and nutritional supplements might be potentially effective in OCD treatment, further double-blind randomised controlled longitudinal studies with structured measurement procedures in larger samples are needed.

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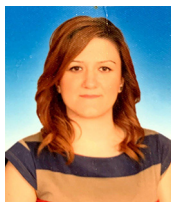
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