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OBM Integrative and Complementary Medicine

Review

What is the Current Evidence to Support the Use of Herbs and Supplements to Treat Mood and Anxiety Disorders?

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Academic Editor: James D. Adams

Special Issue: Complementary and Alternative Medicine in Nervous System Conditions

OBM Integrative and Complementary Medicine
2018, volume 3, issue 4
doi:10.21926/obm.icm.1804030

Received: March 10, 2018
Accepted: November 9, 2018
Published: November 13, 2018

Abstract:

***Background*:** Treatment of mood and anxiety disorders with supplements, herbs and nutraceuticals (dietary supplements) is at this point viewed as an integrative or alternative treatment, however these substances have been around for quite some time and are regarded as basic to the understanding of human biochemistry, physiology, health and illness in medicine.

***Methods*:** This review article was done using a literature search utilizing the National Library of Medicine online data base and the PCOM electronic library data base of 1,707,669 academic journals to include studies utilizing herbs and supplements for depression and anxiety published in the past 10 years. Studies of a positive and negative type were both included in this review article.

***Results*:** Step wise approach to depression and anxiety should first address insomnia.
Reduction of the risk of self-harm should be addressed and reduction of oxidative stress is desirable especially for young adults and adolescents.
Effect size differs between supplements.
***Conclusions*:** Side effect profile should be taken into consideration when choosing supplements or herbal preparations.
Gender may impact response to different herbs and supplements.
Future research trials are needed to confirm best practices.

Keywords
Depression; anxiety; sleep; insomnia; probiotics; vitamin C; vitamin D; vitamin B1;, vitamin B6; Zinc; Magnesium; saffron (*C. Sativus*); curcumin; crocin; fatty acids; rhodiola; walnuts, SAMe; Tryptophan; Theanine; camomile; lavendula; inositol; N-Acetyl Cysteine; St. Johns Wort; passiflora incarnata L. (*Passifloraceae*); valeriana officinalis L.; personalized treatment

1. Introduction

Treatment of mood and anxiety disorders with supplements, herbs and nutraceuticals (dietary supplements) is at this point viewed as an integrative or alternative treatment, however these substances have been around for quite some time and are regarded as basic to the understanding of human biochemistry, physiology, health and illness in medicine. Multivitamins and mineral supplementation have been found to have a favorable safety ratio. [1]

It is important to keep in mind that many accepted psychiatric treatments (for example, cognitive behavioral therapy (CBT) took years to be regarded as an evidence based treatment due to the lack of sufficiently powered studies because of the challenges to getting these types of studies funded. [2] Treatments to facilitate healthy sleep may prevent as well as to intervene in depression and anxiety; this is important due to the recent research that has found that impaired sleep has a deleterious impact on the default mode network, which may be a root cause of both depression and anxiety [3].

2. Materials and Methods

No human, animal, plant subjects were involved as this article is a review article. The authors do not have any conflicts of interest to report for this review article.

This review article was done using a literature search utilizing the National Library of Medicine online data base and the PCOM electronic library data base of 1,707,669 academic journals to include studies utilizing herbs and supplements for depression and anxiety published in the past 10 years. Studies of a positive and negative type were both included in this review article.

The studies included in this review used scales and checklists to assess level of severity and remission in response to treatment interventions for major depressive disorder: the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS or HAM-D), and Patient Health

Questionnaire-9 (PHQ-9). The BDI quantifies characteristic aspects of depression. It asks participants to scale twenty-one aspects of depression from zero to three, and adding each grade for a total score. The total score is then categorized into different severity levels of depression. A sample BDI is found in the Index. The HDRS also quantifies the severity of depression, but uses a seventeen factor measurement. Each aspect is ranked from either zero to two or zero to four. The total summation gives a patient a score, which is then categorized into severity of depression. The PHQ-9 is a nine item questionnaire that was created from the 20 item short form general health survey to measure increase in depression severity; a score greater than or equal to 10 had a sensitivity of 88 percent and a specificity of 88 percent for major depression, scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe and severe depression [3].

3. Results

3.1 Probiotics

Probiotics are microorganisms naturally found within the human digestive tract, aiding in digestion, protection against harmful microorganisms, and vitamin production [4]. Akkasheh et al. (2016) performed a study analyzing the effects of probiotic administration on major depressive disorder (MDD). After 8 weeks of supplementation with a probiotic capsule containing *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum*, researchers noticed a decrease in Beck Depression Inventory (BDI) total scores compared to the placebo.

Metabolic parameters also improved with probiotics as a decrease in inflammatory marker, high-sensitivity C-reactive protein (hs-CRP), was found as well as a decrease in insulin resistance. Unfortunately the study results might not be valid as the study did not tease out possible confounding factors that might have played a role in reduction of inflammation, the study was short in duration (8 weeks), did not provide guidance on whether the type of probiotic makes a difference even though the P value was at the level of 0.05 showing a significant difference between the probiotic and placebo groups as the BDI Score was -5.7 ± 6.4 vs -1.5 ±4.8 for probiotic group vs. placebo, respectively, and p = 0.001. After adjustments, BDI score decreased -5.3 ±1.2 and -1.8 ± 1.2 for probiotic and placebo group respectively, where p* = 0.05 [5].

Further support for the use of probiotics in decreasing the risk of mood disorders was demonstrated by Huang et al. in a meta-analysis of randomized controlled trials. They found that regular intake of probiotics, whether through diet or as a supplement, had a beneficial effect on mental health biomarkers, MDD, and overall mood. This specifically applied to patient populations less than 60 years old, and in populations with and without depression. Therefore, both depressed and non-depressed people may benefit from probiotics [6].

3.2 Vitamins and Micronutrients

Vitamin C. Vitamin C (ascorbic acid) is involved in various functions of the human body. Despite being a vital requirement, humans are unable to synthesize it. Therefore, it is obtained through the diet naturally in foods, as a supplement in other foods, and as a supplement on its own. It is

hypothesized that Vitamin C can adjust catecholamine activity, thereby decreasing reactions to stress. [7].

Oliviera et al. [8] studied the effect of Vitamin C supplementation on blood pressure and possible improvement in anxiety. Anxiety can have a pathophysiological tie to oxidative stress, where decreased levels of ascorbic acid are associated with increased levels of anxiety. Vitamin C, being an antioxidant, should prevent oxidative stress, thus improving anxiety. In this study, high school students received a 14-day supply of either 500 mg of Vitamin C or a placebo. The results demonstrated a significant decrease in the Beck Anxiety Inventory (BAI) in the Vitamin C group compared to the placebo group. While there was no effect on blood pressure, there was a significant decrease in the mean heart rate of the Vitamin C group compared to the placebo group, thus Vitamin C supplementation may be helpful to reduce anxiety.

Vitamin D. Vitamin D is a vitamin found in few foods, but can be produced within the body as a response to ultraviolet rays from the sun coming into contact with the human skin. This activates Vitamin D synthesis within the kidneys. Vitamin D appears to be a relatively cheap and safe supplement [9, 10].

There has been long standing interest in the use of vitamin D for depression and anxiety as well as in the treatment of ADHD as a clear association has been found for low vitamin D levels and depression [11, 12, 13, 14] and several research studies attempted to answer the question whether Vitamin D supplementation hastens rates of recovery from major depression, as it has been known that lower levels of Vitamin D correlate with symptoms of depression especially in middle aged [15, 16, 17] and elderly individuals [18].

Belzeaux confirmed what Vidgren et al. had determined that decreased vitamin D levels are associated with a major depressive episodes, and also that low vitamin D levels can result in cognitive impairment. [19] Belzeau et al. performed a study including patients with a major depressive episode not currently on medication. Using the Stroop Color Test, they found during a major depressive episode, those patients with hypovitaminosis had impaired cognitive inhibition [20].

Several studies of vitamin D supplementation were negative studies, where no improvement was observed with supplementation [21].

A review article found that of 7 studies reviewed that were without flaws, only one study found Vitamin D supplementation to be beneficial for depression however overall all- cause mortality was reduced for older adults taking vitamin D [22].

These negative findings could be attributed to weaknesses in the design of the studies: dosage too low for effect, short duration, use of a non-standard measure of depression, lack of agreement on what is the cut off score to indicate remission unfortunately were present in these studies [22, 23, 24, 25].

Frandsen et al. in a 2014 study, focused on seasonal affective disorder (SAD) in healthcare professionals and measured outcome using a self-reported questionnaire: the *Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders* (SIGH-SAD). Treating for longer than the usual length of time (12 weeks instead of 8 weeks), they showed no significant difference in SIGH-SAD scores between the Vitamin D-supplemented group and the placebo group [26].

Shaffer et al (2014) found that a subgroup analysis of adults with clinically significant depressive symptoms to gain moderate benefit of Vitamin D supplementation for depression [24].

An older study done by Kjaergaard et al. in 2012 found that patients with lower serum 25-hydroxyvitamin D (25(OH)D) levels demonstrated worse depression symptoms than patients with higher (25(OH)D) levels; the study did not find significant improvement in severity of depression with supplementation of 40,000 IU of Vitamin D_3 a week for 6 months [27].

Sepehrmanesh, et al. performed a double-blinded, randomized, placebo-controlled 8-week clinical trial looking at Vitamin D supplementation and its effect on BDI, insulin resistance, and biomarkers of oxidative stress in patients with MDD. Supplementation with Vitamin D resulted in a greater decrease in BDI than the placebo group, as well as decreased insulin resistance in the Vitamin D-supplemented group despite the lack of improvement in serum hs-CRP levels [28].

Focker et al. are currently in the midst of a study looking at the possible relationship between mood and Vitamin D supplementation in children and adolescents with Vitamin D deficiency. The future findings may provide a deeper insight into the relationship between pediatric psychiatry and Vitamin D supplementation, as well as a more definitive approach to treatment with supplementation [29]. In conclusion, additional studies are needed to validate the connection between hypovitaminosis and cognitive impairment.

Thiamine. Thiamine (or thiamin), also known as Vitamin B1 is involved in multiple functions within the human body, including growth, development, and cell functioning. Most importantly, thiamine is a cofactor involved in obtaining energy from nutrients in food [30]. Ghaleiha et al. performed a study looking at the effects of thiamine supplementation on MDD. Although the overall impact of supplementation was not greater than placebo at the 12 week mark, as measured by the Hamilton Depression rating scale, at 6 weeks, there was significant improvement in HDRS scores in the thiamine-supplemented group compared to the placebo group. Thus, thiamine might be effective for immediate improvement in mood despite the lack of effect after 12 weeks, and may be helpful as an adjunctive bridge therapy during the antidepressant lag time for a faster effect on MDD [31].

B vitamins. Vitamin B6 is obtained through the diet and is a cofactor in many enzymatic reactions, primarily for protein metabolism [32].

Folate (or folic acid) is involved as a coenzyme in DNA and RNA production, as well as the metabolism of amino acids [33].

Vitamin B12 is also a cofactor for enzymatic reactions, especially the conversion of homocysteine to methionine, as methionine is required to make S-adenosylmethionine, an important methyl donor for various biological reactions [34].

Using the Montgomery-Asberg Depression Rating Scale (MADRS), Almeida et al. researched the impact of B vitamin supplementation along with standard antidepressant treatment utilizing citalopram over a one year time period for the treatment of MDD. This study also used the Mini-International Neuropsychiatric Interview (MINI) to allocate participants into diagnostic groupings. The results demonstrated that the group receiving vitamin B supplementation in addition to citalopram did not experience a positive response after 12 weeks of treatment, but had an enhanced response after 52 weeks. When looking at the participants who relapsed, those who received vitamin B supplementation experienced relapse less frequently than those treated with the placebo. Future

studies that show replication of the Almeida study findings is needed to support a recommendation to provide B vitamin supplementation when treating MDD [35].

Zinc. Zinc is a mineral found in foods and dietary supplements and is required for numerous enzymatic reactions within the human body. Because the body is unable to store zinc, its level is managed daily to participate in the "immune system, protein synthesis, wound healing, DNA synthesis, and cell division" [36].

Salari et al. researched the effects of zinc supplementation on MDD in patients with multiple sclerosis (MS). MDD was rated using the Beck questionnaire, and after 12 weeks of zinc supplementation, there was a significant decrease in Beck questionnaire scores even though Zinc, did not affect any neurological signs of MS [37].

Magnesium. Magnesium, like many other vitamins and minerals within the body, is involved as a cofactor in various enzymatic reactions. It is especially important in ion transportation, an important aspect of nerve impulse conduction, muscle contraction, and heart rhythm [38].

Tarleton et al. performed a randomized clinical trial assessing the effects of 6 weeks of magnesium supplementation in patients with mild-moderate depression. Depression was graded using a PHQ-9 scale, with mild-moderate depressed patients scoring between 5 and 19.

Participants either had magnesium supplementation during the first 6 weeks or during weeks 7-12 of the study, and the supplements contained 248 mg of elemental magnesium (in a 500 mg $MgCl_2$ tablet). During the period of treatment with magnesium, there was significant improvement in pHQ-9 scores. Secondarily, there was also improvement in anxiety with magnesium supplementation based off of GAD-7 scores. Additional positive side effects included some decrease in severity of both headaches and muscle cramps. Unfortunately, this study has limitations, including the lack of a placebo group and it was not double-blinded, thus, additional research is necessary on magnesium supplementation [39].

3.3 Saffron

Saffron is produced from the dried stigmas of the *Crocus sativus* plant. While it is well known in the realm of cooking, it also contains some medicinal properties [40].

Kashani et al. [41] compared saffron to fluoxetine in the treatment of postpartum depression. The diagnosis of postpartum depression was made using DSM-IV-TR (text revision) criteria, and the treatment options contained either 15 mg of saffron extract or a fluoxetine capsule. Depression was graded using the Hamilton Depression Rating Scale (HDRS), and after 6 weeks, the study found "no significant difference between the 2 groups in terms of reduction in HDRS score from baseline to each time", as well as almost equal remission rates between the two groups. Saffron had similar efficacy in treating depression when compared to fluoxetine, and had a lower incidence of side effects. Fluoxetine was associated with more side effects, such as headache, dry mouth, drowsiness and constipation.

A review article of 12 randomized control trial studies from the University of Florida and Jacksonville University found that saffron improves depressive symptoms, premenstrual syndrome, sexual dysfunction and reduced snacking behaviors similar to Fluoxetine without significant negative effects [42].

More studies are needed to confirm saffron as an effective depression treatment, as Kashani's study lacked a placebo group and was a relatively small size study for a short time period. [43, 44].

3.4 Curcumin

Curcumin is derived from turmeric, and has been known for its anti-inflammatory properties, as well as aiding in the treatment of metabolic syndrome, pain and degenerative eye conditions [45].

Yu et al. performed a study analyzing curcumin supplementation in combination with escitalopram and its effects on various aspects of depression. The Chinese versions of HDRS-17 and MADRS scores were used for assessment of depression. The study also measured inflammatory cytokines, IL-1B and TNF-a, substances that other studies have found to be elevated in depressed patients. Both the placebo and curcumin groups were being treated with escitalopram. After 6 weeks of curcumin supplementation, patients had decreased HDRS-17 and MADRS scores compared to those in the placebo group, demonstrating a significant antidepressant behavioral response. Those supplemented with curcumin also had significantly decreased inflammatory markers, IL-1B and TNF-a, compared to the placebo group. This study demonstrated enhanced efficacy of escitalopram with curcumin supplementation [46].

Lopresti et al. analyzed the effect of curcumin on major depression and atypical depression using the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) and Spielberger State-Trait Anxiety Inventory (STAI), both alone and in conjunction with antidepressant treatment. Improvement with curcumin supplementation was more beneficial after the first 4 weeks. Although the IDS-SR_{30} scores in both the placebo and supplementation groups improved in the first 4 weeks, in weeks 4 to 8, improvement continued only in the curcumin group.

Anxiety also decreased with curcumin, paralleling the improvement found for depressive symptoms as STAI anxiety scores improved more during weeks 4 to 8, despite seeing improvement within the first 4 weeks of treatment. As the study by Lopresti et al. was a small size, larger scale studies should be performed [47].

Another study performed by Lopresti and Drummond found continued improvement with curcumin treatment in major depressive disorder, but there was no significant improvement with the addition of saffron to a low-dose curcumin supplement [48].

3.5 Crocin

Crocin has a long history of use in herbal medicine; Crocin is derived from *Crocus sativus*, and is what gives saffron its color. Talaei et al. analyzed the efficacy of Crocin in the treatment of major depression in addition to an SSRI (fluoxetine, sertraline, or excitalopram) for 4 weeks. The effects were measured using the Beck Depression inventory (BDI), Back Anxiety Inventory (BAI), and Mood Disorder Questionnaire (MDQ).

Safety and tolerability were demonstrated as crocin did not result in side effects, and efficacy was shown as depressive symptoms in the group treated with crocin improved compared to the placebo group. As the study had a small sample size and was performed over a short time, additional research is necessary with a larger sample size and over a longer time frame [49].

3.6 Fatty Acids

There have been various studies of polyunsaturated fats and their effects on depression, and Park et al. analyzed the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on depressed patients. Using the Center for Epidemiological Studies Depression Scale Korean version (CED-D-K), the Hamilton Depression Rating Scale 17-item version, the Clinical Global Impression Scale (CGI-S) and Clinical Global Impression Improvement (CGI-I), they looked at the effects of fatty acid on depression. Results showed a significant improvement in CGI-I scores with n-3 polyunsaturated fatty acid (PUFA) supplementation, but no effects on HAM-D-17, CGI-S scores compared to the placebo group. It should be known that the placebo group had an initial higher intake of fish, a source of n-3 PUFAs, compared to the supplement group. This shows n-3 PUFAs may be a beneficial adjuvant to treatment, rather than as monotherapy in the treatment of depression. This study was performed in Asia. Because diets vary geographically, this study should be reproduced with various populations and diets, and with a larger population [50].

A meta-analysis performed by Mocking et al. provided additional insight into whether PUFAs actually had a beneficial impact on the treatment of depression. Various issues were address from previous meta-analyses, such as the ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA), publication bias, effect size, duplicate publication, and lack of focus on MDD only. Ultimately, this current meta-analysis found support for the use of omega-3 PUFAs in the treatment of MDD, with higher doses of EPA having a greater effect. The improvement in MDD was greater in studies where supplementation was in addition to concurrent use of antidepressants [51]. Looking beyond the scope of MDD, Wozniak et al. conducted a 12-week study analyzing the effects of high EPA/DHA omega-3 fatty acids and inositol on children with bipolar spectrum disorder. The study was broken down into three treatment arms: inositol and placebo, omega-3 fatty acids with placebo, and omega-3 fatty acids with inositol. They found the treatment group receiving the omega-3 fatty acids plus inositol demonstrated the greatest improvement in bipolar spectrum disorder, in regards to the Young Mania Rating Scale, the Children's Depression Rating Scale, and the Brief Psychiatric Rating Scale. This study does have limitations, such as a 54% completion rate, a small sample size, and the lack of inclusion of severely ill patients [52].

A review by Schneider et al. further endorsed the beneficial aspects of PUFAs. Treatments with DHA were found to increase the serotonin concentrations in multiple studies. Additional studies also found a similar trend of decreased DHA and increased n-6:n-3 ratios of fatty acids in patients with depression and anxiety. Those who committed suicide from depression had lower levels of DHA. Bipolar patients also had a similar pattern of lower DHA levels. The meta-analyses found efficacy of PUFAs in the treatment of depression, especially with EPA or EPA and DHA combination therapy [53].

Further research should be performed with a focus on potential side effects of EPA supplementation and any possible biochemical interactions between EPA and antidepressants [53].

3.7 Rhodiola rosea

Rhodiola rosea also known as rose root has been used in folk medicine and has been considered an adaptogen to improve health status and to treat a variety of health conditions, including depression.

A review of eleven randomized placebo controlled trials [54] found that although few adverse effects were reported it was unclear if there was a definite benefit as far as general mental functioning was concerned as would be hoped from an adaptogen [55].

Limited research has kept its exact mechanism unknown, but has been found to have effects on serotonin, dopamine, and acetylcholine, all important components in mood regulation. Mao et al. performed the first study looking at *R. rosea* and its effects on major depressive disorder compared with sertraline and a placebo group. Depression was scored using HAM-D. The findings demonstrated a clinically meaningful reduction in HAM-D scores between *R. rosea* and sertraline. There was no overall significant difference in improvement between all groups, but the *R. rosea* group experienced less side effects compared to treatment with sertraline. This suggests possible use for *R. rosea* in patients unable to tolerate the side effects of other antidepressant medications [54].

3.8 Walnuts

Walnuts contain various neuroprotective compounds including Vitamin E, folate, melatonin, and polyphenols. Pribis performed a trial looking at the effect of walnut intake on mood in healthy college students. Mood was assessed using the Profiles of Mood States (POMS) in non-depressed participants. Walnut intake appeared to improve the mood of males but not females. The reason for the differential outcome was not elucidated, thus further research and study replication should be done to confirm these results [56].

3.9 S-Adenosyl-L-Methionine (SAMe)

S-adenosyl-$_L$-methionine (SAMe) is produced naturally within the body, made from $_L$-methionine, an amino acid, and adenosine triphosphate. It is involved in donating methyl groups to neurotransmitters in the brain [57].

Multiple trials have demonstrated the positive effect of SAMe and its use as an antidepressant when compared to placebo and other tricyclic antidepressants.

Mischoulon et al. researched the effect of SAMe on depression compared to the effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). HAM-D-17 was used to assess antidepressant efficacy. Inventory of Depressive Symptomatology – Clinician Rated (IDS-C) and CGI-I were used to assess secondary improvement. Results showed a decrease in HAM-D-17 scores in all groups (SAMe, escitalopram, and placebo) however the trial was considered a failed trial due to the lack of clinical significant effects of SAMe on depression after 12 weeks of supplementation and a lack of significant difference between supplemental, escitalopram and placebo groups [58]. This trial,however, was one of many looking at the efficacy of SAMe as an antidepressant.

A review of research conducted in 2017 found in double-blind, randomized controlled trials, SAMe was as effective or better than tricyclic antidepressants. SAMe was found to have a positive effect in depression treatment, demonstrating to be as effective, if not more beneficial, than anti-depressant medications. Additional studies found a beneficial effect of SAMe as adjunctive treatment with antidepressants as well [59].

3.10 Tryptophan

5-Hydroxy-L-tryptophan (5-HTP) is the precursor of serotonin. It has been taken as a treatment for depression, insomnia, and fibromyalgia. Many studies have been conducted looking at the use of 5-HTP in the treatment of depression, but only few have held statistical significance. Overall, it has been shown that 5-HTP is beneficial as adjuvant treatment for depression when used in conjunction with nialamide, clomipramide, and nomifensine, but limited data is available for the use of 5-HTP as an adjuvant with anti-depressant medication. Reported side effects associated with the use of 5-HTP include nausea, vomiting, and diarrhea, and no adverse effects have been found when used with monoamine oxidase inhibitors [60].

3.11 Theanine

Camellia sinensis, or theanine, is an amino acid found in the green tea herb. While the exact mechanism is unknown, it is thought the calming effect of green tea is due to inhibition of cortical excitation. It is important to consider possible antioxidant and antiproliferative effects as well. More research must be done to determine the efficacy of the antianxiolytic properties of theanine [61]. A recent review article found that phytochemicals including carbatrol found in oregano and thyme as well as Lavandula may have antidepressant effects without the hepatotoxicity concerns that exist for other agents such as kava kava [63, 71].

3.12 Camomile

Although over the counter product teas advertised to encourage sleepiness may contain chamomile (as well as other ingredients such as Passiflora), the amount of active ingredient may not be enough to promote sleep. Gerbarg and Brown discuss the limited amount of research on the effects of chamomile. It can be used to treat anxiety and insomnia, as it has been shown to act on GABA-metabolizing enzymes in rat brain homogenates. Specifically, spigenin, a component of chamomile, “has high affinity for benzodiazepine GABA receptors… but causes minimal sedation”.

Chamomile demonstrated a significant improvement in anxiety compared to the placebo group after 8 weeks of supplementation in patients with generalized anxiety disorder. The effects were mild, and therefore, it is thought that chamomile can be used in addition to other sedatives and herbs [61].

3.13 Passiflora and Valeriana

Basic neuroscience research done by Guerrero and Medina found that Passiflora incarnata had sleep induction effects on rats. Administration of the extracts of Passiflora incarnate induced a significant decrease in the total time spent in a state of wakefulness ($p<0.05$; statistical power=0.85); concomitantly, an important increase in the amount of slow wave sleep ($p<0.05$; statistical power=0.98) however there was no overall change in rapid eye movement sleep for rats.

Valeriana officinalis L. has been utilized for treatment of insomniac patients. Subjective analysis indicates a shortening of the sleep latency, a decrease in number of awakenings through the night, self-perception of having a repairing sleep after administration of the extracts of this plant [62].

3.14 Lavendula

Lavender has been used for many years for its sleep-inducing and anxiolytic effects. Lavender oil aromatherapy and massages have been shown to ease some symptoms of anxiety in patients. Fißler, and Quante performed a retrospective study on eight patients to determine the effects of Lasea (a brand of lavender oil capsule) on MDD, symptoms of anxiety, insomnia, and psychomotor agitation. They found six out of eight patients had a decrease in HAMD-17 scores after treatment with Lasea. Three patients experienced decreased time falling asleep with treatment, and six patients experienced a decrease in agitation as well. This retrospective analysis demonstrates positive benefits for the use of lavender oil capsules for patients with MDD. Because this was a retrospective case study, more research is necessary, including randomized, double-blinded, placebo-controlled studies [63].

3.15 Inositol

Inositol is produced by the body as a precursor of phosphatylinositol, which is a component of neurological membranes. Phosphatylinositol is important in the regulation of signaling in multiple pathways.

A literature review by Akhondzadeh et al. concluded that inositol had a greater positive effect in the treatment of depression, panic and obsessive compulsive disorder compared to the placebo group. Inositol was also effective when combined with fluvoxamine, and less side effects were reported with inositol than with fluvoxamine alone. Inositol shows promise as an adjuvant treatment for multiple psychiatric conditions, including depression, panic, OCD, bipolar depression, binge eating, and bulimia nervosa [60].

3.16 N-Acetylcysteine

As a precursor to the essential amino acid, cysteine, N-Acetylcysteine (NAC) has many potential benefits. NAC can cross the blood-brain barrier secondary to oral intake, whereas cysteine cannot. NAC can increase the amount of cysteine in the brain, thus modulating glutaminergic and dopaminergic pathways. N-acetylcysteine and methylcobalamin (discussed earlier in this article) target the problem of oxidative stress. NAC is available over the counter, and is both an antioxidant and a prodrug for cysteine as well as glutathione. [61] NAC can scavenge reactive oxygen species, protecting the brain. The anti-inflammatory effects of NAC could potentially protect the brain, preventing aging due to inflammatory cytokines. [62] The role of NAC in these metabolic pathways sets the foundation for its use in various psychiatric conditions. One hypothesis is that increased oxidative stress is thought to contribute to the development of bipolar disorder. [63] NAC may potentially play a role as an anti-inflammatory and as a dopamine modulator [64].

A recent study by Cullen et al. of thirty five adolescents and young adults found a reduction in non-suicidal self harm (NSSI) and depression scores using the Beck Depression Inventory with oral NAC twice daily even though no decrease in impulsivity was found [65].

3.17 St. John's Wort

St. John's Wort contains extracts from hypericum, an herb that has been used to treat depression for hundreds of years. Hypericum has many undesired drug interactions as it induces cytochrome P450 isoenzymes CYP3A4m 2C19, and 2C9 as well as the P-glycoprotein transporter. The drug interactions with St. John's Wort make it less desirable in the treatment for females of childbearing age, as hypericum increases the clearance of estradiol, and in turn, can change the efficacy of oral contraceptives. Hypericum also has a variety of neurological effects, acting on serotonin, norepinephrine, dopamine, and other neurotransmitters, in addition to its neuroendocrinologic and neuroimmunologic properties [66].

A review article looking at eleven randomized controlled trials found an overall lack of efficacy of St. John's Wort in the treatment of depression and anxiety as compared to standard treatments and troublesome side effects of St. John's Wort that parallel the typical side effects of SSRIs (sexual side effects, serotonin syndrome and discontinuation syndrome, as well as changes in appetite, diarrhea, constipation, nausea, dyspepsia) led to a conclusion that St. John's Wort does not offer a significant benefit over treatment with conventional SSRIs for depression or anxiety [67].

4. Discussion

Principles of personalized medical care such as population health considerations help with the choice of a supplement whether it be a single micronutrient or a broad-spectrum micronutrient blend to be used adjunctively with conventional treatments or as a stand-alone option. When comparing the potential benefits, broad-spectrum micronutrient formulas have shown promise for use to reduce anxiety especially traumatic anxiety [68, 69]. The use of herbs was found to have more significant potential adverse side effects in a case study that found psychotic symptoms from herbal supplementation [70].

5. Conclusions

A first step approach should include addressing insomnia, especially as recent studies have shown promising basic science research with a constituent of Lavender, Lavendula, active agent, linalool [71] a potentially safe alternative to conventional treatment of insomnia that may not worsen depressive symptoms, result in daytime grogginess or cause rebound anxiety and other agents such as Valeriana, and Chamomile may also be helpful. Inositol's ability to reduce repetitive worry and associated agitation which can disturb sleep especially when given with omega-3 fatty acids may provide a more health promoting alternative that is appropriate for youth with bipolar depression for whom typical mood stabilizers can cause problematic adverse metabolic consequences, especially due to the long duration of treatment.

Reduction of the risk of self-harm should also be a high priority when determining effective treatment; supplements that reduce oxidative stress such as vitamin C, NAC, B12 and Zinc are especially attractive for use with young adults and adolescents with a favorable side effect profile which includes possible reduction of cold sores (as cold sores may be a contributor to low self-esteem).

SAMe may have a higher effect size than some other supplements such as 5-HTP without the side effects that 5-HTP can have such as nausea, vomiting and diarrhea.

Magnesium supplementation for depression may be a more appropriate choice in persons who also suffer headaches due to the side effect profile.

Gender may also be an important consideration when picking a supplement. Walnuts may be helpful for males but not for females to improve mood. Women of childbearing age should avoid include St. John's wort due to the potential to reduce efficacy of oral contraceptives due to drug interactions; saffron and crocin may be more desirable choices. Older individuals who may be more prone to vitamin D deficiency and cognitive impairment may benefit more from vitamin D supplementation, although youth may also benefit from supplementation.

Future research trials are needed with larger numbers of individuals of varied gender and age as well as cultural background to further elucidate what person is more likely to benefit from a particular treatment.

Acknowledgments

This review article would not have been possible without the support of the PCOM electronic library and support and encouragement of the Department of Psychiatry at PCOM.

Author Contributions

Ms. Berberich and Dr. Bernstein contributed equally to this article.

Funding

No financial support was provided for this review article.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

1. Attachment of BDI.
Source: Beck Depression Inventory.
https://www.bmc.org/sites/default/files/For_Medical_Professionals/Pediatric_Resources/Pediatrics_MA_Center_for_Sudden_Infant_Death_Syndrome__SIDS_/Beck-Depression-Inventory-BDI.pdf.
Accessed March 3, 2018.
2. Attachment of Hamilton Depression Rating Scale.
Source: Hamilton Depression Rating Scale. http://www.npcrc.org/files/news/hamilton_depression_scale.pdf. Accessed March 3, 2018.

3. Beck Depression Inventory. American Psychological Association (2018). http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/beck-depression.aspx
4. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. Validity of a Brief Depression Severity Measure. J Gen Intern Med. 2011; 16: 606-613.

References

1. Biesalski H.K., Tinz J. Multivitamin/mineral supplements: Rationale and safety—A systematic review. Nutrition. 2017; 33: 76–82.
2. Simkin DR, Popper CW. Overview of integrative medicine in child and adolescent psychiatry. Child Adolesc Psychiatric Clin N Am. 2013; 22: 375-380.
3. McKinnon AC, Hickie IB, Scott J, Duffy SL, Norrie L, Terpening Z, et al. Current sleep disturbance in older people with a lifetime history of depression is associated with increased connectivity in the Default Mode Network. J Affect Disord. 2018; 229: 85-94.
4. Probiotics: In Depth. National Institute of Health. October 2016. NCCIH Pub No.: D345. https://nccih.nih.gov/health/probiotics/introduction.htm
5. Akkasheh G., Kashani-Poor Z., Tajabadi-Ebrahimi M., Jafari P., Akbari H., Taghizadeh M., et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition. 2016; 32: 315-320.
6. Huang R, Wang K, Hu J. Effect of probiotics on depression: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2016; 8: 483.
7. Vitamin C. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/
8. Oliviera I., Souza V., Motta V., Da-Silva S. Effects of oral vitamin C supplementation on anxiety in students: A double-blind, randomized, placebo-controlled trail. Pak J Biol Sci. 2015; 18: 11-18.
9. Vitamin D. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/
10. Aloia JF, Katumuluwa S, Stolberg A, Usera G, Mikhail M, Hoofnagle AN, et al. Safety of calcium and vitamin D supplements: a randomized controlled trial. Clin Endocrinol (Oxf). 2019. doi: 10.1111/cen.13848.
11. Amini S, Jafarirad S, Amani R. Postpartum depression and vitamin D: A systematic review. Crit Rev Food Sci Nutr. 2018: 1-7.
12. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, et al. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. PLoS One. 2017; 12: e0180512
13. Hoffmann MR, Senior PA, Mager DR. Vitamin D supplementation and health-related quality of life: a systematic review of the literature. J Acad Nutr Diet. 2015; 115: 406-418.
14. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients. 2014; 6: 1501-1518.
15. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al.. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. Psychosom Med. 2014; 76: 190-196.
16. Li G, Mbuagbaw L, Samaan Z, Falavigna M, Zhang S, Adachi JD, et al. Efficacy of vitamin D supplementation in depression in adults: a systematic review. J Clin Endocrinol Metab. 2014; 99: 757-767.
17. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013; 202: 100-107.

18. Vidgren M, Virtanen JK, Tolmunen T, Nurmi T, Tuomainen TP, Voutilainen S, et al. Serum concentrations of 25-hydroxyvitamin D and depression in a general middle-aged to elderly population in Finland. J Nutr Health Aging. 2018; 22: 159-164.
19. Belzeaux, R., Annweiler, C., Bertrand, J., Beauchet, O., Pichet, S., Jollant, F., et al. Association between hypovitaminosis D and cognitive inhibition impairment during major depressive episode. J Affect Disord. 2018; 225: 302-305.
20. Hoffman MR, Senior PA, Mager DR. Vitamin D supplementation and health-related quality of life: A systematic review of the literatures. J Acad Nutr Diet. 2015; 115: 406-418.
21. Li G, Mbuagbaw L, Samaan Z, Falavigna M, Zhang S, Adachi JD, et al. Efficacy of vitamin D supplementation in depression in adults: a systematic review. J Clin Endocrinol Metab. 2014; 99: 757-767.
22. Rejnmark L, Bislev LS, Cashman KD, Eiriksdottir G, Gaksch M, Grubler M, et al. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. PLoS One. 2017; 12: e0180512.
23. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients. 2014; 6: 1501-1518.
24. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. Psychosom Med. 2014; 76: 190-196.
25. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013; 202: 100-107.
26. Frandsen T., Pareek M., Hansen J., Nielsen C. Vitamin D supplementation for treatment of seasonal affective symptoms in healthcare professionals: a double-blinded randomized placebo-controlled trial. BMC Res Notes. 2014; 7: 528.
27. Kjaergaard M., Waterloo K., Wang C.E., Almas B., Figenschau, Y., Hutchinson M.S., et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: Nested case-control study and randomised clinical trial. Br J Psychiatry. 2012, 201: 360–368.
28. Sepehrmanesh Z., Kolahdooz F., Abedi F., Mazroii N., Assarian A., Asemi Z., et al. Vitamin D supplementation affects the beck depression inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: A randomized, controlled clinical trial. J Nutr. 2016; 146: 243-248.
29. Focker M., Antel J, Grasemann C., Fuhrer D., Timmesfield N., Ozturk D., et al. Effect of a vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients – a randomized controlled trial: study protocol. BMC Psychiatry. 2018; 18: 57.
30. Mayo Clinic Staff. Thiamin. October 25, 2017. https://www.mayoclinic.org/drugs-supplements-thiamin/art-20366430
31. Ghaleiha A., Davari H., Jahangard L., Haghighi M., Ahmadpanah M., Seifrabie M., et al. Adjuvant thiamine improved standard treatment in patients with major depressive disorder: results from a randomized, double-blinded, and placebo-controlled trial. Eur Arch Clin Neurosci. 2016; 266: 695-702.

32. Vitamin B6. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/
33. Folate. National Institute of Health. April 20, 2016. https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/
34. Vitamin B12. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/
35. Almeida O., Ford A., Hirani V., Singh V., van Bockxmeer F., McCaul K., et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomized, double-blind, placebo-controlled trial. Br J Psychiatry. 2014; 205: 450-457.
36. Zinc. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/
37. Salari S., Khomand P., Arasteh M., Yousefzamani B., Hassanzadeh K. Zinc sulphate: A reasonable choice for depression management in patients with multiple sclerosisL A randomized, double-blind, placebo-controlled clinical trial. Pharmacol Rep. 2015; 67: 606-609.
38. Magnesium. National Institute of Health. February 11, 2016. https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/
39. Tarleton E., Littenberg B., MacLean C., Kennedy A., Daley C. Role of magnesium supplementation in the treatment of depression A randomized clinical trial. PLoS One. 2017; 13: 1-15.
40. Gohari A., Saeidnia S., Mahmoodabadi M. An overview on saffron, phytochemicals, and medicinal properties. Pharmacogn Rev. 2013; 7: 61-66.
41. Kashani L., Eslatmanesh S., Saedi N., Niroomand N., Ebrahimi M., Hosseinian M., et al. Comparisson of saffron versus fluoxetine in treatment of mild to moderate postpartum depression: A double-blind, randomized clinical trial. Pharmacopsychiatry. 2016; 50: 64-68.
42. Hausenblas HA, Heekin K, Mutchie HL, Anton S. A systematic review of randomized controlled trials examining the effectiveness of saffron (*Crocus sativus L.*) on psychological and behavioral outcomes. J Integr Med. 2015; 13: 231-240.
43. Lopresti AL, Drummond PD. Saffron (*Crocus sativus*) for depression: A systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. Hum Psychopharmacol. 2014; 29: 517-527.
44. Lopresti AL, Drummond PD. Curcumin and a Saffron/Curcumin combination for the treatment of major depression: A randomized, double-blind, placebo-controlled study. J Affect Discord. 2017; 207: 188-196.
45. Hewlings S, Kalman D. Curcumin: A review of its' effects on human health. Foods. 2017; 6: 92.
46. Yu J, Pei B, Zhang Y, Wen Z, Yang J. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder. J Clin Psychopharmacol. 2015, 35: 406-410.
47. Lopresti A, Maes M, Maker G, Hood S, Drummond P. Curcumin for the treatment of major depression a randomized, double-blind, placebo controlled study. J Affect Disord. 2014; 167: 368-375.
48. Lopresti A, Drummond P. Efficacy of curcumin and a saffron/curcumin combination for the treatment of major depression: A randomized, double-blind, placebo-controlled study. J Affect Disord. 2017; 207: 188-196.

49. Talaei A, Moghadam M, Tabassi S, Mohajeri A. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. J Affect Disord. 2015; 174: 51-56.
50. Park Y, Park Y, Kim S, Oh D, Park Y. Supplementation of n-3 polyunsaturated fatty acids for major depressive disorder: A randomized, double-blind, 12-week, placaebo-controlled trial in Korea. Ann Nutr Metab. 2015; 66: 141-148.
51. Mocking R., Harmsen I., Assies J., Koeter M., Ruhe H., Schene A. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. Transl Psychiatry. 2016; 6, e756.
52. Wozniak J., Faraone SV., Chan J., Tarko L., Hernandez M., Davis J., et al. A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: A pilot study. J Clin Psychiatry. 2015; 76: 1548-1555.
53. Schneider M., Levant B., Reichel M. Gulbins E., Kornhuber J., Muller C. Lipids in psychiatric disorders and preventative medicine. Neurosci Biobehav Rev. 2017; 76: 336-362.
54. Mao J., Xie S., Zee J., Soeller I., Li Q., Rockwell K., et al. Rhodiola rosea versus sertraline for major depressive disorder: A randomized placebo-controlled trial. Phytomedicine. 2015; 22: 394-399.
55. Hung SK, Perry R, Ernst E. The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. Phytomedicine. 2011; 18: 235-244.
56. Pribis P. Effects of walnut consumption on mood in young adults – A randomized controlled trial. Nutrients. 2016; 8: 668.
57. Bottiglieri TS. Adenosyl-L-methionine (SAMe): From the bench to the bedside-Molecular basis of a pleiotrophic molecule. Am J Clin Nutr. 2002; 76: 1151S–1157S.
58. Mischoulon D., Price L., Carpenter L., Tyrka A., Papakostas G., Baer L., et al. A double-blind, randomized, placebo-controlled clinical trial of S-Adenosyl-$_L$-Methionine (SAMe) vs. Escitalopram in major depressive disorder. J Clin Psychiatry. 2014; 75: 370-376.
59. Sharma A., Gerbarg P., Bottiglieri T., Massoumi L., Carpenter L., et al. S-Adenosylmethionine (SAMe) for neuropsychiatric disorders: A clinician-oriented review of research. J Clin Psychiatry. 2017; 78: e656-e667.
60. Akhondzadeh S., Gerbarg P., Brown R. Nutrients for prevention and treatment of mental health disorders. Psychiatr Clin N Am. 2013; 36: 25-36.
61. Gerbarg P., Brown R. Phytomedicines for prevention and treatment of mental health disorders. Psychiatr Clin N Am. 2013; 36: 37-47.
62. Guerrero FA, Medina GM. Effect of a medicinal plant (*Passiflora incarnata L*) on sleep. Sleep Sci. 2017; 10: 96-100.
63. Fißler A., Quante A. A case series on the use of lavendula oil capsules in patients suffering from major depressive disorder and symptoms of psychomotor agitation, insomnia and anxiety. Complement Ther Med. 2014; 22: 63-69.
64. Bent S, Hendren RL. Complementary and alternative treatments for autism part I: Evidence-supported treatment. AMA J Ethics. 2015; 17: 369-374.

65. Cullen KR, Klimes-Dougan B, Westlund Schreiner M, Carstedt P, Marka N, Nelson K, et al. N-acetylcysteine for nonsuicidal self-injurious behavior in adolescents: An open-label pilot study. J Child Adolesc Psychopharmacol. 2018; 28: 136-144.
66 Maher AR, Hempel S, Apaydin E, Shanman RM, Booth M, Miles JN, et al. St. John's Wort for major depressive disorder: A systematic review. Rand Health Q. 2016; 5: 12.
67. Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JN, Sorbero ME, et al. A systematic review of St. John's wort for major depressive disorder. Syst Rev. 2016; 5: 148.
68. Popper CW. Single-micronutrient and broad-spectrum micronutrient approaches for treatment of mood disorders in youth and adults. Adolesc Psychiatr Clin N Am. 2014; 23: 591-672.
69. Rucklidge JJ, Kaplan BJ. Broad-Spectrum micronutrient formulas for the treatment of psychiatric symptoms: A systematic review. Expert Rev Neuroth. 2013; 13: 49-73.
70. Arnold LE, Fristad MA, Gracious BL, Johnstone JM, Kaplan BJ, Popper CW. Psychosis resulting from herbs rather than nutrients. Prim Care Companion CNS Disord. 2016; 18. Doi: 10.4088/PCC.16l01940.
71. Lee BK, Jung AN, Jung Y. Linalool ameliorates memory loss and behavioral impairment induced by REM-sleep deprivation through the serotonergic pathway. BIomol Ther. 2018; 26: 368-373.