

The Role of Supplements in Treatment of Depression

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ABSTRACT

Along with dietary intake, nutrition can also be obtained from nutrient supplements. They are widely used in the general population and their market is growing. It has been assumed adequate intake of them contributes to better overall mental health. This review explores studies regarding the role of different nutrients in treatment of depression. After searching among them we found Testosterone, Omega 3 fatty acid, Thyroid hormones, Modafinil, Folate, Vitamin B12, S-Adenosyl Methionine (SAMe), Magnesium, and Zinc as supplements which has some effect in combination with anti-depressant medications. They have advantages and also some disadvantages. In this review paper, we have taken a look at each of these agents individually and mentioned their current status in the treatment of depression.

Keywords: Depression; Supplement nutrient; Testosterone; Omega 3 fatty acid; Thyroid hormones; Modafinil; Folate; Vitamin B12; SAMe; Magnesium; Zinc

INTRODUCTION

Mental disorders are common diseases. They affect patients by major consequences including a decrease in patient's social functioning and workplace productivity [1]. Among them, depression is a critical one and leading disability worldwide. In the U.S. alone, over 40 million people - roughly 1 in 5 adults - have depressive symptoms while the majority of them are not receiving treatment [2]. Patients with major depression respond to antidepressant treatment, but 10% to 30% of them do not improve or show a partial response which leads to functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behaviour, and a high relapse rate [3]. Adding an anti-depressant from a different class or second-generation antipsychotics may lead to some positive responses however it increases undesired side effects.

LITERATURE REVIEW

Although there is an increasing prevalence of treatment-resistant depression, finding a beneficial psychopharmacology approach is still challenging [4]. So, there is a need for new agents that augment or accelerate response to anti-depressant therapy and do not inflict an additional systemic burden on the patient [5].

Studies present some evidence regarding the role of nutrients in the treatment of mental health particularly depression [6].

Testosterone

Per some studies, there is a positive correlation between lower levels of testosterone and depression. It is suggested lower-than-normal testosterone levels may be common in depressed men who fail to get better when taking antidepressants. So, replacement therapy by Testosterone can improve the signs and symptoms of depression in these types of patients [7,8]. In a small study from Harvard Medical School's McLean Hospital, they studied 22 subjects with resistant depression and low to low normal testosterone levels. There was a dramatic improvement after getting a supplement of testosterone gel over 8 weeks [9]. In addition, some shreds of evidence have found the role of endogenous testosterone in the treatment of obesity [10]. If low testosterone depressive patients improve by increasing testosterone level, it helps them to lose weight and get in shape.

On the other hand, there are not enough studies in the medical literature which support the relationship between low testosterone levels and depression [11]. Although there is a role for a trial of testosterone therapy, we have to consider that there could be placebo effects [12]. It seems we need further studies to

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evaluate this issue. Also, there is a controversy between scientists about cardiovascular complications and also prostate cancers as consequences of testosterone supplement therapy in MDD patients [13]. It also may include breast swelling; headache, anxiety; increased facial or body hair growth, male-pattern baldness, increased or decreased interest in sex, numbness or tingly feeling, and pain or swelling where the medicine was injected [14]. Since there is not enough evidence to support or rule out testosterone therapeutic effect in the treatment of depression so the use of testosterone in depressive patients is still controversy [11].

Omega 3 fatty acid

Depression is often found with some gastrointestinal inflammation, autoimmune disease, cardiovascular problems, neurodegenerative disease, diabetes type 2 and cancers [15-18]. Chronic low-grade inflammation could have a significant contributing role to develop these diseases [19]. Per some studies, dysfunction of the gut-brain axis leads to chronic inflammatory conditions with neuropsychiatric features and those features could develop as depression. [15]. The brain contains 60 percent fat. DHA (docosahexaenoic acid) an animal-based omega-3 fat, along with EPA (eicosapentaenoic acid), helps the brain to function well. Lack of DHA increases corticotropin-releasing hormone which may contribute to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. This axis has an important part of the neuroendocrine system that regulates mood, aggression, and anxiety [20]. Some clinical trials mentioned supplementation with omega-3 fatty acids, in particular, the long-chain varieties EPA and DHA, may relieve the clinical depression associated symptoms [21].

Studies report omega-3 fatty acid intake enhances the cognitive processes which lead to attention increase and aggression reduction [22,23]. Three studies have done regarding the role of fatty acids in the depression treatment:

As an adjunct to antidepressant treatment in 20 unipolar patients with recurrent major depression;

In children with major depression; and

In bipolar depression.

The study concluded to the significant benefit of EPA treatment in the adult with unipolar and bipolar depression as well. It mentioned omega-3 has a significant effect on children with major depression [24].

Despite there is some evidence about the role of these supplements in the treatment of depression, scientists could not find any specific diet that has been proven to relieve depression yet. Maybe these supplements could be a part of the overall treatment approach in depressive patients [25]. On the other hand, there are some concerns about the Omega-3 fatty acids' anti-thrombotic effects which could be risky in patients on Warfarin or other types of anticoagulant medications [26].

Overall, the therapeutic dose of omega-3 could be considered as adding agent to the treatment of depressive patients who are not responding to an anti-depressant. There are some studies which show the improvement of these approach in depressive patients

compare with groups who only take antidepressant medications and there is some evidence of the high rate of depression in the population who do not eat fish or other types of foods which contain omega-3 [27]. Studies suggest omega-3 fatty acids could be beneficial by subsiding depression intensity, anxiety, sleep disturbance and sexual dysfunction among those patients who are still depressed despite the use of an antidepressant [28]. However, we cannot ignore the preventive role of omega-3 PUFA may depend on other factors, such as overall diet quality and the social environment [29].

Thyroid hormones

Depression and thyroid conditions such as hypothyroidism have some common symptoms. Thyroid hormones accelerate Tricyclic Acids (TCA) response in treatment of depression. Some evidence shows they could be a good adjuvant to Selective Serotonin Reuptake Inhibitors (SSRIs) as well [30,31]. Some studies endorsed the role of thyroid hormones in treatment of depression. T3 increased cortical 5-HT levels, probably by reducing the auto-inhibitory effect of the pre-synaptic 5-HT_{1A} receptor [32]. T3 increases the level of 5-HT when it combines with Clomipramine. It increases treatment regimen efficiency greater than T3 or Clomipramine alone [33]. Although either T3 or T4 can be used as augmentation, T3's antidepressant properties are considered more effective than those of T4. One approach could be Start T3 augmentation and if tolerated, increase the dose after 1 week [30]. Despite the role of thyroid hormones in the treatment of depression, it is not predictable the euthyroid MDD patient's body response to thyroid adjuvant therapy based on their baseline thyroid hormones level [34].

There is no guideline about how long to keep thyroid hormones after the initial response to antidepressant regimen. TSH levels become suppressed after 4 weeks of T3 (50 mcg/d) in patients with normal baseline thyroid function. So thyroid hormones efficiency is self-limited and may not be a good choice to continue after 2 to 3 months, even when there is a good response [35]. In addition, some anti-depressant medications such as Lithium may cause hypothyroidism in patients which limit their use in treatment of clinical depression [36].

Although some evidence supports 5-HT release theory, this theory cannot explain why thyroid hormones have a rapid clinical effect in MDD. Most studies report the hormones have clinical efficacy in MDD within 4 weeks. Similarly, selective serotonin reuptake inhibitors (SSRIs) increase 5-HT levels within hours of treatment onset, but the clinical effect occurs 4 to 6 weeks later. Therefore, increased 5-HT levels cannot fully explain thyroid hormones' early effect. In addition, an open trial of T3 augmentation in 14 severely depressed patients who had not responded to 6 weeks of tricyclics, showed a greater response to a monoamine oxidase inhibitor (MAOI) or electroconvulsive therapy than thyroid hormone [37]. We also should not ignore the side effect of Thyroid hormones such as tachycardia in patients with cardiovascular problems and hypoglycemia in diabetic patients. Depressed patients given T3 with tri-cyclic antidepressants may be twice as likely as controls to respond to

treatment [38]. We have to consider men and women might respond differently to T3 augmentation of SSRIs [39,40].

The use of T3 in other ways to accelerate and enhance antidepressant treatment, as well as the clinical utility of other hormones of the thyroid axis, requires further study. Another important issue for future study is whether particular subtypes of depression respond preferentially to thyroid hormone or in fact any hormonal treatment. As greater knowledge is obtained about genetic and biological variability of major depression as well as the regulation of thyroid hormones in the body in general and the brain in particular, we may be able to identify preferential responders to thyroid hormone and, analogously, to other hormone strategies

Modafinil

Modafinil works in treatment of depression by promoting wakefulness and reduce sleepiness. It is more efficient stimulant compare to others such as amphetamine and methylphenidate according to the Clinical Global Impression of change (CGI-C) scale. It targets specifically orexin neurons of the tuberomammillary nucleus in hypothalamic regions which are peptide neurotransmitters that promote wakefulness [41]. Some studies provide preliminary evidence that modafinil treatment may be beneficial to those with major depression following 2 weeks and following 3 months of modafinil treatment even when unresponsive to other treatments [42]. Due to lack of euphorogenic properties, the risk of abuse is less unlike other stimulants [43].

It tends to improve symptoms of major depression such as energy level, fatigue, and slow psychomotor activity. Minor dopamine reuptake inhibition (DRI), histamine increase in the hypothalamus, and stimulation of orexin receptors take place due to Modafinil. It promotes glutamatergic circuits' activity, enhance electronic coupling, and simultaneously inhibits GABAergic activity. It may also slightly increased levels of norepinephrine and serotonin in the brain [44].

On the other hand, there are some studies which did not show any improvement by Modafinil in depressive patients. Even sometimes adverse effect was occurred such as headache, dizziness, back pain, diarrhea and dyspepsia. Since it inhibits CYP 2C19, so Modafinil may have some interaction with citalopram, diazepam, serteralin, and OCPs [45]. It may exacerbate underlying anxiety particularly in patients with co-morbid anxiety disorders [46].

Since it is a new medication and introduced to the market in the 1990s, its long-term side effects are relatively unknown. There are some case reports about Modafinil dependence and withdrawal which may proceeds to some sever symptoms such as low energy, fatigue, and sleepiness. Patients who became dependent upon the medication for functioning are at greater risk of dependence [47,48].

Modafinil is being investigated for potential roles in managing inattention, excess sleepiness, fatigue, and cognitive dysfunction associated with mood disorders (major depression and bipolar depression), attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and cocaine dependence. Additional studies are

needed to find evidence for a mood-elevating effect. In future studies adjunctive modafinil should compare head to head with conventional stimulants in patients with mood disorders.

Folate and vitamin B12

Not only studies reported low levels of vitamin B12 and folate in a patient with depression but also there is a relation between depression and low level of them in general population. Patients with recurrent mood disorders who are on Lithium have been found with low plasma level or low serum levels of folate. There is the same relation between depression and low folate which is common in alcoholic patients. People of Hong Kong and Taiwan have a very low rate of depression which could be due to their traditional folate-rich Chinese diet. In addition to depression preventing effect, folate could enhance patient body response to the antidepressant medication. Studies suggest that 800 micrograms folic acid daily and 1 mg vitamin B12 daily could be tried to improve depression treatment outcomes [49,50].

High level of plasma homocysteine which is a marker of folate and vitamin B12 deficiency is found in the patient with depression. Homocysteine metabolism impairment runs by MTHFR C677T polymorphism which is common in the general population. This impairment is shown to be more common in the depressive patient population [51]. Another proposed protective mechanism of action is via the hypomethylation hypothesis, which suggests that folate and vitamin B12 have direct effects on the central nervous system through their role in 1-carbon transfer or transmethylation reactions in the brain. Lack of folate inhibits the synthesis of methionine, an essential amino acid, and S-adenosylmethionine, a methyl donor, which, in turn, inhibits other methylation reactions important to the brain, including the metabolism of neurotransmitters such as dopamine, norepinephrine, and serotonin [52].

In addition to folate, its derivatives such as L-methyl folate could have a positive effect on depression pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). It regulates the synthesis of neurotransmitters such as serotonin, dopamine, and norepinephrine [53,54].

However, there is some evidence shows that treatment with folate and vitamin B12 does not decrease the severity of symptoms over a short period of time but may be helpful in long term management of a special population [55]. One meta-analysis results do not conclusively demonstrate that these vitamins reduce depressive symptoms and syndromes, but neither do they suggest that these vitamins have no role in the management and prevention of depression. The limited number of studies available and the irrelatively undersized samples may have hindered the ability of this meta-analysis to detect small beneficial effects of treatment if they do exist. In addition, three of the studies that reported some benefits associated with the use of vitamins included vitamin B6, which plays a role in facilitating the excretion of homocysteine. This would suggest that lowering plasma homocysteine, either by facilitating its conversion to methionine (vitamin B12 and folic acid) or by increasing its excretion (vitamin B6), may be critical to

decreasing depressive symptoms [55]. Alcohol use disorder, eating disorders, genetic C677-T polymorphism, and gastrointestinal disorders put patients with major depressive disorders in the risk of low folate levels [49].

Patients with C677-T polymorphism and patients from Hispanic or Mediterranean populations have shown impaired ability to convert folic acid to L-methyl folate. Its beneficial effects are greater in doses of more than 15mg and in MDD patients with obesity. Methylfolate is one of the useful supplements as an adjunct treatment for major depressive disorder in addition to standard treatment [56]. Since folate contributes to cell division, so there is some worry about its risk in MDD patients with colon cancers. However, it seems the risk for methyl folate is lower than folic acid [57]. Methyl folate may mask the symptoms of B12 deficiency anemia because it shrinks the blood cells back to normal [58].

Despite some studies results that raise concerns about the role of folate in increasing cancer risk, masking B12 deficiency, and worsening depressive symptoms, folate is generally well-tolerated supplement in depression treatment. In addition, 5-MTHF may be less likely to cause these risks. Although several forms of folate could be helpful in the treatment of patients with major depressive disorder, more studies are needed about dosage and populations who benefit the most from folate therapy [59].

S-Adenosyl Methionine (SAMe)

S-Adenosyl-L-Methionine (SAMe) is a derivative of amino acids that contributes to a couple of biological reactions in all cells. It transfers the Methyl group to DNA, phospholipids, proteins and biogenic amines. SAMe could be beneficial in the treatment of depression. One of its important characteristics is capability to cross the blood-brain barrier which is impenetrable to many drugs. Some studies on animals concluded the transmethylation pathway can increase the level of neurotransmitters such as serotonin, norepinephrine, and dopamine; the process which plays a crucial role in antidepressant action. A combination of SAMe and SSRI could be effective for the treatment of MDD and in higher doses, SAMe could be equal to TCAs. Furthermore, the SAMe improves post-methamphetamine depression and drug craving in these patients [60].

Since most studies applied SAMe for a short period of time, there is a lack of scientific information regarding the long-term safety of SAMe. However, in one study which was done with SAMe for two years, no serious side effect was reported by authors. SAMe can worsen mania symptoms, so bipolar patients should avoid of these supplements for targeting their depressive symptoms except under the supervision of their healthcare providers. For pregnant patients it's safety has not been proven although it has a therapeutic effect on the treatment of cholestasis in pregnancy. Furthermore, Due to decreasing the effect of levodopa by SAMe, it has some contraindication in patients with Parkinson. Another group of patients that SAMe needs to be used by cautious is immunocompromised people. They are at risk of opportunistic infections such as Pneumocystis Carini which it's growth accelerates with SAMe. Generally, SAMe's side effects is not common and cause minor complications such as nausea and GI upsets [61].

Per scientific studies, for treatment of depression, SAMe can be prescribe up 1600 mg orally which divided into two doses. This regimen needs to take up to 8 weeks alone or with a combination of antidepressant medications. A combination product could be DDM Metile which contains 250 mg of SAMe and can be prescribe twice daily for 12 months. SAMe could prescribe as an IV injection [62].

Given the lack of enough evidence and the inability to reach an evidence-based conclusion, SAMe© use needs more investigation in the future. High quality large randomized controlled clinical trials, with particular attention to randomization, and the managing of missing data are needed [63].

Magnesium and zinc

Low level of Magnesium could be due to mal-absorption, renal diseases, or inadequate intake. It could contribute to depression in young population. A group of scientists reported depression symptoms are correlated with serum Magnesium level in patients with long standing and remission depression [64]. In a study they found more than 50% higher rate of depression in the lowest quintile of intake although those finding is uncertain. Magnesium supplementation was effective in treatment of depression in older adults with hypomagnesaemia and type two diabetes in a randomized controlled trial [65]. One of magnesium side effects is GI upset which includes vomiting, nausea, and diarrhea. Increasing magnesium intake by adding to the food would be more favorable for patients who already had side effects of depression medications. On the other hand, reverse causality could not be rolled out. It means dietary intake of magnesium might be resulted to mental illness such as depression [66].

Zinc is an important part of the CNS structure. It plays role as a vesicle in pre-synaptic neurons [67]. Clinical studies show lower serum zinc levels in groups of cases with major depression [68]. Recent meta-analyses reported lower serum zinc levels are associated inversely with severity of depression symptoms. It also represents the significant effect of zinc level in treatment of depressive patients who admitted to the hospitals. In groups of cases with depression compared to controls, there was significant inverse associations between depression severity scores and serum zinc levels. It also demonstrating larger effect sizes in hospitalized cases [69]. Low dietary zinc intake was positively associated with depression symptoms in females. One possibility is that depression is associated with low appetite and it might cause low zinc level. Female patient with decent level of zinc responded better to SSRI anti-depressant treatment compare to those with low level of zinc [70].

DISCUSSION AND CONCLUSION

Greater attention to nutritional factors in mental health is warranted, given that nutrition intervention can be inexpensive, easy to administer, and generally acceptable to patients. On the other hand, toxicity of supplying nutrient needs considering if they use under pharmacologic conditions. The evidence available at present supports the recommendation of some of the nutritional supplements for the treatment of depressive

symptoms however there is not enough evidence at this stage to recommend all of them. More research is needed, and no supplements can replace proven depression treatment such as antidepressant and physiological counselling.

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