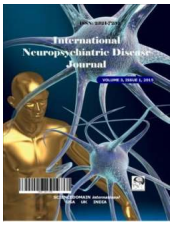

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The use of Nutraceuticals as Mono- or Adjuvant Therapy to Pharmacotherapies in Major Depressive Disorder

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Authors' contributions

This work was carried out in collaboration between both authors. Author LAEMVH performed the literature search and wrote and reviewed the manuscript. Author JBD wrote and reviewed the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Objectives: The present review provides an overview of the appropriate literature on the use of nutraceuticals in depression. The goal was to examine whether nutraceuticals, in combination with the current pharmacotherapies or even as mono-therapies, could be effective in depressive patients.
Methods: A literature search was conducted on PubMed database for articles using the terms: 'major depressive disorder', 'tricyclic antidepressants', and 'SSRIs' combined with 'nutraceuticals', 'pharmacotherapies', 'adjuvant therapies', 'amino acids', 'biochemical disturbances', '(precursors of) neurotransmitters', 'tryptophan', 'tyrosine', 'phenylalanine', 'omega-3 fatty acids', 'omega-6 fatty acids', 'S-adenosylmethionine', 'B-vitamins', 'folate', 'methyl folate', or 'vitamin B12'. Search results were manually reviewed, and relevant reviews and studies were selected for inclusion as suitable.
Results: Nutraceuticals may relieve depressive symptoms. In particular tryptophan, omega-3 fatty acids, S-adenosylmethionine, and folate as mono- or adjuvant therapy to current pharmacotherapies in depressive disorder may enhance response and increase efficacy.

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Discussion: Some nutraceuticals administered as mono- or adjuvant therapy may be useful in the treatment of depressive disorder. Nevertheless, accurate medical diagnoses and consideration of all possible treatments should always be the first step in addressing depressive disorder. Therapy with nutraceuticals should be supervised and doses be adjusted for each patient individually to achieve optimal outcomes.

Keywords: Depressive disorder; nutraceuticals; amino acids; omega-3 fatty acids; B-vitamins; S-adenosylmethionine; pharmacotherapies; adjuvant therapies.

ABBREVIATIONS

MDD: Major depressive disorder; 5HT: 5-hydroxytryptophan; NE: Norepinephrine; DA: Dopamine; GABA: γ-aminobutyricacid; PFC: Prefrontal cortex; NAcc: Nucleus accumbens; VTA: Ventral tegmental area; MAOIs: Monoamine-oxidase inhibitors; SSRIs: Selective serotonin reuptake inhibitors; SARIs: Serotonin antagonists / reuptake inhibitors; TCAs: Tricyclic antidepressants; HAM-D: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory; AA: Arachidonic acid; PUFAs: Polyunsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoicacid; PPARs: Peroxisomal proliferator-activated receptors; SAMe: S-adenosylmethionine; ATP: Adenosine triphosphate; DNA: Deoxyribonucleic acid; SAH: S-adenosylhomocysteine; CSF: Cerebral spinal fluid; SNRI: Serotonin-norepinephrine reuptake inhibitor.

1. INTRODUCTION

Worldwide, more than 350 million people suffer from depressive disorders and many more do have mental problems [1]. The most common disorder within the depressive spectrum of mental disorders is major depressive disorder (MDD) [2]. MDD is characterized by decreased mood, increased sadness and anxiety, changes in weight or sleep patterns, lack of ability to concentrate, fatigue, feelings of worthlessness or guilt, loss of interest in favorable activities (anhedonia), and suicidal thoughts. The DSM-V stipulates that at least five of these depressive symptoms must be present, including either increased sadness or anhedonia, for a period of at least two weeks to diagnose a major depressive episode [3]. As depressive patients have long-lasting disturbances in psychosocial functioning and wellbeing [4,5], MDD has an enormous impact on quality of life.

Currently it is known that MDD can partly be explained by biochemical disturbances, e.g. deficiencies in serotonin; 5-hydroxytryptophan (5HT), norepinephrine (NE), dopamine (DA), and γ-aminobutyric acid (GABA), which are all important neurotransmitters in the human brain. This notion has been covered by the monoamine hypothesis, which postulates that depression is associated with a decreased monoamine function at key sites in the brain, such as the prefrontal cortex (PFC), hypothalamus, hippocampus, nucleus accumbens (NAcc), ventral tegmental area (VTA), and amygdala [6,7,8]. Nevertheless, it has been shown that the cause of depression is not just merely a deficiency of central monoamines in the brain. The intake of antidepressant agents such as monoamine-oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin antagonists / reuptake inhibitors (SARIs) immediately leads to an increase in monoamine transmission, while positive effects on mood are observed only after weeks of treatment [9]. In order to elucidate this discrepancy between the time of intake and the therapeutic effect of antidepressants, the up- and down-regulation of monoamine receptors (5-HT and NE) was investigated. It was shown that desensitization of the β-adrenoceptor, a NE receptor, was induced by tricyclic antidepressants (TCAs) [10]. Furthermore, Blier and De Montigny [11] have proposed that the use of SSRIs leads to desensitization of 5-HT receptors and an increased firing rate of serotonergic neurons originating in the raphe nuclei. These results may confirm the therapeutic effects of antidepressants on the neural correlates of MDD. However, these findings were only seen in SSRI-like antidepressants and the time required for sensitivity changes of the receptors is still shorter than the onset time of therapeutic effect [12].

Nowadays it is been thought that the 'hypothesis of neuroplasticity', which encompasses post-receptor intracellular cascades, gene expression

mechanisms (including epigenetic modifications), synaptic mechanisms, neurotrophic mechanisms, and neurogenesis, may explain depression, but exact mechanisms still need to be revealed [12]. The diversity of the etiology of depression together with the complexity and plasticity of the central nervous system makes it difficult to develop effective pharmacological treatments [13]. Despite the widespread availability of pharmacological and psychological interventions for depressive disorders, up to a quarter of the patients show little or no response even with appropriate treatment, and also a chronic course of illness is very common. Other obstructions to patient compliance and full recovery in depressive disorders can be the side effects of medications, the time and accessibility in accordance to accomplish psychotherapy, and additional cost factors of the therapies (e.g. increased health care utilization and hospitalization), factors that all can result in therapy discontinuation [14,15]. In light of these limitations, nutraceuticals, which are concentrated forms of naturally occurring substances such as vitamins and minerals, may be useful as mono- or adjuvant therapies to pharmacotherapies in people suffering from MDD [15].

The main question of this review is whether nutraceuticals (i.e. any substance which is considered (a part of) a food, a vitamin, or a mineral (e.g. amino-acids that are precursors to neurotransmitters or omega-3 fatty acids)), in combination with the current pharmacotherapies or even as mono-therapies, could be effective in depressive patients [16].

2. METHODS

A literature search was conducted on PubMed database for articles using the terms: ‘major depressive disorder’, ‘tricyclic antidepressants’, and ‘SSRIs’ combined with ‘nutraceuticals’, ‘pharmacotherapies’, ‘adjuvant therapies’, ‘amino acids’, ‘biochemical disturbances’, ‘(precursors of) neurotransmitters’, ‘tryptophan’, ‘tyrosine’, ‘phenylalanine’, ‘omega-3 fatty acids’, ‘omega-6 fatty acids’, ‘S-adenosylmethionine’, ‘B-vitamins’, ‘folate’, ‘methyl folate’, or ‘vitamin B12’.

Search results were manually reviewed, and relevant reviews and studies were selected for inclusion as suitable.

3. USEFUL PRECURSORS OF NEUROTRANSMITTERS IN DEPRESSIVE DISORDER

To build the neurotransmitters 5-HT, NE, and DA, the essential amino acids tryptophan, phenylalanine, and tyrosine need to be converted. The catechol amines NE and DA are synthesized in the same cascade; after DA transformation DA can be converted into NE by DA beta-hydroxylase [17]. The rate of synthesis of these neurotransmitters by the human brain depends on the availability of the different dietary precursors [18]. The human body itself cannot synthesize the precursors tryptophan and phenylalanine, so they must be ingested to transform it into 5-HT or NE and DA, respectively. After ingestion, phenylalanine needs to be converted into tyrosine by phenylalanine hydroxylase, before it can be converted into NE and DA. Tyrosine itself is not an essential amino acid, as the body is able to form tyrosine from phenylalanine [19]. Increasing these precursors within the diet of depressive patients may lead to a boost in neurotransmitter availability and release, which in turn may result in changes in brain functioning and as a consequence antidepressant benefits.

3.1 Tryptophan as Mono- or Adjuvant Treatment in Depressive Disorder

A dietary tryptophan intake of 4 mg/kg of adult body weight per day is recommended [20]. Examples of foods plentiful in tryptophan are soybeans, cheese, sesame seeds, sunflower seeds, eggs, poultry, fish, pork, red meat, oats, chickpeas, bananas, peanuts, milk, and yogurt. In our Western society, an average diet contains around 0.5 g of tryptophan daily. From this amount only 2-3% is used for serotonin production in the CNS [21]. The entry of tryptophan to the brain is regulated by a carrier mechanism that also transports other large neutral amino acids,such as tyrosine, phenylalanine, leucine, isoleucine, and valine. A higher amount of dietary tryptophan increases the proportion of tryptophan transported across the blood-brain barrier, whereas higher amounts of the other large neutral amino acids transported by the same carrier compete with both bound and free tryptophan, thereby reducing the transport of tryptophan [18,19]. Since a normal diet includes all kinds of large neutral amino acids, competition will be induced and thus a more equal transportation of these amino acids

across the blood-brain barrier can be expected. As a consequence, the ingestion of extra dietary tryptophan can be assumed not to lead to increased tryptophan levels in the human brain.

However, studies in rats have shown that ingestion of a *specific* meal can alter the blood levels of large neutral amino acids, such as tryptophan, which in turn influences the brain's level of tryptophan, and thereby serotonin levels. Specifically, a carbohydrate meal has been found to increase the levels of tryptophan and serotonin, whereas a protein-containing meal does not modify tryptophan or serotonin brain levels [18,19]. Ingestion of a carbohydrate meal stimulates insulin secretion, which decreases blood levels of the aromatic and branched-chain amino acids, but not those of tryptophan. As a consequence, tryptophan has a competitive advantage to bind to the carrier that transports it into the brain. Ingestion of a protein meal also stimulates insulin production, but at the same time it provides more amino acids in the body. This results in increased blood levels of tryptophan as well as the other large neutral amino acids, abolishing the competitive advantage for tryptophan uptake into the brain [18,19]. Therefore, a combination of a carbohydrate- and tryptophan-rich diet may yet increase brain serotonin levels in depressive patients, which might relieve their symptoms.

Over the years, the efficacy of tryptophan as mono- or adjuvant therapy in depressive disorder has been frequently studied [21,22]. For instance, Thomson and colleagues [23] conducted a double blind placebo-controlled study comparing antidepressant effects of tryptophan, the TCA amitriptyline, the combination of tryptophan and amitriptyline, and a placebo. In total, 115 depressive patients participated in this 12-week trial. All three active treatments were more effective than placebo (greater decline in Hamilton Depression Rating Scale (HAM-D) scores), with no significant differences of efficacy between these active treatments. In a more recent double blind placebo-controlled trial the effectiveness of the SSRI fluoxetine in combination with tryptophan as augmentation in 30 patients with MDD was studied [24]. All patients received 20 mg fluoxetine per day combined with either tryptophan (2 to 4 g/day) or a placebo during an 8-week trial. They found a more rapid antidepressant effect (faster decrease in both the HAM-D score and Beck Depression Inventory (BDI) score) as well as a protective effect on slow-wave-sleep of using fluoxetine in combination with tryptophan, compared to the placebo-group [24]. This indicates that administration of adjuvant tryptophan can be beneficial in the early phase of treatment of depression. Overall, these studies suggest that tryptophan may have at least limited effectiveness in the treatment of depressive disorder, since replications of positive findings have been shown [22]. However, due to several methodological flaws (e.g. small sample sizes, uncontrolled trials) in the included studies, inconclusive efficacy of tryptophan has been reported [15,21,22]. Moreover, the administration of tryptophan may have several side effects including drowsiness, dry mouth, nausea, and gastrointestinal symptoms, which need to be taken into account [15,21,22]. This preliminary support for tryptophan as mono- and adjuvant therapy in depressive disorder needs to be confirmed with subsequent large randomized controlled studies.

3.2 Tyrosine and Phenylalanine as Mono- or Adjuvant Treatment in Depressive Disorder

It is known that dietary supplements containing tyrosine and the essential amino acid phenylalanine can induce alertness and arousal [25]. Tyrosine and phenylalanine can be ingested through a normal diet. According to the World Health Organization [20], a dietary intake of tyrosine a well as phenylalanine of 25 mg/kg of adult body weight per day is recommended. Foods rich in tyrosine are soy products, cheese, sesame seeds, pumpkin seeds, poultry, fish, avocados, bananas, peanuts, almonds, milk, and yogurt. Phenylalanine is mainly found in protein-rich foods, like fish, red meat, poultry, gelatin, cheese, milk, eggs, walnuts, almonds, chickpeas, and soy products. After ingestion of phenylalanine, it is converted into tyrosine. The converted tyrosine and the directly ingested tyrosine are converted into dopamine, which is packaged in neuronal vesicles. The dopamine in these vesicles is then released in the synaptic cleft when a presynaptic action potential takes place [19]. In noradrenergic neurons dopamine is beta-hydroxylated to norepinephrine. As with tryptophan, ingestion of a meal modifies the ratio in blood of tyrosine and phenylalanine to the sum of the other large neutral amino acids, competing with these amino acids for transport through the blood-brain-barrier by a carrier mechanism [19].

Although it is well known that deficiencies of the monoamines norepinephrine and dopamine are associated with depression, little research has been done to investigate whether also deficiencies of the precursors tyrosine and/or phenylalanine do play a role in depressive disorder. In the rat's brain, the rate-limiting enzyme to convert tyrosine to dopamine and norepinephrine, tyrosine hydroxylase, is saturated with tyrosine for about 75%. This indicates that there is less scope to increase dopamine and norepinephrine synthesis with precursor loading as with serotonin [26]. However, if the firing rate of dopaminergic and noradrenergic neurons is increased, the precursor tyrosine can increase the activity of tyrosine hydroxylase and in turn DA and NE syntheses, which might be useful in treating depressive disorder [26]. Ruhé and colleagues [17] performed a meta-analysis to investigate the effect of acute depletion of phenylalanine and/or tyrosine on mood. In healthy controls, no decrease in mood was found after depletion. However, in vulnerable depressive patients who are in remission while still using antidepressants, mood decreased after phenylalanine and/or tyrosine depletion. In addition, the mood of healthy controls with a family history of depression was negatively affected by depletion of these precursors [17].

In the 1980s, two case studies indicated that tyrosine may have a potential as an antidepressant, but sample sizes were very small [27,28]. In 1990 Gelenberg and colleagues [29] compared the effectiveness of tyrosine (100 mg/kg/day), imipramine (2.5 mg/kg/day), and a placebo in 65 depressive patients (HAM-D score ≥ 20) during a 4-week trial. The depression alleviating effects of tyrosine did not differ significantly from those of placebo in HAM-D score declines, while imipramine showed a trend towards superiority. Thus, no evidence for the use of tyrosine as an antidepressant was found.

Also studies on the effectiveness of phenylalanine in depressive patients are scarce and show mixed results. Beckmann and colleagues [30] performed a double-blind controlled study in which phenylalanine (150-200 mg/day) or imipramine (150-200 mg/day) was administered to 40 depressive patients during 30 days. Both groups showed a significant decline in HAM-D scores as well as in a self-rating depression questionnaire with no significant differences in decline between the two groups. This result suggests that phenylalanine could be at least as effective as imipramine in treating depressive disorder. In another study, phenylalanine (mean 350 mg/day) was administered to 11 depressive patients (HAM-D score ≥ 18) for four weeks, in which no significant decline in HAM-D score, thus no effect of treatment was found [31]. However, in a subsequent study phenylalanine was administered at higher doses (up to 14 g/day) in which 31 of 40 depressive patients responded to the therapy [32]. These studies suggest that high doses of phenylalanine may be as effective for depressive patients as the TCA imipramine [30,32,33].

4. OTHER USEFUL NUTRITIONAL SUPPLEMENTS IN DEPRESSIVE DISORDER

4.1 Omega-3 Polyunsaturated Fatty Acids

In the human body, one of the highest levels of lipids can be found in the brain. These brain lipids are composed of fatty acids, which are structural components of cell membranes. The grey matter of the brain contains around 50% fatty acids that are polyunsaturated in nature, which means that these fatty acids need to be supplied through the diet [25]. Unsaturated fatty acids have one or more double bonds between carbon atoms; when the double bonds are in position 6, they are called omega-6 fatty acids, while those with a double bond in position 3 are called omega-3 fatty acids [34]. In the Western diet, omega-6 fatty acids and their precursors (e.g. linoleic acid), that are mainly found in vegetable oils (e.g. sunflower oil, corn oil), are much more abundant than omega-3 fatty acids and their precursors (e.g. alpha-linoleic acid). The omega-6 fatty acid arachidonic acid (AA), which is found in cell membranes, serves as a precursor of inflammatory eicosanoids (e.g. prostaglandins and thromboxanes). As a high omega-6 to omega-3 fatty acids ratio can alter biochemical and biophysical cell membrane properties and also may increase neuro-inflammation [34], it has been hypothesized that a lack of omega-3 fatty acids in the diet (e.g. in fish and nuts) may lead to depressive disorder.

Since the consumption of omega-3 fatty acids from fish, nuts and other sources has declined in most populations worldwide, the incidence of depressive disorder has increased [35]. The two omega-3 polyunsaturated fatty acids (PUFAs) found in fish oil, highly purified estyl esters of

eicosapentaenoic acid (EPA) that the human body converts into docosahexanoic acid (DHA), have been shown to induce antidepressant effects in humans [2]. For example, Su and colleagues [36] conducted a double-blind placebo-controlled trial comparing the omega-3 PUFAs DHA (220 mg/capsule) and EPA (440 mg/capsule) with placebo as augmentation therapy in 28 depressive patients (HAM-D score ≥ 18). In total, the patients received 5 capsules with combined PUFAs or placebo twice daily, resulting in 9.6 g per day. They found that the reduction rate of the HAM-D score was significantly larger in the omega-3 PUFAs group compared to placebo at week 4 and week 8, suggesting that EPA and DHA improve depressive symptoms. These neuropsychiatric treatment effects of EPA and DHA may result from modulation of neural communication and their impact on mono-aminergic neurotransmitters, like serotonin and dopamine [15]. Increased omega-3 PUFAs concentrations in the diet may also alter the CNS cell membrane fluidity and phospholipid composition, which in turn can alter the structure and function of other proteins [34]. For instance, it has been suggested that EPA as well as DHA influence neuronal signal transduction by triggering peroxisomal proliferator-activated receptors (PPARs), while at the same time inhibiting G-coupled proteins, protein kinase C, and calcium, sodium, and potassium ion channels [2]. Case-control studies have shown that depressive patients do have a higher AA to EPA ratio in cell membrane cholesteryl esters and serum phospholipids, and a significantly increased omega-6 to omega-3 ratio as well as decreased omega-3 levels in erythrocyte membranes, as compared to non-depressed controls [37,38].

Clinical trials and epidemiological data have shown that EPA and DHA can effectively improve depressive symptoms [35,39,40]. Also the efficacy of omega-3 PUFAs as mono- or adjuvant therapy in depressive patients has been reviewed in several meta-analyses [34,40-42]. The results of these studies on mono- as well as augmentation therapies are inconclusive, with significant heterogeneity between the different studies and evidence for publication bias [15]. Next to depressive disorder, most of these meta-analyses included studies that investigated depressed mood as a symptom in patients with other psychiatric disorders, such as bipolar disorder, schizophrenia, personality disorders, obsessive-compulsive disorder, anxiety disorders or chronic fatigue syndrome, which further increases heterogeneity between studies. Nevertheless, Kraguljac and colleagues [41] concluded that omega-3 PUFAs could be used as a potential treatment of depressive disorder. Furthermore, Appleton and colleagues [42] performed, in addition to a meta-analysis with various psychiatric disorders, a meta-analysis with trials in depressive patients only. In this additional study a beneficial effect of omega-3 PUFAs supplementation on depressed mood was found, although heterogeneity of the populations studied and interventions used in the different trials remained. This heterogeneity questions the reliability and validity of the findings and suggests a need for considerable caution of decisive conclusions. In contrast, a meta-analysis in depressive patients by Bloch and Hannestad [34] did not indicate a significant benefit of omega-3 PUFAs. Despite the inconclusive results of omega-3 PUFAs benefits in major depressive disorder, all meta-analyses showed that omega-3 PUFAs are well tolerated and only have mild side effects, such as diarrhea, nausea, and a fishy aftertaste, resulting in less treatment discontinuation [15]. Further research in more homogeneous and larger samples is needed to establish the effects of omega-3 supplementation [42].

4.2 S-adenosylmethionine (SAMe)

S-adenosylmethionine (SAMe) is a naturally occurring substance produced in mammals from the essential amino acid methionine and adenosine triphosphate (ATP). To produce methionine, a methyl group from folate (vitamin B9) is transferred to the amino acid homocysteine (which cannot be obtained from the diet) supported by vitamin B12, which uses the methyl group from folate and adds it to homocysteine. Thus, folate and vitamin B12 are both essential nutritional compounds for the production of methionine, and in turn SAMe [15,43]. SAMe is a methyl donor for molecules such as deoxyribonucleic acid (DNA), phospholipids, proteins, and is also involved in membrane fluidity, receptor, and neurotransmitter function. After methyl donation, SAMe is converted to S-adenosylhomocysteine (SAH) and then back to homocysteine by SAH-hydrolase, which completes the methionine cycle [15,43,44]. One hypothesis for the role of SAMe in MDD is that SAMe may induce antidepressant effects via DNA methylation by influencing DNA transcription. Additionally, the synthesis of neurotransmitter monoamines requires methylation reactions which are dependent on

SAMe, so an increase of SAMe may result in increased synthesis of neurotransmitters [45]. According to the World Health Organization [20], a healthy adult requires 10.4 mg methionine per kg body weight daily. Methionine can be found in sesame seeds, Brazil nuts, and high-protein animal based foods like seafood (especially yellowtail fish which contains 2.5 mg methionine), dairy products such as milk and cheese, eggs, pork, beef, and cereal grains. Methionine is the only essential amino acid containing sulfur (an essential component of all living cells), and therefore the precursor of the other amino acids containing sulfur (cysteine, taurine, homocysteine and cystathionine). It has been found that dietary methionine is essential for DNA methylation; reduced DNA methylation can cause genetic instability, aberrant gene expression, and increased risk for cancer [46].

To our knowledge, no research has been done concerning the efficacy of methionine as mono- or adjuvant therapy in depressive disorders. However, the efficacy of SAMe as mono-therapy in depressive patients is well supported in several reviews and meta-analyses [45,47,48]. Placebo-controlled studies have found parentally administered (either intravenously or intramuscularly) SAMe to be more efficacious than placebo and equal in efficacy to TCAs for treating depressive disorders [45]. For example, Delle Chiaie and colleagues [49] compared intramuscularly SAMe administration (400 mg/day) with administration of the TCA imipramine (150 mg/day) in two groups of depressive patients (n = 147 SAMe vs. n = 148 imipramine; HAM-D score ≥ 18) during a 4-week trial. Responders to the treatment were defined as those showing a decrease in HAM-D score of≥ 50%. After 4 weeks, no significant differences were found between the two groups in proportion of responders (SAMe group 58.9% vs. imipramine group 50.3%). Furthermore, both treatments were equal in safety, and adverse events were reported more frequently among patients using imipramine than SAMe [49]. Unfortunately, the route of administration considerably limits the clinical usefulness of these findings [45]. Oral SAMe is a highly labile compound, and may be too labile and too polar to survive absorption without losing its methyl group. Nevertheless, oral SAMe administration is associated with increased cerebral spinal fluid (CSF) SAMe levels, indicating that it crosses the blood-brain-barrier in humans [43]. In contrast to parentally administered SAMe, less evidence has been found for the efficacy of oral SAMe, although some studies do support oral SAMe to be more efficacious than placebo and equal in efficacy to TCAs as well [45,49,50]. For example, De Vanna and Rigamonti [50] performed a double-blind trial to investigate the efficacy and tolerance of oral SAMe in 30 MDD patients (HAM-D score ≥ 18). 15 patients received oral SAMe (1600 mg daily), while the other 15 patients received the TCA imipramine (140 mg daily) for 6 weeks. No significant differences were found between the two groups in depressive improvement, although the onset of action in the SAMe group was more rapid during the trial. These results indicate that oral SAMe is at least as effective and tolerable as imipramine in treating depressive disorders [50].

Despite the large amount of research on SAMe as mono-therapy, only two studies have investigated the effects of SAMe as adjuvant therapy in depressive disorder. Alpert and colleagues [51] evaluated the safety, tolerability, and efficacy of SAMe as an adjunct to different SSRIs or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine in 30 partial- or non-responsive depressive patients (HAM-D score ≥ 14). These patients received 800 to 1600 mg SAMe tosylate daily during a 6-week trial. Response to SAMe augmentation treatment was defined as a 50% reduction in HAM-D score from baseline to week 6. Remission was defined as a final HAM-D score of ≤7. Augmentation with SAMe resulted in a response rate of 50% and a remission rate of 43%. However, mild side effects such as gastrointestinal symptoms and headaches were reported, and a placebo control group was lacking. In a second placebo-controlled study, 73 non-responsive depressive patients using SSRIs or SNRIs received oral SAMe (800 mg/twice daily) as augmentation therapy during a 6-week trial. The HAM-D response and remission rates were higher in depressive patients using adjunctive SAMe (36.1% and 25.8%, respectively) compared to the placebo group (17.6% and 11.6%, respectively). No significant differences between the SAMe and placebo group were found in the proportion discontinuation, side-effects, or inefficacy [52]. These studies indicate that augmentation with SAMe may be an effective, well tolerated, and safe antidepressant therapy for SSRI or SNRI non-responsive depressive patients.

Altogether, placebo-controlled studies have found parentally administered (either intravenously or intramuscularly) SAMe, and to a

lesser extent oral SAMe, to be more efficacious than placebo and equal in efficacy and tolerability to TCAs for treating depressive disorders. Also adjuvant SAMe appears to be an effective, well tolerated, and safe antidepressant. Future research on SAMe as mono-therapy should also take into account other antidepressants than TCAs, such as SSRIs and SNRIs, to optimize treatment effects. As far as we know, the efficacy of the essential amino acid methionine as mono- or adjuvant therapy in depressive disorder is not yet investigated. However, since methionine is the precursor of SAMe, which is a suitable candidate in treating depression, research on the efficacy of methionine supplementation and tracking methionine levels in depressive disorder is warranted.

4.3 The B Vitamins: Folate and Vitamin B12

All B vitamins are water-soluble and are mainly present in foods. These vitamins are necessary for the growth, division and metabolism of cells, as well as for immune and nervous system functioning. As mentioned in the previous section, vitamin B12 and folate (vitamin B9) are major determinants of one-carbon metabolism in the methionine cycle, to form SAMe. Increased plasma homocysteine is a biological marker of folate and vitamin B12 deficiency, and this increased plasma homocysteine, as well as decreased levels of vitamin B12 and folate have been found in depressive patients [53,54]. Folate deficiency leads to decreased SAMe levels together with increased homocysteine levels, causing decreased methylation function, which may impair neurotransmitter synthesis, and thus may increase depressive symptoms [55]. In addition, Papakostas and colleagues [56] have found that depressive patients with low folate levels (≤ 2.5 ng/ml) using the SSRI fluoxetine, are more likely to experience a delayed onset of clinical improvement than patients with normal folate levels, although this delay was not seen with respect to vitamin B12 and homocysteine levels [56]. Also Kamphuis and colleagues [57] did not find a relationship between a low dietary intake of the B vitamins, increased homocysteine levels, and depressive symptoms, although this study was performed in elderly men only.

Folate is implicated in the synthesis of dopamine, norepinephrine, and serotonin [58]. It naturally occurs in a wide range of foods, such as vegetables (mainly avocado, spinach, asparagus, and Brussels sprouts), fruits, beans, peas, dairy products, poultry, meat (liver), eggs, seafood, grains, and yeast [59]. For adults, a dietary intake of 400 μg folate daily is recommended. Several studies investigated the efficacy of folate in depressive disorder. Godfrey and colleagues [60] performed a double-blind placebo-controlled study to establish the efficacy of methylfolate (15 mg daily; a biologically active form of folate that can cross the blood-brain-barrier directly) as augmentation therapy in 24 depressive patients using their standard medications, TCAs or MAOIs during a 6-month trial. These patients had a red-cell folate level below 200 μg/l and no vitamin B12 deficiency. They found that methylfolate augmentation was superior to placebo in improving depressive symptoms measured by the HAM-D and the BDI, although sample size was small and data of tolerability were not reported [60]. Subsequently, Coppen and Bailey [61] studied whether folate administration would enhance the antidepressant effects of the SSRI fluoxetine in men and women with depressive disorder (baseline HAM-D score ≥ 20). A total of 127 severely depressed patients received either 500 μg folic acid (a synthetic form of folate) or an identical placebo in addition to 20 mg fluoxetine daily. After 10 weeks of administration, the patients who received folic acid showed a significant increase in plasma folate; this increase was more abundant in women than men. Furthermore, plasma homocysteine was significantly decreased in women (20.6%), but not in men. In women who received fluoxetine and folic acid, the mean Ham-D score was 6.8 (SD 4.1); women who received fluoxetine and a placebo had a mean HAM-D score of 11.7 (SD 6.7); in men the score differences between the folic acid (mean 14.2; SD 5.0) and placebo (mean 14.0; SD 5.5) group were not significant. Folic acid in combination with fluoxetine was also better tolerated than a placebo in combination with fluoxetine [61]. From these findings it was concluded that depressive patients with low as well as normal folate levels may benefit from augmenting their primary antidepressant medication with folate [55]. In addition, it was concluded that the use of folate as mono-therapy might be effective in the treatment of depressive disorder [62]. More recently, a retrospective analysis of 242 depressive patients evaluated the efficacy of methyl folate (7.5 mg or 15 mg) in combination with SSRI or SNRI compared to SSRI or SNRI mono-therapy. The use of methyl folate together with SSRI/SNRI antidepressants was found to be associated with significantly better treatment response, faster improvement onset and less

discontinuation of the treatment due to side effects than SSRI/SNRI mono-therapy [63].

Altogether, these studies suggest that several folate forms appear to be well tolerated and efficacious for some depressive patients, as mono-therapy as well as adjuvant therapy. Furthermore, there are no known drug interactions or contra-indications to the use of methyl folate [58]. Nevertheless, high folate doses (>800 μg) may lead to increased un-metabolized serum folic acid levels, which can decrease levels of natural killer cells and methylfolate in the brain, as well as deplete monoamines, which in turn may worsen depression [15,58,62]. In addition, high folic acid doses (e.g. 15 mg) have been associated with more severe depression [15].

With respect to the B vitamins that are necessary in the methionine cycle (to form SAMe), research on vitamin B12 as mono- or adjuvant therapy in depressive disorder is much less abundant. For adults, a dietary intake of 6 μg vitamin B12 daily is recommended. Vitamin B12 can be found in animal-derived foods, such as fish, meat (especially liver), poultry, dairy, and eggs. Results of studies on the associations between vitamin B12 levels and treatment outcome in depressive disorder are mixed. Hintikka and colleagues [64] performed a 6-months follow-up study to investigate the associations between vitamin B12 and treatment outcome in 115 patients with depressive disorder. Higher vitamin B12 levels were significantly associated with a decline in HAM-D scores after 6 months of treatment with antidepressants, suggesting that supplementation of vitamin B12 may improve antidepressant treatments. Kamphuis and colleagues [57] investigated in an elderly cohort of 332 men between 70 and 90 years whether low dietary vitamin B12 was associated with high levels of serum homocysteine and depressive symptoms measured with the Zung Self-rating Depression Scale. No correlations between depression scores and vitamin B12 intake were found, which could be due to malabsorption of vitamin B12 in elderly people [57]. To our knowledge, no research has been done yet to investigate the efficacy of vitamin B12 administration as mono-therapy in depressive disorders, and only one study investigated vitamin B12 as augmentation therapy to SSRIs or TCAs. In this study, 73 depressive patients (HAM-D score ≥ 16) with a low normal vitamin B12 level (between 190 pg/ml and 300 pg/ml) were randomized to the group receiving SSRI/TCA in combination with vitamin B12 injections of 1000 μg weekly during 6 weeks, or to the control group receiving SSRI/TCA medication only. After three months of follow-up, 44% of the vitamin B12 group showed a reduction in HAM-D score of 50% or higher, compared to 5% in the control group, indicating that supplementation of vitamin B12 to antidepressants could be beneficial for patients with depressive disorder [65]. However, sham injections were not given to the control group, so the treatment improvement of vitamin B12 injections may be due to a placebo effect. In addition, only depressive patients with low normal levels of vitamin B12 were taken into account, while most depressive patients show a vitamin B12 deficiency [53,54]. Further studies on vitamin B12 supplementation are required to replicate and extent these findings.

5. DISCUSSION

Depressive disorder is a worldwide common mental illness with very serious health implications as well as burdens of costs for both the patient and society. Current treatments have been shown to have benefits but do not achieve complete remission of the disease in one-third of the cases and also show limited tolerability and accompanying side effects [2]. Therefore, the present review aimed to figure out whether nutraceuticals in combination with the current pharmacotherapies or even as mono-therapies, could be beneficial for depressive patients [16].

Review of the literature revealed that encouraging evidence may exist for the use of several nutraceuticals in relieving depressive symptoms (see Table 1). In addition, it has been suggested that the administration of adjuvant tryptophan is an effective early phase treatment of depression [24]. Overall, these studies suggest that tryptophan may have at least limited effectiveness in the treatment of depressive disorder, since replications of positive findings have been shown [22]. However, due to several methodological flaws (e.g. small sample sizes, uncontrolled trials) in the included studies, inconclusive efficacy of tryptophan has been reported, and also side effects should be taken into account [15,22]. In contrast to tryptophan, no evidence for the use of tyrosine as an antidepressant was found, and only one study reported that high doses of phenylalanine may be as effective as imipramine [33].

Table 1. Study outcomes of nutritional supplements as mono- or adjuvant therapy to pharmacotherapies in depressive disorder

Nutritional supplement	N	Duration of treatment	Dose of supplement	Antidepressant	Study with positive or negative* outcomes
Tryptophan					
Mono-therapy	115	12 weeks	unknown	Comparison with TCA amitriptyline	Thomson et al. [23]
Adjuvant therapy	115	12 weeks	unknown	Adjuvant to TCA amitriptyline	Thomson et al. [23]
	30	8 weeks	2-4 g/day	Adjuvant to SSRI fluoxetine	Levitan et al. [24]
Tyrosine					
Mono-therapy	65	4 weeks	100 mg/kg/day	Comparison with TCA imipramine	*Gelenberg et al. [29]
Phenylalanine					
Mono-therapy	40	30 days	150-200 mg/day	Comparison with TCA imipramine	Beckmann et al. [30]
	40	unknown	up to 14 g/day	Comparison with TCA imipramine	Sabelli et al. [32]
	11	4 weeks	mean 350 mg/day	Comparison with placebo only	*Mann et al. [31]
Omega-3 PUFAs					
Adjuvant therapy	28	8 weeks	9.6 g/day	Adjuvant to current antidepressant of the patients	Su et al. [36]
S-adenosylmethionine (SAMe)					
Mono-therapy	30	6 weeks	1600 mg/day	Comparison with TCA imipramine	De Vanna and Rigamonti, [50]
	295	4 weeks	400 mg/day	Comparison with TCA imipramine	DelleChiaie et al. [49]
Adjuvant therapy	30	6 weeks	800-1600 mg/day	Adjuvant to SSRIs and SNRI venlafaxine	Alpert et al. [51]
	73	6 weeks	1600 mg/day	Adjuvant to SSRIs and SNRIs	Papakostas et al. [52]
Folate					
Adjuvant therapy	24	6 months	15 mg/day methylfolate	Adjuvant to TCAs and MAOIs	Godfrey et al. [60]
	127	10 weeks	500 μg/day folic acid	Adjuvant to SSRI fluoxetine	Coppen and Bailey, [61]
	242	Minimum of 60 days	7.5-15 mg/day methylfolate	Adjuvant to SSRIs and SNRIs	Ginsberg et al. [63]
Vitamin B12					
Adjuvant therapy	73	6 weeks	1000 μg/week	Adjuvant to SSRIs and TCAs	Syed et al. [65]

Abbreviations: TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; MAOI = monoamine oxidase inhibitor

Next to precursors of neurotransmitters, also other nutritional supplements were reviewed. A high omega-6 to omega-3 fatty acids ratio was shown to alter biochemical and biophysical cell membrane properties and increase neuro-inflammation [34]. The possible neuropsychiatric treatment effects of the omega-3 PUFAs EPA and DHA may result from modulation of neural communication and their impact on mono-aminergic neurotransmitters like serotonin and

dopamine [15]. Increased omega-3 PUFAs concentrations in the diet may also alter the CNS cell membrane fluidity and phospholipid composition, which in turn can alter the structure and function of other proteins [34]. Despite inconclusive findings of omega-3 PUFAs benefits in depressive disorder, meta-analyses showed that omega-3 PUFAs are well tolerated and do have mild side effects, resulting in less treatment discontinuation [15]. Furthermore, placebo-controlled studies have found parentally administered (either intravenously or intramuscularly) SAMe, and to a lesser extent oral SAMe, to be more efficacious than placebo and equal in efficacy and tolerability to TCAs for treating depressive disorders. Moreover, adjuvant SAMe appears to be an effective, well tolerated, and safe antidepressant. Also several folate forms appear to be well tolerated and efficacious for some depressive patients, as mono-therapy as well as adjuvant therapy. Furthermore, there are no known drug interactions or contraindications to the use of methylfolate, although cautiousness is warranted with high doses of folate [57]. Finally, vitamin B12 as augmentation therapy to SSRIs or TCAs might be an effective treatment for depressive disorder [65].

6. CONCLUSION

In conclusion, some positive evidence is found that the nutraceuticals tryptophan, omega-3 fatty acids, SAMe, and folate as mono- or adjuvant therapy in depressive disorder enhance response and increase efficacy. However, most of the cited studies have a small sample size, a short duration and a poor design. Therefore, conclusions must be drawn with caution and long-term, adequately powered studies with rigorous methodologies and larger sample sizes are indicated. Moreover, the studies included in this review were only directed at isolated administration of nutraceuticals via concentrated pills or injections, and did not take specific nutraceutical-rich diets into account. Research on specific nutraceutical-rich diets is very sparse, since individual differences can be found in the tolerated and efficacious dose of these diets. Secondly, the doses needed for efficacious treatment outcomes in depressive disorder may be far too high to incorporate in a natural diet. In addition, controlling the diet of human beings is almost impossible. In the meantime, depressive patients should be encouraged to follow guidelines for a healthy diet composed of rich sources of vitamins and essential amino acids. Nevertheless, accurate medical diagnoses and consideration of all possible treatments should always be the first step in addressing depressive disorder. Therapy with nutraceuticals should be supervised and doses be adjusted for each patient individually to achieve optimal outcomes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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