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Nutritional Interventions in Clinical Depression

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Abstract

Depression is one of the leading causes of mental disability worldwide and a significant public health problem in the United States. Individuals with depression have lower quality of life, diminished role functioning, increased comorbidity, and increased mortality. Although psychotherapy and pharmacotherapy are well-validated treatment options for clinical depression, nutritional supplements may be another means of alleviating depressive symptoms while limiting adverse effects. Nutritional supplements can be utilized in tandem with preexisting therapeutic regimens, or as stand-alone therapies. Omega-3 fatty acids, B-vitamins (folate, vitamin B12, and vitamin B6), S-adenosylmethionine (SAMe), 5-hydroxytryptophan (5-HTP), and magnesium have been of interest in the treatment of depression for several decades. This article reviews the literature investigating these nutritional interventions for the treatment of clinical depression, with a particular focus on pathophysiology, epidemiology, and clinical research.

Keywords

depression, clinical trials, epidemiology, intervention, public health

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Psychiatric disorders are one of the most burdensome diseases as a result of their high prevalence, early age of onset, and frequent association with severe disability (Demyttenaere et al., 2013). Depression affects about 151 million people worldwide and is the most prevalent psychiatric disorder in young adults (World Health Organization [WHO], 2008). According to the WHO, major depression is one of the leading causes of disability worldwide (Bromet et al., 2011) and one of the most vital public health problems in the United States (Hasin, Goodwin, Stinson, & Grant, 2005). Among mental and physical disorders worldwide, the burden of depressive disorders was ranked third in 2004 (World Health Organization [WHO], 2012). The WHO predicts that major depression will be the number one cause of disability by 2030, ahead of cardiovascular disease, traffic accidents, chronic pulmonary disease, and HIV/AIDS (WHO, 2008).

Depression is a recurrent disorder linked to diminished role functioning (Kessler et al., 2003), poor quality of life (Bromet et al., 2011; Spijker et al., 2004), meaningful impairment (Hasin et al., 2005; Kupfer, Frank, & Phillips, 2012; Weissman, 1991), comorbidity (Kessler, 1996; Kessler et al., 2003; Regier, 1990), and mortality (Insel, 2003). Studies suggest that it is prevalent for the entire life span, diminishes health in line with other chronic diseases (such as angina, asthma, and diabetes), and substantially decreases mean health scores when comorbid with other diseases (Kupfer et al., 2012). Because depression causes low quality of life and is associated with poorer health outcomes in individuals with comorbid chronic disease, ameliorating depressive symptoms would likely improve health outcomes in individuals with chronic disease by both enhancing quality of life and increasing role functioning.

The incidence of depression has greatly increased and age of onset has decreased over the past century (Meyer & Quenzer, 2005). Although interventions such as psychotherapy and pharmacotherapy are successfully utilized in many cases, the clinical efficacy of current mainstream antidepressant therapies is not always satisfactory;

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medications may induce a variety of adverse effects, and many cases are only partially alleviated by standard therapy (Szewczyk et al., 2008). In fact, it is estimated that as many at 50% of cases of depression qualify as treatment resistant, causing increased comorbid physical and mental disorders, marked functional impairment, and higher medical and mental health care costs (Eby & Eby, 2010). As a result, alternative therapies are of interest. Specifically, assessment of nutrient intake and supplementation with nutrients has been studied as a preventive measure, as a stand-alone therapy, and as adjunctive therapy.

Depression is a complex and heterogeneous condition. As a result, psychotherapy and pharmacotherapy yield unpredictable results. Research demonstrates that neurobiology/physiology, genetics, life stressors, and environmental factors all contribute to vulnerability to depression (Kupfer et al., 2012). Although much of the available research focuses on genetics and environmental factors, a small body of research indicates that nutritional influences on depression are underestimated (Eby & Eby, 2010). Omega-3 fatty acids, vitamin B complex (vitamins B12, B6, and folate), S-adenoxylmethionine (SAMe), 5-hydroxytryptophan (5-HTP), and magnesium have all been studied at length over the past several decades with promising results. Although several other micronutrients have been studied in the treatment of depression, these five have been studied the most extensively. This article reviews each of these nutritional interventions, with a focus on the current neurobiological hypotheses, most relevant available research, and potential clinical efficacy. It is beyond the scope of this article to review all available research concerning each nutrient; rather it is intended to provide the reader with a broad understanding of the literature. All epidemiological and clinical research findings reviewed in this article are unique to depression, except in cases where alternative conditions or populations are specifically noted. In addition, all clinical trials that utilize nutritional supplements use mineral supplements, as opposed to food supplementation, unless otherwise noted.

Omega-3 Fatty Acids

Omega-3 fatty acids are long chain polyunsaturated fatty acids (PUFAs) that are found in both plant and marine life (Logan, 2003). They cannot be synthesized in the human body and therefore must be derived from dietary sources (Logan, 2004). Omega-3 fatty acids with marine origin are primarily composed of preformed eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and appear to be highly bioavailable (Parker et al., 2006). Omega-3 fatty acids with plant origin (primarily found in flaxseed, hemp, canola, and walnuts) are in the form of alpha-linolenic acid (ALA), the parent omega-3 fatty acid, and therefore require endogenous conversion in the liver to the longer chain EPA and DHA; this is an inefficient process that results in the conversion of 5% to 15% of ALA to EPA and DHA (Holub, 2002). The conversion of ALA to EPA and DHA is compromised by aging, illness, stress, and excessive amounts of omega-6 rich oils (primarily found in corn, safflower, sunflower, and cottonseed; Bourre, 2004).

Neurobiology

The brain consists of one of the highest concentration of fatty acids in the body (Sinclair, Begg, Mathai, & Weisinger, 2007). Nervous tissue is composed primarily of lipids, including glycerophospholipids, spingnolipids, gangliosides, and cholesterol; glycerophospholipids consist of PUFAs derived from DHA (omega-3) and archidonic acid (AA; omega-6; Sinclair et al., 2007). AA is an omega-6 PUFA that is derived from linoleic acid (LA), the parent omega-6 PUFA; AA competes with EPA and DHA both for cell membrane space and also for conversion to biologically potent eicosanoids, which are proinflammatory (Freeman et al., 2006). EPA metabolism leads to anti-inflammatory products, which mediate the proinflammatory products of AA metabolism (Simopoulos, 2002).

DHA is selectively concentrated in synaptic neuronal membranes and assists in the mediation of receptor activity and signal transduction (Salem, Litman, Kim, & Gawrisch, 2001). Animal studies indicate that reduced levels of dietary omega-3 fatty acids, primarily DHA, in the brain lead to modifications in neuron size, learning and memory, auditory and olfactory responses, altered nerve growth factor levels, and increases in depression and aggression (DeMar et al., 2006; Sinclair et al., 2007). The physiological changes that occur in the brain as a result of omega-3 deprivation are likely related to both changes in membrane function and changes in gene expression (Freeman et al., 2006; Sinclair et al., 2007).

DHA has been found to influence events in the cellular membranes in the following ways: alteration of plasma membrane phospholipid fatty acid composition, which determines the function of membrane receptors and binding to membrane proteins (Litman, Niu, Polozova, & Mitchell, 2001); regulation of dopaminergic and serotonergic neurotransmission (Zimmer et al., 2000); regulation of sodium-potassium dependent ATPase and regulation of glucose uptake (Bowen & Clandinin, 2002; Pifferi et al., 2005); regulation of signal transduction (McNamara et al., 2006); and increased cerebral blood flow (Tsukada, Kakiuchi, Fukumoto, Nishiyama, & Koga, 2000).

Omega-3 fatty acids are essential components of the central nervous system phospholipid membranes and significantly influence the structure and function of the cellular membranes (Surette, 2008). The proteins embedded in the cellular membranes act as transporters and

receptors for the cell; the structure and placement of these proteins are influenced by the lipid components of the membrane (Schmitz & Ecker, 2008). Therefore, effective neurotransmitter binding and signaling within the cell are influenced by the proper placement and proportion of essential fatty acids in the membrane (Parker et al., 2006). In addition, essential fatty acids can themselves behave as second messengers within and between neurons (Freeman et al., 2006). An abnormal fatty acid composition of cellular membranes therefore alters membrane microstructure and results in abnormal signal transduction; studies have shown that there are lower erythrocyte membrane omega-3 fatty acids and significant decreases in EPA and DHA levels in depressive disorders (Su, Huang, Chiu, & Shen, 2003).

Another important role of omega-3 fatty acids is in cytokine modulation (Logan, 2004). Cytokines, proinflammatory immune chemicals, consisting of interleukin-1 (-2 and -6) beta, interferon-gamma, and tumor necrosis factor alpha, influence the functioning of the central nervous system in the following ways: lowered neurotransmitter precursor availability, activation of the hypothalamic-pituitary axis, and alternation of the metabolism of neurotransmitters (A. H. Miller, Maletic, & Raison, 2009). Studies have shown that elevations of interleukin-1 beta and tumor necrosis factor alpha are associated with the severity of depression and with psychological stress (Suarez, Krishnan, & Lewis, 2003). EPA, and omega-3 fatty acids broadly, have effective anti-inflammatory properties and are potent inhibitors of the proinflammatory cytokines interleukin-1 beta and tumor necrosis factor alpha (Logan, 2004). Notably, some antidepressants, including tricyclic antidepressants and selective serotonin reuptake inhibitors, inhibit the release of inflammatory cytokines (Hashioka et al., 2007).

Laboratory studies have shown a relationship between omega-3 fatty acid status in red blood cells and in adipose tissue and the pathophysiology of depression. Several studies demonstrate that there is a decrease in omega-3 content in the blood of patients with clinical depression (Amin, Menon, Reid, Harris, & Spertus, 2008; Lin & Su, 2007; Sublette, Hibbeln, Galfalvy, Oquendo, & Mann, 2006). Decreased EPA content in red blood cells has been associated with the severity of depression (Martins, 2009). In addition, DHA stores in adipose tissue were negatively correlated with rates of depression; adults with depression had 34.6% less DHA stores in adipose tissue than their nondepressed counterparts (Mamalakis, Kiriakakis, Tsibinos, & Kafatos, 2004).

Epidemiology

Epidemiological studies provide support to the hypothesis that omega-3 fatty acids play a role in the pathophysiology of depression. Epidemiological studies indicate that countries with greater amounts of dietary consumption of omega-3 fatty acids have a significantly lower prevalence of clinical depression and a significantly higher self-reported mental health status (Logan, 2003; Silvers & Scott, 2002). A National Institutes of Health (NIH) study found that there is a significant negative correlation ($p < .01$) between worldwide fish consumption and the prevalence of depression (Hibbeln, 1998). Another study found that countries with frequent fish consumption have a decreased risk of depression (odds ratio = 0.63, 95% CI = 0.43–0.94, $p < .02$) and of suicidal ideation (odds ratio = 0.57, 95% CI = 0.35–0.95, $p = .03$; Tanskanen et al., 2001). In addition, studies have found that countries with higher total seafood consumption have corresponding lower prevalence of postpartum depression, bipolar disorder, and seasonal affective disorder (Cott & Hibbeln, 2001; Hibbeln, 2002; Noaghiul & Hibbeln, 2003).

Epidemiological studies that have examined the relationship between changes in diet and rates of depression have shown an association between the changes in the Western diet and the rates of depression. For example, as the Western diet changed from one of primarily fish, wild game, and plants to one of domestic animals with high levels of saturated fats and vegetable oils with high levels of omega-6 fatty acids, the rates of depression, seasonal affective disorder, and suicide rose simultaneously (McGrath-Hanna, Greene, Tavernier, & Bult-Ito, 2003). The ratio of omega-6 to omega-3 fatty acids in the Western diet has changed from 1:1 to more than 10:1 in the past century, leading to a higher proportion of AA rather than EPA and DHA in the cellular membranes, and a resulting high proportion of inflammatory eicosanoids and altered cellular membrane function (Blasbalg, Hibbeln, Ramsden, Majchrzak, & Rawlings, 2011; Holub, 2002).

Clinical trials

Treatment studies exploring the effect of omega-3 supplementation on individuals with clinical depression support the hypothesis that omega-3 fatty acids play a role in the pathophysiology of clinical depression. Numerous randomized controlled trials (RCTs) have demonstrated the effectiveness of omega-3 fatty acid supplementation in clinical depression (Jazayeri et al., 2008; Marangell et al., 2003; Nemets, Stahl, & Belmaker, 2002; Peet & Horrobin, 2002; Su et al., 2003). A double-blind, placebo-controlled trial found that supplementation with omega-3 fatty acids compared with placebo in clinically depressed patients already receiving standard antidepressant therapy (4.4 g EPA and 2.2 g DHA) significantly improved depressive symptoms based on the Hamilton Depression Rating Scale (Su et al., 2003). In this same study, investigators found that the mean level of DHA in erythrocytes

was significantly higher than EPA in the treatment group after supplementation; there were no significant differences in the placebo group. In a similar RCT, supplementation with EPA (2 g) compared with placebo in clinically depressed patients already receiving standard antidepressant therapy significantly improved depressive symptoms based on the Hamilton (Nemets et al., 2002).

An RCT investigating different doses of EPA in patients with clinical depression already receiving standard antidepressant therapy found that supplementation with 1 g of EPA significantly decreased depression, anxiety, and suicidality, and improved libido and sleep compared with placebo (Peet & Horrobin, 2002). Patients receiving 2 g of EPA showed minimal improvement, whereas patients taking 4 g showed no improvement. This study suggests that there is an important dose–response relationship in omega-3 fatty acid supplementation.

An RCT investigating DHA (2g) as a stand-alone therapy compared with placebo in patients with clinical depression who were not receiving pharmacotherapy found that there were no significant differences in depressive symptoms between groups (Marangell et al., 2003). A similar trial comparing EPA (500 mg) as a stand-alone therapy to placebo and to a combination of EPA (500 mg) and fluoxetine (20 mg) found that EPA as a stand-alone therapy had equal therapeutic effects to fluoxetine as a stand-alone therapy based on the Hamilton, whereas the combination of EPA and fluoxetine had super effects to either alone (Jazayeri et al., 2008). In a study investigating plasma levels of PUFAs in patients with clinical depression who were not receiving pharmacotherapy, lower plasma DHA level and low omega-3 to omega-6 ratio predicted risk of suicidal behavior (Sublette et al., 2006). Clinical trials support the use of PUFAs as effective therapies for clinical depression as both stand-alone and adjunctive treatments. Although additional research is indicated to further define the parameters of ideal use, the standing research is at least sufficient to suggest utilization of PUFAs in clinical practice as part of a combination of therapies.

Critical issues

Although the suspected pathophysiology of omega-3 fatty acids, epidemiological data, and a small group of treatment studies all point to the likely involvement of omega-3 fatty acids in clinical depression, more research is required to confirm this hypothesis and to determine the mechanism by which omega-3 fatty acids augment depressive symptoms. In addition, more research is required to determine whether EPA, DHA, or both contribute to the improvement of depressive symptoms and, if so, in what dose and for how long. Last, the role of the ratio of omega-3 to omega-6 fatty acids to understanding the etiological factors of depression needs to be further examined, including investigation of how the ratio in the diet, in red blood cells, and in adipose tissue contributes to depressive symptoms.

Although treatment studies demonstrate efficacy of omega-3 fatty acid supplementation as a stand-alone therapy and in addition to pharmacotherapy, these studies are all of relatively small sample size and generally include a variety of adjunctive treatments. As a result, it is difficult to draw definitive conclusions from these studies. In addition, appropriate placebo needs to be utilized in future studies as omega-6 oils (such as olive oil) are frequently utilized as placebo and may negatively influence the depressive symptoms in the control group. Therefore, current treatment studies certainly indicate a need for further research.

The available data, although inconclusive, do suggest that it would be worthwhile for a clinician to consider utilizing omega-3 fatty acid supplements in clinical practice. There are few, if any, adverse effects to be concerned with. Omega-3 fatty acids benefit cardiovascular health, among other systems. Supplementation may potentially increase effectiveness of current regimens, and may also be helpful as a stand-alone therapy. There is no need to taper the dose over time; as a result, nonadherence has no known adverse effects.

Folate, Vitamin B12, and Vitamin B6

The role of folate, vitamin B12, and vitamin B6 in psychiatric illnesses has been explored through both epidemiological and experimental studies for the past three decades. There are several mechanisms that may be responsible for the protective role of these B vitamins on depressive symptoms. Because these three vitamins play critical roles in the production of many chemicals in the central nervous system, most importantly neurotransmitters, it is challenging to isolate the exact mechanism through which they affect depressive symptoms; it is likely the result of a combination of several pathways. The pathways that have been most studied include one-carbon metabolism (methylation) and the tryptophan-serotonin pathway. Folate, vitamin B12, and vitamin B6 all influence these pathways in different ways.

Neurobiology

Folate, vitamin B12, and vitamin B6 are critical components of one-carbon metabolism (methylation); all three are cofactors for the enzymes involved in this process. One-carbon metabolism is a pathway that generates individual carbon units through association with tetrahydrofolate, creating 5,10-methylenetetrahydrofolate (Selhub, Bagley, Miller, & Rosenberg, 2000). This resulting

product, 5,10-methylenetetrahydrofolate, is reduced to 5-methyltetrahydrofolate, which participates in the methylation of homocysteine to methionine and the synthesis of thymidylate and purines; these reactions are catalyzed by folate and vitamin B12 (Rosenberg, 2001). Purines are then used for nucleic acid synthesis, whereas methionine is used for protein synthesis and numerous biological methylations in the central nervous system (Selhub et al., 2000).

Much of the methionine produced generates S-adenoxylmethionine (SAM) through activation by ATP (Rosenberg, 2001). SAM is a universal methyl donor and SAM-dependent methylations are extensive in the brain, including production of neurotransmitters, phospholipids, and myelin (Selhub et al., 2000). Therefore, SAM independently influences the rate of synthesis of serotonin, norepinephrine, and dopamine (Brocardo, Budni, Kaster, Santos, & Rodrigues, 2008). Hypomethylation resulting from decreased availability of methyl donors due to vitamin B deficiency interferes with protein synthesis and decreases neurotransmitter metabolism, causing cognitive impairment through neuronal DNA damage (Bottiglieri, 2005; Reynolds, 2002; Stahl, 2007).

After donating its methyl group through methylation, SAM is converted to S-adenosylhomocysteine (SAH), which is then reversibly converted into homocysteine and adenosine (Rosenberg, 2001). The process of converting SAH to homocysteine and adenosine is catalyzed by folate and vitamin B12 (Selhub et al., 2000). In a state of folate or vitamin B12 insufficiency, SAH accumulates, as the body is unable to methylate homocysteine to methionine (Selhub et al., 2000). SAH behaves as an inhibitor of SAM-dependent methylations; therefore, in folate, vitamin B12, and vitamin B6 deficiency, the generation of SAM is reduced and the rates of SAM dependent methylations are simultaneously decreased by the accumulation of SAH (Rosenberg, 2001). Impaired methylation may result in neurologic or psychiatric disease due to neuronal DNA damage, which can be irreversible without adequate maintenance (Bottiglieri, 2005; Karakuła et al., 2009).

Homocysteine is often used as an indicator of folate and vitamin B12 status because its production depends on these B vitamins; high plasma homocysteine results from B vitamin deficiency (Rosenberg, 2001). Homocysteine is remethylated to methionine by vitamin B12; therefore, vitamin B12 deficiency leads to homocysteine accumulation. Accumulation of homocysteine or its metabolites also likely has a direct neurotoxic effect through overstimulation of the N-methyl-D-aspartate glutamate receptors, causing calcium influx and apoptosis; therefore, any disruption in the methylation pathway has a negative effect on the central nervous system (Feng & Fan, 2009; Reynolds, 2006).

Folate also plays a role in the synthesis of tetrahydrobiopterin, which is the cofactor for the hydroxylation of phenylalanine and troptophan, and is also the rate-limiting step in the synthesis of the monoamine neurotransmitters dopamine, noradrenaline, and 5-hydroxytryptamine (5HTP), the precursor of serotonin (A. L. Miller, 2008; Stahl, 2008). The monoamine hypothesis of affective disorders suggests that depression is due to a deficiency of either 5HTP or noradrenaline, or both. In fact, studies have shown a connection between an abnormality of tetrahydrobiopterin and major depression (Coppen & Bolander-Gouaille, 2005; A. H. Miller et al., 2009). In addition, folate also independently methylates phospholipids on neuronal membranes, thereby altering membrane-bound receptors, second-messenger systems, and ion channels; changes in any of these components of cellular metabolism may significantly affect CNS function (Bottiglieri, 2005; Troen et al., 2008).

Aside from its direct role in one-carbon metabolism, vitamin B12 also acts as a coenzyme in both the demethylation of the folate derivative needed for thymidylate synthesis and in the conjugation of folic acid into the active polymer forms of folate (Bottiglieri, 2005). Therefore, vitamin B12 deficiency produces a functional folate deficiency by trapping folate in the above pathways and preventing its regeneration, thereby inducing all of the metabolic consequences of folate deficiency (Coppen & Bolander-Gouaille, 2005; Eussen et al., 2006; Reynolds, 2006). Neurotransmitter synthesis is slowed in vitamin B12 deficiency as a result of the functional unavailability of folate.

Vitamin B6 is also a cofactor in the tryptophan-serotonin pathway, another possible route by which vitamin B6 status affects mood, because depression has long been associated with serotonin and catecholamine deficiency (Hvas, Juul, Bech, & Nexø, 2004). Pyridoxal 5'-phosphae (PLP) is the metabolite of vitamin B6 and a necessary coenzyme in the tryptophan-serotonin pathway; PLP regulates the extent of decarboxylation of 5-hydroxytryptophan (5-HTP; Mooney, Leuendorf, Hendrickson, & Hellmann, 2009). PLP-dependent enzymatic decarboxylation also results in the production of dopamine, norepinephrine, gamma-amino butyric acid (GABA), and taurine (Dakshinamurti, Sharma, & Geiger, 2003). Therefore, vitamin B6 plays a role in the production of neurotransmitters in two ways: through its role in one-carbon metabolism and through its role in the tryptophan-serotonin pathway.

There are several different underlying pathways by which folate, vitamin B12, and vitamin B6 deficiency manifest in depressive symptoms, all of which are intimately tied together. Although depressive symptoms are likely due to the accumulation of these various pathways, the exact mechanism is unknown because the consequences

of B vitamin deficiencies in the CNS are so widespread. Therefore, the neurobiology offers various explanations of how the relationship of B vitamins and depressive symptoms might work, but does not offer a conclusive explanation. Several epidemiological studies and treatment studies further support this hypothesis, adding to the evidence that folate, vitamin B12, and vitamin B6 are involved in the development of depressive symptoms.

Epidemiology

Several epidemiological studies demonstrate the association between low B vitamin status and poor neurocognitive function (Kado et al., 2005; Morris, Jacques, Rosenberg, & Selhub, 2007). This association was first explored as a result of epidemiological evidence connecting cognitive dysfunction, low B vitamin status, and hyperhomocysteinemia (Hao et al., 2007; Obeid, McCaddon, & Herrmann, 2007). For example, healthy elderly patients with low blood concentrations of folate and vitamin B12 scored poorly on tests of memory and nonverbal abstract thinking as compared with patients with normal B vitamin status (de Lau, Refsum, Smith, Johnston, & Breteler, 2007; Malouf & Grimley Evans, 2008; Nurk et al., 2005). In a similar study, low folate, low vitamin B12, and high homocysteine concentrations were associated with declines in constructional praxis (understanding of three dimensional manipulation), measured by spatial copying skills (G. Kim et al., 2013; Tucker, Qiao, Scott, Rosenberg, & Spiro, 2005). Therefore, folate, vitamin B12, and vitamin B6 likely have a protective role in cognitive decline (Tucker et al., 2005).

The association between low B vitamin status and clinical depression has also been established (Beydoun, Shroff, Beydoun, & Zonderman, 2010; Sánchez-Villegas et al., 2009; Skarupski et al., 2010). Epidemiological studies demonstrate that individuals with vitamin B12 deficiency have a twofold increase of severe depression (Penninx et al., 2000). Similarly, individuals with depression have increased plasma homocysteine, indicating a deficiency of vitamin B12 and folate, and impaired neurotransmitter metabolism (Bottiglieri et al., 2000). In a sample of the general U.S. population, low folate status in serum and in red blood cells was linked to clinical depression (Morris, Fava, Jacques, Selhub, & Rosenberg, 2003); in addition, folate deficiency has been noted in up to one third of psychiatric outpatients with varying mental illnesses (Bottiglieri, 1996). Low folate status is also linked to duration and severity of depressive episodes (Beydoun et al., 2010; Coppen & Bolander-Gouaille, 2005; Gilbody, Lightfoot, & Sheldon, 2007). Other studies have demonstrated a significant association between low plasma PLP (indicating low vitamin B6 status) and major depression (Hvas et al., 2004).

Clinical trials

Experimental studies also support the relationship among low B vitamins status, poor neurocognitive function, and depression. Animal studies indicate that supplementation with B-vitamins, specifically B-6, leads to an increased level of serotonin in the brain through regulation of the decarboxylation of 5-HTP (Shabbir et al., 2013). Supplementation and replacement therapy in humans also point to the connection between B vitamins and depression.

Studies demonstrate that both folate and vitamin B12 replacement therapy produce significant improvements in depressive symptoms (Taylor, Carney, Geddes, & Goodwin, 2003; Taylor, Carney, Goodwin, & Geddes, 2004). Similarly, supplementation with vitamin B12 in cobalamin (vitamin B12) deficient patients significantly improves neuropsychiatric function and leads to cognitive recovery (Andrès & Kaltenbach, 2003; Eussen et al., 2006; Moretti et al., 2004). Stand-alone therapy with folate leads to improvements in mood and neuropsychological function (Balk et al., 2007; Durga et al., 2007).

Supplementation with folate also improves the therapeutic benefit of fluoxetine and enhances recovery from psychiatric illnesses, not exclusively depression (Coppen & Bailey, 2000). In a double-blind, placebo-controlled trial, folate significantly increased clinical and social recovery in depressed patients when added to standard psychotropic medication (Godfrey et al., 1990). When used as an adjunctive therapy in patients treated with SSRIs, folate improved depression scores on the Hamilton and the CGI-I (Alpert et al., 2002). Similarly, patients with low plasma folate responded less well to antidepressant therapy (Papakostas et al., 2004). Longitudinal studies demonstrate that supplementation with vitamins B12 and B6 are associated with a decreased likelihood of depression through 12 years of follow-up (Skarupski et al., 2010). Although the existing clinical trials suggest that folate, vitamin B12, and vitamin B6 are likely useful in the treatment of clinical depression, the evidence is not yet sufficient to recommend use in clinical practice. Because it is unclear which supplement is most effective, additional research is required to determine whether the combination of these supplements is superior to individual therapy.

Critical issues

Although the neurobiology demonstrates that folate, vitamin B12, and vitamin B6 play important roles in the production of chemicals that are likely involved in the pathophysiology of depression, there is not yet enough evidence to determine how best to use this information in clinical practice. Because folate, vitamin B12, and

vitamin B6 all play roles in a few possible etiologies of depression, it is not possible to pinpoint the exact mechanism through which all or one of these supplements impacts depressive symptoms. Similarly, it is possible that patients with different underlying causes of depression might require different combinations of these supplements.

Epidemiological studies point to the relationship between low B vitamin status and depression but do not account for whether low B vitamin status results from depression or leads to depression. In addition, most of the epidemiological evidence available is in elderly populations or patients who already have various psychiatric diagnoses, including, but not limited to, depression. And finally, not all of the epidemiological evidence agrees in terms of which of the three B vitamins are most important in depression. Perhaps this is because B vitamin impacts depressive symptoms differently in different populations.

Similarly, experimental studies point to the potential efficacy of B vitamin supplementation as a stand-alone therapy or in addition to psychotropic medications in patients with depression, but are inconclusive. Most of the clinical trials available rely on small sample sizes and as a result are vulnerable to a variety of biases. However, although the body of evidence available certainly points to the need for additional studies to determine exactly how this information can be best utilized in clinical settings, the research is still insufficient to be applied uniformly in clinical practice.

Much like omega-3 fatty acids, the risks of utilizing B vitamins does not outweigh the potential benefits. If supplementation improves depressive symptoms or increases the efficacy of the current treatment regimen, it is an inexpensive and safe way to benefit the patient. If supplementation is ineffective, it can easily be discontinued or utilized for its other health benefits. As a result, clinicians would benefit from considering the introduction of a B-complex to patients when appropriate.

S-adenoxylmethionine (SAMe)

As discussed in the previous section, one-carbon metabolism (methylation) is implicated in a variety of psychiatric disorders, including clinical depression. Although adequate intake of folate, vitamin B12, and vitamin B6 are essential to the proper functioning of one-carbon metabolism, likely due to the production of SAMe, it is also possible to directly supplement with SAMe (Bottiglieri, 2002). In fact, SAMe has been used as an antidepressant in Europe for over 30 years (Delle Chiaie, Pancheri, & Scapicchio, 2002). Initial treatment with SAMe was through intramuscular and intravenous administration; however, more recent studies have demonstrated that oral SAMe is also effective and crosses the blood brain barrier (Delle Chiaie et al., 2002). Because it has been utilized outside of the United States for several years, SAMe is one of the most studied supplements for clinical depression; as a result, there is an existing body of literature on the use of SAMe in clinical depression that points to its effectiveness as a stand-alone therapy and as an adjunctive treatment.

Neurobiology

As detailed in the previous section, the one-carbon cycle results in the conversion of folate into SAMe through the intermediary molecule 5-methyltetrahydrofolate (5MTHF), a product of folate (Papakostas, Cassiello, & Iovieno, 2012). L-methylfolate readily crosses the blood–brain barrier and joins with homocysteine in the CNS to form methionine, which is then metabolized by methionine adenosyltranferase (MAT) and vitamin B12 to form SAMe. SAMe serves as the primary donor of methyl groups required in a variety of methylation reactions, including phospholipids, DNA, ribonucleic acid, neurotransmitters, and proteins; it is therefore essential not only in the CNS, but also in the liver, adrenal glands, and pineal gland (Papakostas, Alpert, & Fava, 2003).

Although the role of SAMe in methylation reactions is certain, the exact mechanism by which it exerts an antidepressant effect is still debated (Mischoulon & Fava, 2002). One possible mechanism is through its relationship to plasma phospholipids. SAMe methylates plasma phospholipids and increases the conversion of phosphatidylethanolamine to phosphatidylcholine, altering the fluidity of the cellular membrane; therefore, it affects the interaction of proteins and the cellular membrane, including monoamine receptors and transporters, and other second messenger systems (Cimino et al., 1984; Mischoulon & Fava, 2002). Specifically, it increases neurotransmission by increasing the density of available receptors as well as increasing the receptor–effector coupling (Mischoulon & Fava, 2002).

Another possible mechanism is through the relationship between SAMe and monoamine neurotransmitter synthesis. Several studies suggest a relationship between methylation and the production of monoamine neurotransmitters (Bottiglieri, 2002; Bottiglieri et al., 2000). The association between low folate levels (which result in decreased SAMe production) and low dopamine, norepinephrine, and 5-HTP in the CNS has been demonstrated because folate is closely linked to neurotransmitter synthesis (Gilbody et al., 2007; A. L. Miller, 2008). Therefore, by inhibiting the production of monoamine neurotransmitters, patients with low SAMe levels will be at an increased risk of depression based on the monoamine hypothesis. Because there are myriad biological effects of SAMe, pinpointing the exact mechanism that contributes to its therapeutic effects is challenging. In

both of the proposed mechanisms, however, SAMe deficiency decreases the level of monoamine neurotransmitters accessible to the cell either through decreased production of the neurotransmitters themselves, or by inhibiting the cell's ability to absorb neurotransmitters as a result of the membrane structure. Therefore, the effectiveness of SAMe points to likelihood of the monoamine theory of depression.

Epidemiology

Epidemiological studies also point to the connection between SAMe and depression. Levels of SAMe in the CNS have been studied in a variety of neuropsychiatric disorders, especially in major depression (Bottiglieri et al., 2000). Low serum and CSF SAMe levels have been identified in patients with depression (Mischoulon & Fava, 2002; Raison, Capuron, & Miller, 2006). Administration of both parenteral (IV administration) and enteral (through gastrointestinal administration) SAMe led to a significant rise of SAMe in the CSF (Bottiglieri, 2002; Echols, Naidoo, & Salzman, 2000). Studies have shown that as plasma SAMe levels increase, there is a corresponding alleviation of depression (Sabina, 2005). In addition, erythrocytes of patients with MDD had lower levels of activity of MAT enzyme compared with a control group, implicating one-carbon metabolism in MDD; notably, treatment with antidepressants led to an increase in MAT activity (Smythies, Gottfries, & Regland, 1997).

Clinical trials

SAMe has been studied in more than 40 RCTs both in intramuscular and oral forms. To date, six studies have compared the efficacy of parenteral SAMe with placebo in major depression (Papakostas et al., 2012). Five of these studies demonstrated that SAMe delivered intravenously or intramuscularly is more effective than placebo. One larger study found that IV SAMe was superior to placebo (Echols et al., 2000). The data available also indicate that SAMe delivered through intramuscular injection is equally effective or more effective than tricyclic antidepressants, has an earlier onset of action (3 to 7 days), and has fewer adverse effects (Delle Chiaie et al., 2002; Pancheri, Scapicchio, & Chiaie, 2002; Sabina, 2005). For example, two large RCTs of outpatients with major depression found that intramuscular SAMe for 4 weeks had comparable efficacy to oral imipramine for 6 weeks (Delle Chiaie et al., 2002).

Because parenteral preparations of SAMe significantly reduce the clinical application of this supplement (Bottiglieri, 2002), enteral formulations were also studied. Supplementation with oral SAMe leads to a significant rise in CSF SAMe, indicating that the oral preparation does cross the blood–brain barrier (Bottiglieri, 2002; Kaplan, Crawford, Field, & Simpson, 2007). Double-blind, placebo-controlled studies demonstrate that oral SAMe is more effective than placebo in inpatients with major depression, has a rapid onset of action, and has few adverse effects; therefore, it is likely just as effective as parenteral formulations (Mischoulon & Fava, 2002). RCTs also demonstrate that oral SAMe is just as efficacious as tricyclic antidepressants in alleviating depressive symptoms with no clinically significant side effects (Delle Chiaie et al., 2002). In addition, degree of clinical improvement in depressed patients, regardless of therapy type, was directly correlated with plasma SAMe levels (Al-Gazali et al., 2001; J. M. Kim et al., 2008).

SAMe has also been studied as an adjunctive treatment in patients whose symptoms were not alleviated with standard pharmacotherapy. In 30 outpatients who did not experience symptom relief from an SSRI, supplementation with oral SAMe led to symptom improvement in 4 weeks in 50% of the patients (Alpert et al., 2004). In an open trial of 20 outpatients with major depression, oral SAMe supplementation significantly improved depressive symptoms without side effects; in addition, 2 of 9 treatment-resistant patients experienced full antidepressant response (Carvalho, Cavalcante, Castelo, & Lima, 2007; Shelton, Osuntokun, Heinloth, & Corya, 2010). In 73 patients with MDD who were partial responders to an SSRI or an SNRI, adjunctive supplementation with oral SAMe was compared with placebo; response rates were significantly higher in the group receiving SAMe than those receiving placebo (Papakostas, Mischoulon, Shyu, Alpert, & Fava, 2010). In addition, in 40 patients receiving either intramuscular SAMe, imipramine, or both, patients receiving combined therapy showed a superior antidepressant effect compared with those receiving either SAMe alone or imipramine alone (Alpert et al., 2004; Fava & Rush, 2006; Papakostas et al., 2005). It is interesting that the superior efficacy was significant only for the first 2 weeks, indicating that combination therapy served to accelerate symptom improvement rather than alter the ultimate level of symptom remittance. Existing clinical data do suggest that oral SAMe supplementation does have efficacy in the treatment of clinical depression and can be utilized in clinical practice. Further research is needed to pinpoint ideal dosing and to further explore long-term outcomes. In addition, caution should be exercised in patients who are receiving additional pharmacotherapies as SAMe does lead to neurobiological alterations similar to those of tricyclic antidepressants.

Critical issues

The available research strongly suggests the efficacy of SAMe in clinical depression. Further clinical trials, with

larger sample sizes, will serve to further elucidate the role of SAMe in depressive disorders. Additional research is needed to determine precise dosing of both parenteral and enteral forms. Available data indicate that 1,200 to 1,600 mg/day of oral SAMe and 200 to 400 mg/day of intramuscular SAMe appear to be effective. However, because there does not appear to be a dose ceiling giving the lack of adverse effects, it is still unclear at what, if any, dosing toxicity is a concern. Questions about long-term safety, efficacy, and integration into current pharmacotherapy remain.

Use of SAMe in depression appears to have many advantages over standard treatment. It has a more rapid onset of action than pharmacotherapy and a minimal adverse effect profile. It is therefore helpful in patients who are unable to tolerate pharmacotherapy due to adverse effects or who do not experience full symptom remittance from pharmacotherapy. In addition, it is useful as a stand-alone therapy in patients who prefer not to utilize pharmacotherapy and would be appropriate as a potential first line intervention. It can also be used as a helpful adjunct to standard pharmacotherapy. Because SAMe has the potential to have a more significant adverse effect profile than other nutritional supplements, and because the ideal dosing is not yet well known, patients utilizing SAMe should be monitored for adverse effects. Most interesting, these results implicate methylation in psychiatric illness, particularly in the pathophysiology of depression. Further exploration into the role of methylation in psychiatric illness may lead to additional advances in our understanding of and ability to treat clinical depression.

5-hydroxytryptophan

The precursor of serotonin production, 5-hydroxytryptophan (5-HTP) is an amino acid that is produced from the essential amino acid L-tryptophan. The ingestible form is extracted from the seeds of an African plant, *Griffonia simplicifolia*. Oral 5-HTP easily crosses the blood–brain barrier, thereby increasing synthesis of serotonin in the CNS (Gendle & Golding, 2010; Turner & Blackwell, 2005; Turner, Loftis, & Blackwell, 2006). As a result, 5-HTP can potentially be used to increase serotonin synthesis in the brain, which theoretically should mitigate depressive symptoms based on the monoamine hypothesis of depression. Furthermore, it may also have utility in the treatment of other psychiatric disorders that result from serotonin insufficiency or deficiency. The utility of 5-HTP in clinical depression has been of interest for several decades.

Neurobiology

As discussed earlier, the monoamine hypothesis of depression suggests that an etiological factor of depression may be related to a deficit in serotonergic activity in the CNS. Many pharmacologic therapies attempt to mitigate depressive symptoms by inhibiting the reuptake of serotonin in the CNS to increase synaptic serotonin levels. Another possible way of increasing synaptic serotonin levels is to increase the availability of the substrate for serotonin synthesis, 5-HTP.

Synthesized from L-tryptophan, an amino acid, 5-HTP, is then converted to serotonin centrally and peripherally (Walther et al., 2003). The most efficient way to influence serotonin synthesis is to intervene at a point in the synthetic pathway that is downstream from tryptophan. Both tryptophan and 5-HTP penetrate the blood–brain barrier (Shaw, Turner, & Del Mar, 2002). As a result, tryptophan has also been explored as a potential antidepressant. Increases in dietary tryptophan and dietary 5-HTP increase the amount of each of these products in the CNS (Le Floc'h, Otten, & Merlot, 2011).

When 5-HTP penetrates the CNS, it is locally converted to serotonin within serotonergic neurons (Walther et al., 2003). It is important that the enzyme required for the conversion of L-tryptophan to 5-HTP depends on adequate vitamin B6 supply (Turner et al., 2006). The advantages of supplementing directly with 5-HTP instead of its precursor, L-tryptophan, is that 5-HTP does not require a transport molecule to enter the CNS; in addition, bypassing the conversion of L-tryptophan into 5-HTP eliminates the rate-limiting step in the synthesis of serotonin (Meyers, 2000).

Epidemiology

To determine the role of the serotonergic pathway in depression, plasma levels of tryptophan have been examined in samples of patients with clinical depression. However, studies have revealed inconsistent results. Lowered free tryptophan levels were found in female patients with depression, with a significant increase in levels of tryptophan postrecovery (Almeida-Montes et al., 2000; Raison et al., 2006). Similar studies found decreased total tryptophan levels in patients of both genders with depression (Widner, Laich, Sperner-Unterweger, Ledochowski, & Fuchs, 2002; Young & Leyton, 2002).

Additional studies found that total plasma tryptophan was significantly lower in patients meeting criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* for clinical depression with melancholia or psychosis, but not for those with nonmelancholic depression. Similarly, decreased total plasma tryptophan levels have been reported in patients with clinical depression compared with controls (Jans, Riedel, Markus, & Blokland, 2006). Additional studies support the link between lowered plasma tryptophan levels and patients meeting criteria for clinical depression (Middlemiss, Price,

& Watson, 2002); in addition, a link between lowered tryptophan levels in female patients with depression has been found (Deecher, Andree, Sloan, & Schechter, 2008). Despite this evidence, some studies of depressed patients have reported normal total plasma tryptophan levels (Young & Leyton, 2002).

Clinical trials

The efficacy of 5-HTP as an antidepressant has been explored in a variety of clinical trials over the past four decades. Most of the trials are limited by their small sample sizes. Among the double-blind, placebo-controlled studies, seven found that 5-HTP was superior to placebo in mitigating depressive symptoms (Turner et al., 2006). A 2-year crossover relapse prevention study found that 5-HTP as a stand-alone therapy was superior to placebo (Lovieno, Dalton, Fava, & Mischoulon, 2011). Three additional studies of 5-HTP as a stand-alone therapy demonstrated that 5-HTP supplementation is superior to placebo. An augmentation study found that clomipramine with 5-HTP was superior to clomipramine with placebo (Lovieno et al., 2011). Another augmentation study found that 5-HTP with dopamine was superior to both placebo and 5-HTP alone (Shaw et al., 2002). A study comparing nialamide and 5-HTP to nailaminde with placebo found that the combination group was more effective than the placebo group (Kemper & Shannon, 2007). Another trial found that 5-HTP is as effective as imipramine, a tricyclic antidepressant.

In addition, animal studies have demonstrated the effect of 5-HTP supplementation on the brain. Studies demonstrate that 5-HTP can be used to manipulate serotonin levels in rats (Smith & Kennedy, 2003). In addition, 5-HTP supplementation in rats decreases avoidance responses induced by sleep deprivation, indicating that 5-HTP attenuates the hyperalgesia induced by sleep deprivation and restores serotonin levels (Turner et al., 2006).

Open-label studies have had mixed results. Two studies demonstrated that 5-HTP had comparable effectiveness to both imipramine and fluvoxamine based on the Hamilton Rating Scale (Meyers, 2000; Turner et al., 2006). Supplementation with 5-HTP in 107 patients led to significant improvement in symptoms in over half of the study population by the fourth week (Turner et al., 2006). A similar study found that 5-HTP improved mood in 69% of the population by the fourth week (Meyers, 2000). Despite these results, other studies have demonstrated the inferiority of 5-HTP. For example, two open-label studies found that 5-HTP was less effective than tranylcypromine for treatment-resistant depression (Carvalho et al., 2007). Another study comparing 5-HTP as a stand-alone therapy to 5-HTP plus a peripheral decarboxylase inhibitor found no statistically significant improvement in either group (Turner & Blackwell, 2005). The available literature on the use of 5-HTP suggests that supplementation of 5-HTP may have efficacy as both a stand-alone therapy and as an adjunctive therapy in the treatment of clinical depression, but additional research is required before this can be concluded. As a result, 5-HTP should be utilized with caution in clinical settings. In addition, because 5-HTP has the potential to increase serotonin levels, serotonin syndrome may be a risk in patients concurrently receiving therapies that will increase serotonin.

Critical issues

The number of RCTs is limited and most have small sample sizes, rendering the combination of results difficult to interpret. Furthermore, several open-label trials point to the potential efficacy of 5-HTP, but these cannot be used to make a definitive determination. Because these study designs are heterogeneous in nature, it is not possible to draw a singular conclusion from the available information. Despite the conflicting evidence, there is replication of positive findings in many instances; as a result, well-organized, large-scale trials are indicated to further explore the potential efficacy of 5-HTP in clinical depression.

If the literature supported its use as a stand-alone therapy, adjunctive therapy, or both, 5-HTP would have a great deal of clinical utility; however, the available data do not yet suggest this. Oral doses of 200 to 300 mg/day of 5-HTP have been well tolerated; the most common side effects are gastrointestinal (nausea, vomiting, and diarrhea), mild, and occur rarely (Turner et al., 2006). It is easily producible commercially and inexpensive. Although use of 5-HTP in clinical practice would likely not lead to significant adverse effects, the data are too inconclusive to recommend its use. Furthermore, 5-HTP does not have other known health benefits that might make supplementation with it in general worthwhile.

Magnesium

Magnesium is the second most predominant intracellular cation, which functions to activate about 300 different enzymatic reactions (Gums, 2004; Jahnen-Dechent & Ketteler, 2012). It is responsible for the metabolism of ATP; as a result, it contributes to the biosynthesis and maintenance of the structure of nucleic acids as well as protein synthesis (Poleszak et al., 2004). Specifically, magnesium regulates energy metabolism and production, DNA and RNA synthesis and structure, cell growth, cytoskeletal function, membrane structure, and ion homeostasis (Saris, Mervaala, Karppanen, Khawaja, & Lewenstam, 2000). The available literature indicates that

disturbances in magnesium metabolism contribute to many disorders, including ventricular arrhythmias, convulsions, neuromuscular hyperexcitability, apathy, muscle cramping, and increased stress (Johnson, 2001). In addition, magnesium deficiency has been closely linked to affective disorders, and particularly to depressive symptoms (Eby & Eby, 2006; Murck, 2002; Siwek, Wrobel, Dudek, Nowak, & Zieba, 2004). Experimental and epidemiological studies indicate that disturbances in magnesium metabolism play a role in psychiatric illnesses (Murck, 2002). Furthermore, animal studies demonstrate that partial magnesium depletion leads to an increase in depression and anxiety-related behavior (Singewald, Sinner, Hetzenauer, Sartori, & Murck, 2004).

Neurobiology

Several hypotheses have been proposed to explain the connection between magnesium and depression. The exact mechanisms underlying the relationship are still unknown; however, there are a few physiological pathways by which magnesium may influence depressive symptoms. For example, magnesium has an important role in the regulation and release of the following neurochemicals: adrenocorticotropic hormone, y-aminobutyric acid, and glutamatergic neurotransmitters (Murck, 2002). It is also intimately involved in a variety of transduction pathways, such as protein kinase C (Davison, 2010). Magnesium plays a direct role in cellular serotonin uptake, increasing serotonin receptor transmission, directly influencing the amount of serotonin available to brain cells (Szewczyk et al., 2008).

In addition, magnesium modulates glutamatergic transmission through N-methyl-D-aspartate receptor (NMDA), which plays a role in the entrance of calcium into the neuron (Collingridge, 2003). By regulating the entry of calcium into the neuron, magnesium exerts neuroprotective properties, protecting the neuron against cell death (Camardese et al., 2012). High levels of calcium ions and glutamate in the brain that are unregulated by magnesium will likely deregulate brain cell synaptic function leading to depressive symptoms (Eby & Eby, 2010). It is hypothesized that when excessive calcium and glutamate paired with insufficient magnesium leads to brain cell synaptic dysfunction, an increase in nitric oxide production results and manifests as depression, anxiety, apathy, and possibly psychosis (Camardese et al., 2012).

Magnesium also plays a role in the hypothalamic-pituitary-axis (HPA) function. This is likely associated with a reduction in nocturnal ACTH and cortisol release, which influences stress responses and alters the function of the blood–brain barrier, influencing the flow of chemicals to the brain (Sartori, Whittle, Hetzenauer, & Singewald, 2012). The interaction of adrenocorticotropic hormone and the HPA axis is frequently dysregulated in individuals with depression.

Magnesium is involved in the inflammation cascade, which has been implicated in the pathophysiology of depression. As a result, it is possible that the immune system may be the primary mediator of the relationship between magnesium status and depressive symptoms (Jacka et al., 2009). Depressed subjects have been found to exhibit higher levels of C-reactive protein and various other inflammatory markers than nondepressed controls (Uchakin, Tobin, Cubbage, Marshall, & Sams, 2001). Inflammatory markers are secreted in response to proinflammatory cytokines, and play a critical role in the inflammation pathway; this relationship between inflammatory markers and the inflammation pathway is not a unique feature of depression, but instead takes place in all instances in which inflammation occurs (Uchakin et al., 2001). Because magnesium blocks the cytokine inflammatory cascade, magnesium deficiency leads to high C-reactive protein and increased proinflammatory cytokines, which is a possible mechanism by which magnesium contributes to depressive symptoms (Poleszak et al., 2004). This relationship between magnesium deficiency and inflammation is not exclusive to depression; based on this hypothesis, it follows that magnesium deficiency may also lead to other inflammatory pathologies in addition to depression.

Epidemiology

Epidemiological studies suggest that there may be a link between hypomagnesaemia and depressive symptoms. Cross-sectional, interventional, and prospective studies have been carried out and show mixed results. Cross-sectional studies indicate that patients with depression have significantly lower CSF magnesium levels than controls (Nechifor, 2009), that serum magnesium levels are significantly lower among patients with depression than controls and correlate positively and significantly with severity of depressive symptoms (Barragán-Rodríguez, Rodríguez-Morán, & Guerrero-Romero, 2007; Hasey et al., 1993), that plasma magnesium levels are predictive of successful treatment responses (Camardese et al., 2012), and that plasma magnesium levels are significantly lower in patients with depression than controls (Camardese et al., 2012; Derom et al., 2012). However, other cross-sectional studies have found no significant correlations between magnesium levels and depressive symptoms (George, Rosenstein, Rubinow, Kling, & Post, 1994; Joffe, Levitt, & Young, 1996; Kamei et al., 1998), rendering the overall evidence inconclusive. An important limitation of the cross-sectional studies is that 99% of total magnesium is intracellular; therefore, plasma and

serum magnesium levels are often not an accurate reflection of total body magnesium (Derom, Sayón-Orea, Martínez-Ortega, & Martínez-González, 2013). In addition, a prospective study found no association between higher magnesium intake and depression risk in a sample of more than 12,000 university graduates (Derom et al., 2012). Conversely, two case studies found that magnesium supplementation significantly alleviated depressive symptoms, restored sleep, and improved anxiety (Eby & Eby, 2006; Enya et al., 2004).

Clinical trials

Experimental trials, though limited in number, have also yielded mixed results. An RCT demonstrated that depressive symptoms improved in 3 months with supplementation of magnesium sulfate compared with placebo in patients with clinical depression (Bhudia et al., 2006). Another RCT found that magnesium supplementation was similarly effective to imipramine in improving symptoms of major depression (Barragán-Rodríguez, Rodríguez-Morán, & Guerrero-Romero, 2008). However, a third RCT found no significant differences in depressive symptoms between patients supplemented with magnesium compared with those supplemented with placebo in clinical depression (Walker et al., 1998).

Clinical trials exploring the use of magnesium in clinical depression are lacking. Although the neurobiological basis for the use of magnesium in depression is convincing, additional evidence is required to support this hypothesis. As a result, it cannot yet be concluded that magnesium has efficacy in the treatment of clinical depression, even though the existing evidence supports further exploration.

Critical issues

Although the available evidence is inconclusive, it does demonstrate the need for further investigation into the use of magnesium supplementation for prevention or mitigation of depressive symptoms. It is known that the brain requires sufficient magnesium to prevent excessive intraneuronal excitation by calcium and to facilitate numerous enzymatic reactions in the brain. Therefore, the importance of adequate magnesium stores on optimal brain functioning has been established.

Because magnesium supplementation is safe, and efficacious in many cases, it can be used reasonably as an adjunctive treatment in patients with depression currently using other pharmacotherapy. It has other known health benefits and combination in supplements with calcium has even additional benefits for patients. Adequate calcium and magnesium stores are essential for optimal health, and supplementation at appropriate doses has minimal, if any, risks. Larger clinical trials are still required to demonstrate efficacy in clinical depression and to determine appropriate dosing, preparation, and duration of use.

Conclusions

The research reviewed demonstrates that the data, although suggestive, are far from unequivocal. Large trials are required to determine efficacy and appropriate dosing of each reviewed supplement. Continued research into the pathophysiology of supplements and depressive symptoms may also help to elucidate the etiological factors of depression. It is also clear that future research should take into consideration the significant overlap in the way that these supplements interfere in depressive symptoms, possibly utilizing multiple supplements in an attempt to produce a synergistic effect.

Of the supplements reviewed here, omega-3 fatty acids and B-vitamins (folate, B12, and B6) are the most thoroughly researched and have the most promising clinical efficacy. These supplements also appear to be effective as adjunctive therapy, especially when used in addition to SSRIs. Given the safety of these supplements, they are worth utilizing on a trial basis, especially as adjunctive treatments, because the literature indicates that the worst outcome would be no effect. Furthermore, they may be useful in patients who are resistant to trying pharmacotherapies. Although standards for dosing have not yet been established, clinical trials suggest that the best outcomes would result from the use of both EPA and DHA when utilizing omega-3 fatty acids and to the use of a B-complex that includes folate, vitamin B12, and vitamin B6 when utilizing B-vitamins. There is also no reason why these supplements cannot be used in tandem.

SAMe has also been extensively studied in clinical trials as compared with most other supplements because it has been utilized as an antidepressant internationally for several years. The literature indicates that oral SAMe may have efficacy in patients with treatment-resistant depression, has a significantly shorter onset of action than standard pharmacotherapies, and may also serve as an adjunctive treatment. The available data suggest that SAMe is safe at low doses. However, the ceiling dose, if there is one, has not yet been established. SAMe behaves in many ways like tricyclic antidepressants, and therefore should be monitored when utilized and caution should be taken when used in combination with tricyclic antidepressants. The known safety profile is such that it can be utilized in clinical practice, especially in patients who would benefit from a more immediate relief of symptoms and in patients for whom current interventions are not fully beneficial.

The available literature investigating 5-HTP and magnesium is insufficient to recommend use in clinical practice, but does suggest that additional research is indicated to determine whether these supplements have efficacy in clinical depression. The neurobiological basis for use of these supplements is sound; however, the volume of epidemiological and clinical studies is limited, and those that have been conducted have mixed results. Although a trial use of these supplements is unlikely to lead to notable adverse effects, the available data recommend trial use of the previously mentioned supplements first.

The studies reviewed here are all unique to depression except in the cases where alternative populations are noted in the text. Most interesting, several epidemiological studies reveal that the connection between omega-3 fatty acid consumption and rates of clinical depression. Although this association is observational, the evidence is convincing enough to suggest that there may be an underlying causal connection. In addition, several epidemiological studies suggest that there is a relationship between low B vitamin status and overall poor neurocognitive function. The association between low B vitamin status and clinical depression has also been established; epidemiological studies show an association between vitamin B12 deficiency and severe depression. However, the more intriguing relationship between low B vitamin status and depression is the association of increased plasma homocysteine levels in patients with clinical depression. Increased plasma homocysteine is a marker for vitamin B12 and folate deficiency, as well as impaired neurotransmitters function. This suggests that the synthesis of neurotransmitters may be impaired by low B vitamin status, supporting the monoamine hypothesis of depression.

Much of the available evidence establishes an observed association between nutritional deficiencies and clinical depression. The epidemiological evidence especially serves to point out deficiencies that already exist in populations with clinical depression, or broad mental illness/neurocognitive defects when noted. These theories are then tested in clinical trials within populations of individuals with diagnoses of clinical depression. As a result, many of the clinical trials are conducted using nutritional supplements as adjunctive treatments, because patients with a diagnosis are more likely to already be utilizing a treatment regimen. The trials with successful outcomes conducted in patients who are treatment resistant or who are not using pharmacotherapy are more convincing, but these are the minority. As a result, the majority of the data suggest a correlational relationship between clinical depression and nutritional deficiency. Further research is required to establish casual connections between nutritional deficiencies and clinical depression. As the etiology or etiologies of clinical depression become clearer over time, it will likely be easier to establish causal relationships between specific nutritional deficiencies and depressive symptoms.

Another important consideration is the commercial production and uniformity of available products. The bioavailability of these products is essential to their effectiveness and is not uniform throughout all available products. The efficacy of nutritional supplements in clinical practice greatly depends on the quality of the product. Many oral nutritional supplements available for purchase have limited efficacy as a result of low bioavailability. In some cases, accompanying dietary intake influences bioavailable. For example, magnesium is most bioavailable when taken in combination with calcium; however, calcium absorption is blocked by iron, but enhanced by acidic environments. Therefore, ingestion of a combination calcium and magnesium supplement with a protein source high in iron, a vegetable source high in iron, or an iron supplement will ultimately reduce magnesium absorption. Conversely, ingestion of a combination calcium and magnesium supplement with an acidic beverage, such as orange juice, would enhance absorption. Before utilizing nutritional supplements in clinical practice it is critical to identify commercial products that have well established bioavailability and are manufactured in facilities that are regularly monitored by a third party. It would also be helpful to recommend foods to avoid or to take with particular supplements.

Adherence to nutritional supplements has not been well studied and as a result there are no general recommendations for maintaining adherence in clinical practice. As the literature shows, it is unlikely that adverse effects will influence adherence as adverse effects from nutritional supplements in general are rare. Nutritional supplements may be cost prohibitive, however, because they are not covered by insurance and high-quality supplements can be expensive. As a result, identifying supplements with established quality that are as cost effective as possible would likely increase adherence. Another strategy may be to select one or two key supplements to keep the routine simple and inexpensive. For example, a good quality B-complex is inexpensive and readily available.

In addition, specific assessment and monitoring parameters have not been established for health care providers. Although the available evidence indicates that dietary supplementation results in few to no adverse effects, larger trials need to be conducted to determine safest dosing and whether adverse effects may arise at higher doses. It is also still unclear whether long-term use of dietary supplementation will result in the development of adverse effects or whether efficacy decreases over time. Another important consideration in terms of monitoring is the combination of SAMe or 5-HTP with pharmacotherapy.

Because 5-HTP is the biological precursor to serotonin, it is intuitive that serotonin syndrome could possibly result from the addition of 5-HTP to SSRIs. This combination has not been widely researched so this potential adverse effect should be closely monitored. Similarly, the combination of SAMe with tricyclic antidepressants may potentiate the adverse effects of these medications.

The most important lines of future research include large-scale RCTs with omega-3 fatty acids that explore adequate dosing and the appropriate combination of EPA and DHA. A treatment arm that includes omega-3 fatty acids as adjunctive treatments with SSRIs is indicated to build on the current evidence. A second priority would be to perform a large-scale RCT using SAMe as a long-term, stand-alone therapy. Understanding dosing and long-term adverse effects is critical. Third, parsing apart the roles of folate and vitamin B12 versus vitamin B6 in the neurobiology of depression is indicated; however, this task will be more feasible when the biological basis for clinical depression is better understood.

Taken together, the evidence points to the importance of continuing to pursue this area of research and suggests that nutritional supplements may be useful in clinical practice. At a baseline, health care providers should at least consider a patient's dietary quality and ensure adequate intake of omega-3 fatty acids, B-vitamins, and magnesium in the diet. Although dietary supplements can be utilized as a stand-alone therapy for the prevention and mitigation of depressive symptoms in clinical depression, these products would also be efficacious when pharmacotherapy is not indicated or inaccessible, for example, in perinatal depression, in low-income settings, and as combination therapy in treatment-resistant depression.

Author Contributions

K. Rechenberg is the sole author of this article and is responsible for its content.

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The author declared no conflicts of interest with respect to the authorship or the publication of this article.

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