

Review

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Review

Targeting Divergent Pathways in the Nutritional Management of Depression

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Abstract: Nutritional management of depression has long been discussed due to the perceived benefit of a nutritional product having less side effects than pharmaceutical agents. Candidate nutrients for managing depression include Vitamin D, B-vitamins, tryptophan, branch chain amino acids, probiotics, omega-3 fatty acids, folate/methylfolate (aka Vitamin B9), and s-adenosylmethionine. This paper reviews three nutrients which have significant scientific support for the management of depression and have evidence of low levels in subjects with depression, and that correction of the nutritional deficiency provides clinical benefit. We present epidemiological evidence, mechanistic explanation and a review of interventional studies for these nutrients. Finally, relevant nutritional guidelines are presented with their conclusion for the role of each nutrient in the management of depression.

Keywords: depression; nutrition; omega-3; EPA; methylfolate; s-adenosylmethionine; SAME

1. Introduction

Major Depressive Disorder (MDD) is one of the most challenging conditions of our time and constitutes one of the most prevalent mental health diagnoses globally. MDD induces profound impairments in cognitive, affective, and sensory experiences [1]. The World Health Organization (WHO) estimates that approximately 322 million people are currently affected by MDD (inclusive of dysthymia, now termed Persistent Depressive Disorder) [2]. This represents an increase exceeding 18% within the past decade, solidifying MDD's position as the leading global cause of disability and ill health [2].

It is worth noting that first-line antidepressants, typically selective serotonin re-uptake inhibitors (SSRIs) or serotonin-norepinephrine re-uptake inhibitors (SNRIs), fail to achieve remission in approximately two-thirds of patients with depression [3]. The often unsatisfactory experience with first-line medications alone may be partly due to depression arising from a complex interplay of factors. As detailed by Belmaker and Agam [4] "Avoidance of premature closure on any one scientific theory of the mechanism of depression will best serve the search for new, more effective treatments", thus supporting a multi-component approach to depression management.

One potential approach to managing depression, as either mono-therapy or as an adjunct to antidepressants, involves the use of nutritional supplementation, which can include vitamins, minerals, amino acids, phytonutrients, fatty acids, and other nutrient-based compounds. While the efficacy of many nutrient supplements for treating MDD is questionable, several have garnered considerable support from convergent sources of evidence, including preclinical (mechanistic) research to randomised controlled trials.

For instance, Howland (2012) performed a review of 5 nutrients in the management of depression [5]. Of the five products reviewed in this article (L-methylfolate, S-adenosyl-L-methionine

[SAM-e], omega-3 fatty acids, L-tryptophan, and inositol), only omega-3 fatty acids and SAM-e were found to have sufficient supporting evidence for their efficacy to warrant safe use. A similar conclusion was made in the nutraceutical review by Lande in 2020 [6] with the conclusion: “S-adenosylmethionine, l-methylfolate, omega-3 fatty acids, and hydroxyvitamin D have sufficient scientific evidence to support their clinical consideration in the stepped care approach to the management of depression.”

An additional review of clinical trials of nutritional supplements for MDD [7] found support for the use of omega-3, l-methyl-folate and SAMe, as well as Vitamin D, with the conclusion: “Current evidence supports adjunctive use of SAMe, methylfolate, omega-3, and vitamin D with antidepressants to reduce depressive symptoms.” Subsequently, a broad umbrella review conducted in 2019 which aggregated data from 33 meta-analyses of placebo- Randomised Controlled Trial (RCT)s across 10,951 individuals with psychiatric disorders found that the strongest evidence across the nutritional landscape was for eicosapentaenoic acid (EPA) as an adjunctive treatment for depression. This was closely followed by the positive data from RCTs of high-dose methylfolate in major depressive disorder, whilst other nutraceuticals (such as vitamin D, antioxidants and probiotics) had mixed or inconsistent results [8].

Such evidence has also been incorporated and summarised within global clinical guidelines for nutrient-based treatments of mental disorders, with the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines supporting omega-3 and l-methylfolate usage for depression, with SAMe having also potential therapeutic use, while noting limitations with lower doses or poorer quality formulas [9].

2. Materials and Methods

A review of literature relating to the nutritional components omega-3 lipids, methyl-folate and SAMe was performed. Searches were performed for the terms «depression» and «omega-3» or “folate” (for epidemiological studies) or “methyl-folate” (for intervention studies) or “s-adenosylmethionine”. Interventional studies were selected with the PubMed criteria “clinical trial” or “randomized controlled trial”. Generally, all studies deemed relevant are listed, with the exception of omega-3 in which studies reported were no earlier than 2016 (due to the plethora of data).

3. Results

Review of Mechanistic Data

EPA is considered to have an important role in maintenance of mood (e.g., depression) due to its role as an anti-inflammatory agent with neurochemical modulatory properties [10]. This hypothesis is supported by the findings by Firth et al. who reports in a meta-analysis of 14 interventional trials that benefits of EPA were noted in subjects with systemic inflammation and not in those with depression related to illness (i.e., non-inflammatory) [8]. In addition, higher doses of EPA had greatest effect on depression with DHA (docosahexaenoic acid):EPA formulations >50% EPA being most effective.

Neurochemical Modulation

EPA may also affect neuronal function. Synaptic plasticity increases with EPA which may play a role in neurotransmitter release and uptake and ion channel activity and is considered essential in depression [11]. Apoptosis from injury is reduced and EPA stimulates brain derived neurotrophic factor (BDNF) production which plays a role in neuronal function and health. Plasma membrane incorporation of EPA not only influences membrane fluidity, but also competes with arachidonic acid (AA). This is particularly true for EPA which having similar carbon length as AA competes with metabolising enzymes. AA is the precursor for inflammatory signalling molecules and EPA competition reduces the levels of inflammatory signals [12]. In addition, EPA incorporation into mitochondrial membranes stabilises mitochondrial function and reduces oxidative stress, a major factor for neuronal health, particularly in Alzheimer’s Disease [13]

Specialised Pro-Resolving Mediators

In 2000, Serhan et al. reported that inflammation resolution was a biochemically controlled, active process orchestrated by a host of lipid mediators called Specialised Pro-resolving Mediators (SPMs). This umbrella term includes several families of chemically and functionally distinct mediators termed lipoxins, resolvins, protectins and maresins. The SPMs down-regulate gene expression of inflammatory cytokines, blunt polymorphonuclear neutrophil (PMN) infiltration, decrease pro-inflammatory mediator production (both lipid mediators and cytokines), and stimulate macrophage-dependent uptake of apoptotic PMN, as well as bacterial clearance [14]. EPA, as well as DHA, DPA (docosapentaenoic acid) and arachidonic acid (AA) are precursors to a host of SPMs. Rapid metabolism of EPA to these pro-resolving mediators has been proposed as a hypothesis why EPA is barely detectable in the brain. Association of SPMs, inflammation and depression has been recently reported in patients with major depressive disorder [15].

Endocannabinoids

The Endocannabinoid system (ECS) is a neural system involved in the regulation of homeostasis. Cannabinoid receptors (CB1 and CB2) are found throughout the central and peripheral nervous system and play roles in diverse functions such as appetite control, food intake, energy balance, neuroprotection, neurodegenerative diseases, stroke, mood disorders, emesis, modulation of pain, and inflammatory responses. The natural ligands are lipid derived endocannabinoids (eCBs) which are membrane bound long chain fatty acids that are released on neuronal activation. The two principal eCBs, Anandamide (ANA) and 2-AG, are AA derived metabolites, while docosahexaenoyl ethanolamide is derived from the DHA and oleylethanolamide and palmitoylethanolamide and EPA-ethanolamide are derived from EPA [16].

In a clinical trial with MDD patients given either EPA, EPA+DHA or DHA alone, supplementation led to increases in eCBs relevant to the type of supplementation. Rates of clinical remission were significantly higher in those receiving EPA or EPA+DHA compared to DHA alone. The study concludes “Treatments enriched with EPA increased plasma EPEA levels, which was positively associated with clinical remission” [17] This suggests an endogenous role of EPEA in modulating depression.

Observational Studies of Omega-3 in Depression

Epidemiological studies are a beneficial means of showing population effects. This is of particular use in nutritional research where nutritional effects are often long term, mild and subject to influence by co-variants. Table 1 summarizes epidemiological data for omega-3 and depression. Many of the studies reported measure omega-3 fatty acids in blood. This is a more accurate means of measuring the dietary intake of omega-3 fatty acids than monitoring intake of food. Measurements made in plasma are reflective of the acute intake (i.e., values vary according to daily intake) whereas red blood cell measurements reflect the overall intake over several months. The majority of epidemiological studies support an association between omega-3 intake with depression/mood changes.

Studies are taken from the GOED clinical database [18] and PUBMED with the search “omega-3” “depression” from 2005.

Table 1. Epidemiological studies of seafood/omega-3 and depression.

Study	Design	Outcome
Bidirectional longitudinal associations of omega-3 polyunsaturated fatty acid plasma levels with depressive disorders [19]	Baseline and follow-up data collected from 2912 subjects with depressive disorder. Omega-3 levels measured by nuclear magnetic resonance.	n-3PUFA levels were significantly reduced at baseline in depressives compared to healthy. However, the difference dissipated over time. Changes in depressive

		disorders was not associated with a change in omega-3 levels.
Dietary intake of fish and n-3 polyunsaturated fatty acids and risk of postpartum depression: a nationwide longitudinal study—the Japan Environment and Children’s Study (JECS) [20]	81,294 women were followed up for 1 yr post birth. Omega-3 intake was assessed by a food frequency questionnaire and depression rated using the Kessler Psychological Distress Scale.	Multivariable logistic regression showed a reduced risk of postpartum depression at 6 months in the second to fifth quintiles v. the lowest quintile for fish and n-3 PUFA intake, with trend tests also revealing a significant linear association. At 1 year after delivery, fish intake was associated with a reduced risk of serious mental illness in the second to fifth quintiles v. the lowest quintile for fish and in the third to fifth quintiles v. the lowest quintile for n-3 PUFA intake, with trend tests also revealing a significant linear association
Serum n-3 polyunsaturated fatty acids are inversely associated with longitudinal changes in depressive symptoms during pregnancy [21]	Cohort of 172 Brazilian women. Depression measured with the Edinburgh Postnatal Depression scale during pregnancy. Blood measurements made of fatty acids.	Higher concentrations of EPA were associated with lower odds of depressive symptoms (OR 0.92). They detected a decrease in the probability of depressive symptoms as concentrations of total n-3 FA, α -linolenic acid, DPA, and DHA increased.
The Omega-3 Index Is Inversely Associated with Depressive Symptoms among Individuals with Elevated Oxidative Stress Biomarkers [22]	787 US based Puerto Ricans enrolled. Oxidative stress, omega-3 index and fatty acid profile, and depression rates (CES-D) assessed for 2 years.	An inverse association between the omega-3 index and depressive symptoms was observed among participants with elevated oxidative stress biomarkers. These data suggest that oxidative stress status may identify those who might benefit from v-3 FA consumption to improve depressive symptoms
High Levels of Depressive Symptoms in Pregnancy With Low Omega-3 Fatty Acid Intake From Fish [23]	Cohort study of pregnant women in the UK with an initial size of 14,541 pregnant women. Edinburgh Postnatal Depression Scale (EPDS) was measured at 32 weeks gestation.	Compared to women consuming more than 1.5 g omega-3 per week, those consuming none were likely to have high levels of depressive symptoms.
Cross-national comparisons of seafood consumption and rates of bipolar disorders [24].	Population based epidemiological study	Greater intake of seafood was associated with lower prevalence of bipolar disorders.
Fish and n-3 polyunsaturated fatty acid intake and depressive symptoms [25]	Cross sectional study in Japanese high schools with 3067 boys and 3450 girls aged 12-15. Self administered	Higher intake of fish, EPA and DHA was independently associated with a lower prevalence of depressive

	dietary questionnaire and depression measured with Epidemiologic Studies Depression scale score ≥ 16.	symptoms in male but not female adolescents.
Fatty acids intake and depressive symptomatology in a Greek sample: an epidemiological analysis [26]	453 men and 400 women aged 18-65 were assessed for depression using the Zung's self-rating depression scale. A food questionnaire was used to estimate omega-3 dietary intake and omega-3 fatty acids measured in plasma.	Increased plasma levels of polyunsaturated and mono-unsaturated fatty acids, in particular EPA and DHA were associated with lower levels of depression.
Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women [27]	Cohort study of 3317 from a Coronary Artery Risk Development study. Dietary intake of EPA, DHA or a combination was assessed.	The highest intake quintiles were associated with low risk of depressive symptoms. Associations were pronounced for women.
Depressive symptoms during pregnancy in relation to fish consumption and intake of n-3 polyunsaturated fatty acids [28]	Cohort study of 2394 pregnant women assessing pre-natal depression and dietary intake of EPA and DHA. Depressive symptoms were measured using the Center for Epidemiologic Studies—Depression Scale (CES-D). Intakes of fish and EPA+DHA were measured using a validated food-frequency questionnaire.	Depression was not associated with dietary intake of EPA and DHA except in certain sub-populations (smokers and single mothers).
Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults [29]	309 men and 218 women aged 21 to 67 years of age were assessed for depression using the Center for Epidemiologic Studies Depression scale and dietary intake assessed by questionnaire.	No association was noted between dietary intake and depression.
Fish consumption and risk of depression: Epidemiological evidence from prospective studies [30]	A meta-analysis of 10 cohort studies with 6672 cases of depression from 109,764 subjects.	A modest inverse association between fish or omega-3 fatty acid intake and risk of depression, especially in women.
Polyunsaturated Fatty Acids in Perinatal Depression: A Systematic Review and Meta-analysis [31,32]	Assessed levels of PUFA in pre-natally depressed women in 12 studies.	Significantly lower levels of PUFA (EPA and DHA) and increase omega-6:omega-3 ratios in pre-natal depressed women.
Fish consumption and depression: the Northern Finland 1966 birth cohort study [32]	5,689 men and women were followed from birth to 30. Amongst other things, fish consumption and depression were monitored.	In women, the risk of developing depression increased with low fish consumption but no association was seen with men

The observational studies reported in Table 1 strongly support the association of dietary omega-3 with depression. Of the 10 dietary studies, 2 reported no association of mental health with omega-3 intake, and 8 reported an inverse association of omega-3 intake with mental health (with 1 study only showing an association with women). In the 5 studies measuring omega-3 fatty acids in the blood (without intervention), all studies showed an association between omega-3 fatty acids levels and mental health.

A meta-analysis of 14 studies by Lin [33] showed that compared with control subjects, the levels of EPA, DHA, and total n-3 polyunsaturated fatty acids were significantly lower in depressive patients, whereas there was no significant change in AA or total n-6 polyunsaturated fatty acids.

The above data provides two important points, firstly the condition of MDD in some people may create a particular nutrient requirement for anti-inflammatory nutrients such as EPA. Secondly, there is compelling data that MDD patients have lower than normal levels of EPA either due to poor intake, or increased metabolism of EPA.

The 2015-2020 Dietary Guidelines for Americans (DGA) recommends levels of seafood intake of approximately 250mg of EPA and DHA daily [34]. Analysis of actual intakes using the NHANES database shows that women of childbearing age have less than half the DGA recommended intake [35]. NHANES data in women of child-bearing age show that supplementation provides an additional 26mg, 62mg and 88mg of EPA, DHA and EPA+DHA respectively. Consequently, over 95% of the study population did not have the recommended intake of 250mg EPA and DHA daily.

Interventional Studies of Omega-3 in Depression

Pubmed and GOED report a total of 151 intervention studies with omega-3 in the field of depression. A review of studies reported from 2016 to 2024 is given below.

Table 2. Interventional studies of omega-3 in depression (post-2016).

Study	Design	Outcome
Clinical response to EPA supplementation in patients with major depressive disorder is associated with higher plasma concentrations of pro-resolving lipid mediators [15,36]	61 patients with MDD enrolled to 1 of 4 arms, EPA at 1,2 or 4g/day or placebo. Depression was assessed using ICS-C30 scale.	Response rates greater in those taking 4g EPA/day and those with highest resolvins levels. These also showed the greatest reduction in CRP.
Omega-3 polyunsaturated fatty acids in cardiovascular diseases comorbid major depressive disorder—Results from a randomized controlled trial [37].	59 patients with CVD and MDD randomised to take 2g EPA+1gDHA per day or placebo for 12 weeks.	No overall effect of n-3 PUFA, but improvement of core depression symptoms was seen in the very severe MDD group with n-3 PUFA.
Plasma estradiol levels and antidepressant effects of omega-3 fatty acids in pregnant women [38].	108 Pregnant women with Edinburgh Postnatal Depression Scale scores ≥9 at 12-24 weeks of gestation participated. Subjects took 1206mg EPA or placebo daily for 12 weeks.	Increase in EPA was significantly associated with a decrease in depressive symptoms. There were no EPA associated changes in inflammatory cytokines.
Omega-3 polyunsaturated fatty acids and psychological intervention for workers with mild to moderate depression: A double-blind randomized controlled trial [39].	Subjects took 1g EPA and 0,5g DHA daily for 12 weeks or placebo.	The study suffered from a high number of drop-outs reducing the power of the study. The omega-3 and placebo group showed improved depression scores, but no significant difference was seen between the groups.

A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED) [40].	95 subjects suffering with depression were assessed for quality of life at 3 and 6 months following different dietary plans including fish oil supplementation. Red blood cell omega-3 levels were measured	Red blood cell omega-3 levels were associated with improved depression. Healthy dietary changes are achievable and, supplemented with fish oil, can improve mental health in people with depression.
Pilot Randomized Controlled Trial of Omega-3 and Individual-Family Psychoeducational Psychotherapy for Children and Adolescents With Depression [41].	72 youths randomised to omega-3 or placebo for 12 weeks.	Omega-3 was well tolerated and gave better remission rates than psychoeducational therapy alone, and placebo.
Effect of fish oil omega-3 fatty acids on reduction of depressive symptoms among HIV-seropositive pregnant women: a randomized, double-blind controlled trial [42].	282 HIV positive pregnant women enrolled in Nairobi and randomised to omega-3 or placebo for 8 weeks.	No statistical difference in depression score (BDI-II) was seen between the interventions.
Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders—Results from a double-blind, randomized and placebo-controlled clinical trial [43].	50 outpatients with MDD were randomized to omega-3 or placebo for 12 weeks. Questionnaires for depression, anxiety, sleep, intolerance and emotional regulation were taken and experts made a blinded assessment using the Montgomery-Asberg Depression scale	Depression by self-assessment and expert opinion decreased in the O3 group to a greater extent than placebo. PUFA gave greater reduction in anxiety, intolerance of uncertainty, and sleep disturbance.
The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial [44].	60 women with polycystic ovary syndrome were randomised to fish oil (2x1000mg) or placebo for 12 weeks.	Omega-3 led to a significant improvement in Beck Depression Inventory and depression anxiety and stress.
Long-Chain Omega-3 Fatty Acid Supplements in Depressed Heart Failure Patients: Results of the OCEAN Trial [45].	108 coronary heart failure patients with MDD. 3-way randomization, 2g of 400:200 or pure EPA or placebo for 12 weeks.	Omega-3 supplementation resulted in significant increases in omega-3 levels in red blood cell counts, corresponding to a particular compound of omega-3. Changes in cognitive depressive symptoms and social function were in favour of the omega-3 supplementation. Increasing omega-3 indices were associated with improved cognitive depressive symptoms.

A Double-Blind Placebo-Controlled Trial of Omega-3 Fatty Acids as a Monotherapy for Adolescent Depression [46].	51 adolescents with MDD diagnosis randomized to omega-3 or placebo for 10 weeks with increasing doses every 2 weeks	Omega-3 was not superior to placebo on any clinical feature, including depression severity.
The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome [47].	60 women with polycystic ovary syndrome randomised to VitD plus omega-3 or placebo for 12 weeks.	Omega-3 and Vit D resulted in significant improvements in Beck Depression Inventory, anxiety and stress scale scores.
Omega-3 supplementation effects on body weight and depression among dieter women with co-morbidity of depression and obesity compared with the placebo: A randomized clinical trial [48].	65 overweight/obese with depression randomized to 6 capsules of omega-3 (180mgEPA and 120mg DHA per cap) or placebo for 12 weeks.	Omega-3 significantly reduced depression compared to placebo. Weight was also significantly reduced in the omega-3 group.
Omega-3 fatty acids for a better mental state in working populations—Happy Nurse Project: A 52-week randomized controlled trial [49].	80 nurses were randomized to omega-3 (1200mg EPA, 600mg DHA, daily) or placebo for 13 weeks	No effect of omega-3 was seen, however depression scores were measured at weeks 26.
The effects of omega-3 and vitamin E co-supplementation on parameters of mental health and gene expression related to insulin and inflammation in subjects with polycystic ovary syndrome [50].	40 women with polycystic ovary syndrome were randomized to 1g omega-3 plus VitE or placebo for 12 weeks.	The omega-3/Vit E compared with placebo, led to significant improvements in beck depression inventory total score, depression anxiety and stress score scales.
Omega-3 supplementation associated with improved parent-rated executive function in youth with mood disorders: secondary analyses of the omega 3 and therapy (OATS) trials [51].	95 youths with depression or bipolar disorder were randomized to 2 capsules twice daily or placebo for 12 weeks.	Participants receiving Ω3 (aggregating combined and monotherapy) improved significantly more than aggregated placebo
Adjunctive low-dose docosahexaenoic acid (DHA) for major depression: An open-label pilot trial [52].	28 patients with MDD in an open label study taking low dose DHA (260mg or 520mg/day) for 8 weeks.	After 8 weeks there was a >50% reduction in the HAM-D scale. the results suggest that DHA may provide additional adjunctive benefits in patients with mild- to -moderate depression.
Emulsified omega-3 fatty-acids modulate the symptoms of depressive disorder in children and adolescents: a pilot study [53].	38 children with depressive disorder were randomized to omega-3 or omega-6 comparator. Childrens depression inventory ratings	Significant reduction in depression (CDI) scores were seen after 12 weeks intervention with the omega-3 group. A greater improvement was seen

	were performed every 2 weeks during 12 weeks intervention.	with those with depressive disorder compared to mixed anxiety depressive disorder.
Omega-3 supplementation from pregnancy to postpartum to prevent depressive symptoms: a randomized placebo-controlled trial [54].	60 women at risk for postpartum depression were randomized to fish oil (1.08g EPA, 0.72g DHA) or placebo for 16 weeks. The Edinburgh Postnatal Depression Scale (EPDS) was used, and serum fatty acids measured for compliance.	Increases in plasma EPA and DHA were seen with the fish oil group. No difference between intervention and control groups was seen for EPDS ≥ 11 , EPDS over time or from pregnancy to postpartum.
Lipid correlates of antidepressant response to omega-3 polyunsaturated fatty acid supplementation: A pilot study [55].	16 patients with major depressive disorder were given fish oil for 6 weeks. Depression was rated using the Hamilton Depression Rating Scale.	A reduction in depression severity showed a relationship with endpoint DHA plasma phospholipids. 5 patients showed remission and were distinguished from non-responders by higher levels of DHA.
Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients [56].	79 patients with coronary artery disease were recruited with depression measured using the 17-item Hamilton Depression Rating Scale. Patients were randomized to 1.9g PUFA or placebo for 12 weeks.	The n-3 PUFA group was associated with greater depressive symptom improvement. No association was found with the placebo group.
Psychoeducational Psychotherapy and Omega-3 Supplementation Improve Co-Occurring Behavioral Problems in Youth with Depression: Results from a Pilot RCT [57].	72 youths with depression were randomized to one of 4 treatments for therapy (PEP) and omega-3. Treatment were PEP+omega3, PEP monotherapy, omega-3 monotherapy or placebo. Assessments were made every 2 weeks up to 12 weeks. Assessments were made using the Eyberg Child Behaviour Inventory.	Youths receiving combined treatment had a significant behavioural improvement.
Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function and mental health of the oldest elderly in Japanese care facilities and nursing homes [58].	75 participants with dementia were recruited from elderly care facilities and nursing homes and randomized to meals containing 1720mg DHA or placebo for 12 months. Assessments were made using Hasegawa's Dementia Scale-Revised and the Mini-Mental State Examination. Mental health condition and self rating depression were also measured.	The DHA group showed a tendency for greater mental health, less apathy, reduced depression compared to placebo. DHA supplemented meals protect against age related decline.

Of the 23 studies listed, 18 studies reported significant improvements in depression with omega-3 supplementation. Of particular interest is the study by Parletta et al. Although this study did not specifically supplement with omega-3 (the study looked at the effect of a Mediterranean diet), depression was shown to be associated with red blood cell omega-3 levels, implying that an increase, or correction, of omega-3 levels is important in normalisation of mood. Jang et al., confirm this showing that supplementation resulted in increased omega-3 blood levels and improved mood, this study and others showing dose dependency support the concept that supplementation may potentially correct a nutritional requirement of EPA for the management of depression.

Guidelines Relevant to Omega-3 Use in Managing Depression

The International Society for Nutritional Psychiatry Research has developed the following 2019 guideline with regard to use of omega-3 fatty acids in depression:

The subcommittee of the International Society for Nutritional Psychiatry Research organized an expert panel and conducted a literature review and a Delphi process (decisions from a structured group of experts) to develop a consensus-based practice guideline for clinical use of n-3 PUFAs in MDD. With respect to formulation and dosage, both pure eicosapentaenoic acid (EPA) or an EPA/DHA combination of a ratio higher than 2 (EPA/DHA >2) is considered effective, and the recommended dosages should be 1-2 g of net EPA daily, from either pure EPA or an EPA/DHA (>2:1) formula [59].

Clinical Psychopharmacology and Neuroscience published a clinical guideline in 2020 for children and adolescents with MDD with the following recommendation [60]:

A combination of EPA + DHA of 1,000–2,000 mg/d, with EPA:DHA ratio of 2 to 1, for 12–16 weeks

Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytochemicals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce is a publication providing guidelines on nutrient use for depression [9]. The guideline has the following statement:

Omega-3 fatty acids at doses standardised to 1 g to 2 g of eicosapentaenoic acid (EPA) are Recommended for Adjunctive use in MDD; and Not Currently Recommended for Monotherapy use.

This position was held due to EPA having strongly clinical trial evidence for co-use with antidepressants, however some more recent data from monotherapy studies is less compelling, and the weaker effect size may be due to people being included in studies with pre-existing normal or high fish consumption.

Folate and Methyl-Folate in Depression

The Physiological Role of Folate/L-Methylfolate

Folate and its downstream metabolite, L-methylfolate, have pleiotropic activity with a role in 1 carbon metabolism, as an anti-inflammatory agent and as an important component in neurotransmitter synthesis.

Anti-Inflammatory Role

In the case of mood disorders, methylfolate (the bioactive form of folate) is important in the methylation of homocysteine to methionine and thereafter production of S-adenosylmethionine (SAME). A deficiency of folate which results in increased homocysteine is associated with neuroinflammation. Supplementation with 800 micrograms folate over a 2-week period significantly raised plasma folate levels and importantly significantly reduced circulating homocysteine levels [61]. Folate / methylfolate have a role in the homeostatic control of homocysteine and thereby indirectly regulate neuroinflammation [62].

One-Carbon Metabolism

The 1-carbon cycle/folate metabolic pathway is complex and regulates not only nucleotide synthesis but also DNA methylation. DNA methylation is a form of epigenetic control of DNA expression that has an impact throughout the genome and affects all body systems. Methylfolate is the predominant circulating form of folate and donates a methyl group to homocysteine in the generation of S-adenosylmethionine, a major source of methyl groups in the brain.

Synthesis of the depression-associated monoamine neurotransmitters serotonin, dopamine, and norepinephrine is regulated by L-methylfolate. For a review of L-methylfolate activity see Stahl, 2008 [63].

Methylfolate Metabolism

L-methylfolate is the metabolic product of folate metabolism catalysed by the enzyme methylenetetrahydrofolate reductase (MTHFR). The enzyme converts 5,10-MTHF to 5-MTHF. 5-MTHF then donates a methyl group in the conversion of homocysteine to methionine.

Polymorphisms are genetic variations seen in a healthy population and contribute to inter-individual variation. Several polymorphisms have been identified for the gene coding the folate metabolising enzyme MTHFR resulting in reduced enzymatic activity with subsequent lower levels of L-methylfolate. Since only L-methylfolate can cross the blood brain barrier, the concentration of folate in any form in the brain is dependent on the circulating levels of L-methylfolate [64]. Decreased or absent expression of MTHFR leads to decreased levels of 5-MTHF, which then leads to high levels of homocysteine. This results in suboptimal production of mono-amines, including serotonin, dopamine, and norepinephrine [65].

Polymorphisms in the MTHFR gene are seen in 2-20% of the general population with frequency being dependent on ethnicity [66]. However, the prevalence of these polymorphisms appear to 36%–82% higher in people with severe mental illness, with meta-analyses of population data showing MTHFR polymorphisms associated with major depression (Odds ratio (OR) 1.36), schizophrenia (OR 1.44) and bipolar disorder (OR 1.82) [66].

Polymorphisms in the MTHFR gene have been associated with depression. The Hordaland study demonstrated association of the C677T MTHFR and hyperhomocysteinemia with depression with an odds ratio of 1.69 [67]. In the same study the frequency of depression was compared between different variants of the 677 nucleotide. Of the 240 women recruited, approximately half had the C to T variant. A study in a population from Northern Ireland also found significantly higher occurrence of the C677T polymorphism in those with a history of depression [68].

In a separate analysis of the British Women's Heart and Health Study, a total of 3487 women were analysed for MTHFR genotype. The C to T heterozygous genotype was seen in 43.6% of women [69], these women had an associated increase risk of having had diagnosed depression. This finding is supported by a meta-analysis by the same authors of 8 smaller studies with a total of 669 cases which demonstrated the association of C to T transition with depression with an Odds ratio of 1.36 [69].

Interestingly, a study of pregnant women showed that folate supplementation could protect against depression outside of pregnancy. However, the protective function of supplemental folate was lost in women with a C to T polymorphism, indicating that folate supplementation is not effective in women in cases where there is a C to T polymorphism where folate is not efficiently converted to methylfolate and therefore not carried across the blood brain barrier [70].

Observational Studies of Folate in Depression

Studies describing folate levels in psychiatric disorders are presented in Table 3. Studies investigating depression associated with pregnancy have been excluded.

Table 3. Observational studies investigating folate deficiency in psychiatric disorders.

Study	Design	Outcome
Serum and red blood cell folate in depression [71]	Case control. 95 with major depression, 60 controls.	Significantly reduced serum and red blood cell folate levels in major depressive order vs controls. Lower serum levels were associated with severity of depression.
Red cell folate concentrations in psychiatric patients [72]	Case control. 152 psychiatrist-diagnosed depressed, 42 controls	Depressed patients had significantly reduced red cell folate levels compared to euthymic patients.
A controlled study of folate levels in Chinese inpatients with major depression in Hong Kong [73]	Case control. 117 major depressed, 72 without history of depression	Significantly lower mean serum levels of folate were seen in patients compared to control subjects.
Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study [74].	Patients >55 yrs of age. DSM-IV depression or dysthymia, n=112. 416 non-depressed age matched	Folate, Vitamin B12, and hyperhomocysteinemia were associated with depression
Vitamin B (12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study [75].	Women >65 years of age. 122 with severe depression on GDS score >14, 478 controls with GDS<9	No serum folate deficiency seen. Significant Vit B12 deficiency in depressed subjects related to severity.
Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study [67]	Patients 46-49 and 70-74. 243 with HAD>8, 5705 non depressed controls.	Hyperhomocystenemia was significantly related to depression but not plasma folate or Vitamin B12.
Dietary folate and depressive symptoms are associated in middle-aged Finnish men [76]	Population between 42 and 60 years of age. 2682 men and women recruited. 228 had elevated depression.	Population with lowest third of dietary intake of folate levels had significantly higher risk of having depressive symptoms
Dietary folate and the risk of depression in Finnish middle-aged men [77].	Population cohort of men 42-60 years old. 47 with diagnosis of major depression and 2313 controls without diagnosis of depression.	Low dietary intake of folate is a risk factor for severe depression.
Depression and folate status in the US Population [78].	Population cohort of subjects 15-39 years of age. 301 with major depression (DSM-III), 121 with dysthymia and 2526 controls.	Folate concentrations in serum and red blood cell were significantly lower in depressed subjects than those never being depressed. Dysthymic subjects had lower RBC folate but not serum folate compared to never depressed.

Plasma folate concentrations are associated with depressive symptoms in elderly Latina women despite folic acid fortification [79]	Latino population ≥60 years of age. 385 depressed with CES-D score>15, 1125 controls with CES-D ≤15.	Low folate status was associated with depressive symptoms in Latino women but not men.
Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults [29]	309 men and 218 women aged 21 to 67 years of age were assessed for depression using the Center for Epidemiologic Studies Depression scale and dietary intake assessed by questionnaire.	Higher dietary intake of folate was associated with a lower prevalence of depressive symptoms in Japanese men but not women.

Three dietary intake studies demonstrate a negative association of folate intake and depression [29,76,77]. These findings are supported by blood plasma measurements [72,73,78,79]. A study of 2,948 participants in the US in young adults showed significantly lower levels of plasma and red blood cell folate in major depression compared to those who had never been depressed [78].

The studies described above have varying designs in a variety of populations. Seven of the studies demonstrate an association between folate levels and depression, 2 studies showed no association and 1 study was equivocal. From the above studies it would therefore appear that folate deficiency is seen in the MDD population. One study reported low folate levels in Latino women with MDD but no association in men. Further studies would be required to confirm whether depression and folate levels vary in different populations.

In conclusion, the majority of studies support that low folate levels are associated with a number of psychiatric disorders including depression [80,81].

Interventional Studies of Methylfolate in Depression

Intervention studies of supplemental methylfolate in depression are presented in Table 4.

Table 4. Intervention studies with folate/methylfolate in MDD.

Study	Design	Outcome
L-methylfolate Augmentation to Antidepressants for Adolescents with Treatment-Resistant Depression: A Case Series [82]	10 females with treatment resistant depression, with 80% showing SNPs in MTHFR gene.	80% showed improvement in depression, anxiety and irritability with L-methylfolate.
L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials [83].	148 outpatients with SSRI resistant MDD were randomized to arms with l-methylfolate or placebo. A second study included 75 patients with the same protocol but higher doses of L-methylfolate.	The first arm with 7.5mg/day l-methyl folate showed no effect on outcome. The second trial showed significant effect of intervention. No safety findings.
L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode [84]	A retrospective analysis of L-methylfolate plus SSRI/SNRI in 242 subjects after 60 days therapy. Depression was measured with CGI-S.	L-methylfolate plus antidepressant treatment was more effective than monotherapy in depression and numbers showing major improvement and time to improvement.

Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized clinical trial [85].	75 patients with SSRI resistant MDD received 15mg/d methylfolate for 60 days or placebo for 30 days followed by methylfolate for 30 days, or 60 days of placebo.	Biomarkers associated with inflammation or metabolism and genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant depression who are responsive to adjunctive therapy with L-methylfolate 15 mg. Confirmatory studies are needed.
L-Methylfolate For Bipolar I depressive episodes: An open trial proof-of-concept registry [86].	Open label, single group study of 10 subjects with bipolar depression treated with 15 mg methylfolate and concurrent treatment for 6 weeks.	L-methylfolate in combination with treatment as usual has potential to treat bipolar depression.
Long-term efficacy, safety, and tolerability of L-methylfolate calcium 15 mg as adjunctive therapy with selective serotonin reuptake inhibitors: a 12-month, open-label study following a placebo-controlled acute study [87].	Analysis from 2 separate studies. Treatment resistant depression with 15mg methylfolate for 12 months. Of 68 subjects who met criteria for the 12-month open-label phase, 38% (n = 26) achieved full recovery, and none experienced a recurrence of MDD. See study for breakdown of further groups.	Adjunctive L-methylfolate 15 mg/d may be an early option in patients who fail to adequately respond to antidepressant monotherapy, with preliminary evidence demonstrating sustained remission and sustained recovery.
Enhancement of recovery from psychiatric illness by methylfolate [88].	Study measured the folate level in blood and effect of supplementation of 15mg methylfolate for 6 months.	33% of subjects had folate deficiency. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery
Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression [89].	22 adults with MDD and partial or nonresponsive to SSRI after at least 4weeks of treatment. Open label single arm trial with folinic acid (which is metabolised to methylfolate).	Folate levels rose in treated subjects. However, only 31% of completers and 27% achieved response and only 19% of completers and 18% achieved remission. Leucovorin appears to be modestly effective.
A prenatal supplement with methylfolate for the treatment and prevention of depression in women trying to conceive and during pregnancy [90].	12-week open-label study included women with histories of MDD who were planning pregnancy or pregnant < 28 weeks. Group 1 participants were well (not depressed) and planned to discontinue antidepressants for pregnancy. Group 2 participants were depressed	Group 1 participants (N = 11) experienced lower rates of depressive relapse (27.3%; $P = .005$) than expected from a historical comparison group and no significant changes in MADRS scores. Group 2 participants (N = 6) experienced significant improvements in MADRS scores ($P = .001$), with 5 (83.3%) improving >50% and 1 improving 33.3%

Assessing Effects of l-Methylfolate in Depression Management: Results of a Real-World Patient Experience Trial [91].	502 patients with MDD received 15mg or 7.5mg methylfolate for 3 months, without an anti-depressant. Depression was measured with the PHQ-score.	l-methylfolate achieved statistically significant improvements in self-reported depression symptoms and functioning and greater satisfaction with their medication treatment.
A retrospective examination of adjunctive L-methylfolate in children and adolescents with unipolar depression [92].	412 patients were retrospectively assessed for MTHFR genotype. Patients were more likely prescribed methylfolate if they carried a relevant SNP.	No difference was seen between methylfolate treated or non-treated groups
L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode [84].	Retrospective analysis of MDD patients with methylfolate plus SSRI/SNRI at treatment initiation (n=95) and SSRI/SNRI monotherapy (n=147)	Major improvement experienced by 18.5% of methylfolate patients compared to 7.04% with only SSRI/SNRI. L-methylfolate plus antidepressant at treatment onset was more effective in improving depressive symptoms and function measured by CGI-S scores within 60 days than antidepressant monotherapy

Of the 12 intervention studies reported above, 10 showed statistically significant improvements in MDD measurements, whilst 2 showed no effect of supplementation.

The intervention study by Godfrey *et al.* (1990) describes folate deficiency in 33% of depressives and that supplementation with methylfolate was beneficial for depression, implying that correction of the folate deficiency was instrumental in the management of depression [88]. This is further supported by the meta-analysis of MTHFR genotypes in depression, of particular interest in this analysis is the finding that folate concentrations were not associated with depression but the incidence of MTHFR polymorphisms were [68]. Taken together this presents two concepts, first that folate levels are associated with depression, and secondly that a subset of subjects with MTHFR polymorphisms may have folate independent reduction in l-methylfolate.

Guidelines

Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce is a publication providing guidelines on nutrient use for depression. The guideline has the following statements:

Methylfolate (15 mg) per day is Provisionally Recommended for Adjunctive use in MDD. Folic acid is however not recommended [9]. This position was held due to the majority of the evidence being for methylfolate, with certain larger studies involving folic acid not demonstrating antidepressant effects.

S-adenosyl Methionine in Depression

Mechanism of Action

S-adenosyl methionine (SAmE) is an amino acid found throughout the body, and acts as a co-substrate for methyl transfer. Methylation is important in many systems including methylation of genetic material (an important epigenetic mechanism), and cellular growth and repair. SAmE is

synthesized through the pathway known as the 1-carbon cycle and is a derivative of folate metabolism as previously described. Folate and SAME metabolism are intimately associated through 1-carbon metabolism [93]. SAME is also important in the synthesis of various neurotransmitters in the brain such as dopamine, serotonin and norepinephrine (also known as noradrenaline) [94].

Studies by Pfeiffer [95] and Edelman [96] demonstrate that SAME acts as a methyl donor, facilitating the breakdown of histamine into N-methyl-histamine, a non-reactive metabolite. SAME itself is synthesized from L-methionine and adenosine triphosphate (ATP) via the one-carbon cycle, which requires adequate folate and vitamin B12 levels [97]. This suggests that individuals with high histamine may benefit from SAME supplementation, potentially normalizing brain histamine levels through the process of methylation [95]. Conversely, those with low or normal histamine levels might see less benefit, assuming histamine plays a significant role in their depression. Beyond histamine, Cimino et al. suggest SAME may influence neuronal function by increasing the conversion of phosphatidylethanolamine to phosphatidylcholine. This enhances cell membrane fluidity, potentially improving neurotransmission through increased receptor availability or efficiency [98].

Membrane dynamics can also significantly impact cellular communication [99,100]. Studies, including that by Cohen et al. (1987) have detailed a decreased membrane microviscosity in patients with dementia treated with intravenous SAME. Research on depressed outpatients [101] has however yielded inconsistent results with oral SAME. While some patients exhibited increased membrane fluidity, others were found to show a decrease or no change.

Another interesting mechanism of action links methylfolate and SAME metabolism to depression. Homocysteine is normally metabolised to SAME with folate as a co-factor. The MTHFR enzyme is also involved in this activity and polymorphisms leading to reduced enzyme activity, additionally a reduction in folate can lead to reduced levels of SAME which, as explained earlier, reduces the ability to synthesise the neurotransmitters dopamine, serotonin and noradrenalin. Hyperhomocystenaemia can lead to a production of homocysteic acid and cysteine sulfonic acid which is potentially neurotoxic to dopaminergic nerves [102].

Low SAME levels in depression

While there is not dietary deficiency of SAME per se (given it is not available via dietary consumption), people may present with lower levels in the central nervous system. SAME levels in blood have been shown to be significantly lower in women compared to men [103] which is striking, given the higher prevalence of MDD in women [104]. Measurements in cerebral spinal fluid (CSF) show low SAME levels associated with depression [105] as shown in Table 5. Additionally, the enzyme responsible for SAME production is lower in patients with depression and schizophrenia [106].

Table 5. Levels of SAME in CSF.

	N	CSF levels of SAME (ng/mL)
Healthy controls	13	64.5
Depressed	35	56.0*

*p= 0.0054. Ref: [105].

Importantly, oral supplementation of SAME at a dose level of 1200mg daily for 4 -8 months significantly increased the CSF levels of SAME, demonstrating that oral intake is able to correct a SAME deficiency [105] see Table 6. Similar results were also seen in plasma.

Table 6. SAME levels in CSF following oral SAME supplementation.

	N	CSF SAME (ng/mL)
Pre-supplementation	4	35.5
Post-supplementation	4	66.0*

*p=0.0054. Ref: [105].

Observational studies of SAME in depression

No observational studies for SAME have been conducted as SAME is not normally obtained through diet, however deficiency in SAME has been linked to depression [106] as a result of low levels of folate and Vitamin B12 which are precursors to SAME [107].

Interventional studies of SAME in depression

Studies found from Pubmed search with the terms “S adenosyl methionine” and “Depression” from 1990 for interventional studies are presented in Table 7. The search was performed 23 September 2022.

Table 7. Nutritional studies with SAME supplementation.

Study	Design	Outcome
A Prospective Randomized Double-Blind Study Evaluating UP165 and S-Adenosyl-L-Methionine on Depression, Anxiety and Psychological Well-Being [108]	42 subjects were randomized to 8 weeks of supplementation with corn or SAME. Questionnaires performed at baseline, 4 and 8 weeks. Primary endpoint was the effect of corn leaf derivative on depression. Secondary endpoint was to see effect of SAME on depression.	SAME demonstrated a trend for improvement
Dose increase of S-Adenosyl-Methionine and escitalopram in a randomized clinical trial for major depressive disorder [109]	Subjects who showed no effect of 1600mg SAME recruited to test effect of 3200mg SAME	Dose effect was seen 3200mg
S-adenosyl-L-methionine (SAME) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine [110].	Thirty antidepressant-treated adult outpatients with persisting major depressive disorder received 800 to 1600 mg of S-adenosyl-L-methionine tosylate over a 6-week trial.	A response rate of 50% and a remission rate of 43% following augmentation with S-adenosyl-L-methionine
S-Adenosyl-L-Methionine augmentation in patients with stage II treatment-resistant major depressive disorder: an open label, fixed dose, single-blind study [111].	Thirty-three outpatients with major depressive episode who failed to respond to at least 8 weeks of treatment with two adequate and stable doses of antidepressants were treated openly with fixed dose of SAME (800 mg) for 8 weeks, added to existing medication. The study has limitations as single arm	At 8 weeks, a significant decrease in HAM-D score was observed with response achieved by 60% of the patients and remission by 36%
Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAME) in the treatment of major	143 MDD subjects received oral SAME 1600mg daily for 6 weeks vs 138 subjects on imipramine in a second arm. Imipramine is a tricyclic antidepressant.	The antidepressive efficacy of 1600 mg SAME/d orally and 400 mg SAME/d intramuscularly is comparable with that of 150

depression: comparison with imipramine in 2 multi-center studies [112]		mg imipramine/d orally, but SAME is significantly better tolerated.
S-Adenosylmethionine (SAME) monotherapy for depression: an 8-week double-blind, randomised, controlled trial [113]	An 8-week, double-blind, randomised controlled trial testing 800 mg/day of SAME tosylate monotherapy versus placebo in 49 patients with MDD	A clinically relevant differential reduction from baseline to week 8 of 3.76 points occurred on the primary outcome (MADRS) in favour of SAME over placebo (however due to a very high placebo response the effect was not-significant).
S-adenosyl methionine (SAME) versus escitalopram and placebo in major depression RCT: efficacy and effects of histamine and carnitine as moderators of response [114]	144 subjects with MDD randomized to SAME (1600-3200mg/daily), escitalopram (10-20mg/daily), or matching placebo for 12 weeks of double-blind treatment. Data analysis was from a larger study, and involved more men than women.	In this sub-analysis study, on the primary outcome of the Hamilton Depression Rating Scale (HAM-D-17), a significant difference in improvement was observed between groups from baseline to week 12
Bioavailability of S-adenosyl methionine and impact on response in a randomized, double-blind, placebo-controlled trial in major depressive disorder [115]	35 subjects taking placebo or SAME 800-1600 mg/day for 6 weeks in partial SSRI responders with MDD.	Blood levels of SAME were increased with supplementation. No clinical effect was seen
S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant non-responders with major depressive disorder: a double-blind, randomized clinical trial [116]	73 serotonin reuptake inhibitor (SRI) non-responders with major depressive disorder enrolled in a 6-week, double-blind, randomized trial of adjunctive oral SAME (target dose: 800 mg/twice daily). Subjects continued on the standard treatment. The primary outcome measure for the study was the response rates according to the 17-item Hamilton Depression Rating Scale (HAM-D).	The HAM-D response and remission rates were higher for patients treated with adjunctive SAME (36.1% and 25.8%, respectively) than adjunctive placebo (17.6% versus 11.7%, respectively).
Oral Administration of S-Adenosylmethionine (SAME) and <i>Lactobacillus Plantarum</i> HEAL9 Improves the Mild-To-Moderate Symptoms of Depression: A Randomized, Double-Blind, Placebo-Controlled Study [117].	Ninety patients were randomized to SAME (200mg daily) plus <i>L. plantarum</i> HEAL9 (n = 46) or placebo (n = 44) groups for 6 weeks.	A greater reduction for the combination compared to placebo was seen at treatment week 6 in the Z-SDS total score (P = .0165) and the core depression subdomain (P = .0247). Supplementation of SAME and <i>L. plantarum</i> HEAL9 in adults with subthreshold or mild-to-moderate symptoms of depression resulted in fast

		and clinically relevant effects after 2 weeks
An augmentation study of MSI-195 (S-adenosylmethionine) in Major Depressive Disorder [118].	A 6-week double-blind, placebo-controlled, augmentation study (800mg) comparing S-adenosylmethionine or placebo added to antidepressant medication in acutely depressed subjects with Major Depressive Disorder. Scales used were (HamD17, MADRS, IDS-SR30)	There were no overall statistically significant differences found between groups.
Adjunctive S-adenosylmethionine (SAME) in treating non-remittent major depressive disorder: An 8-week double-blind, randomized, controlled trial [119]	An 8-week, double-blind RCT in which 107 treatment non-remittent outpatients with DSM-5 diagnosed MDD were randomized to either SAME tosylate (800mg) or placebo adjunctively to antidepressants.	No significant between-group difference observed. Due to such a distinctly high placebo-response, Author's commented that future studies should employ a placebo run-in period.
Nutraceuticals for major depressive disorder- more is not merrier: An 8-week double-blind, randomised, controlled trial [120].	8-week, double-blind, RCT involving 158 outpatients with a DSM-5 diagnosis of MDD. The intervention consisted of a nutraceutical combination: S-adenosyl methionine (800mg); Folinic acid; Omega-3 fatty acids; 5-HTP, Zinc picolinate, and relevant co-factors versus placebo. The primary outcome was change in MADRS score.	Placebo was superior to the nutraceutical combination in reducing MADRS score (due to a high placebo response rate)
Is S-Adenosyl Methionine (SAME) for Depression Only Effective in Males? A Re-Analysis of Data from a Randomized Clinical Trial [121].	Data from a 2-site, 12-week, double-blind RCT (n=189) assessing the efficacy of SAME (1600-3200mg) vs. placebo and a comparator selective serotonin reuptake inhibitor (escitalopram) were subjected to post-hoc analyses to evaluate effects of patient gender on treatment response.	SAME was superior to placebo among males (n=51), but not among females (n=62). The underlying mechanism is still relatively unknown.
Effects of S-adenosylmethionine augmentation of serotonin-reuptake inhibitor antidepressants on cognitive symptoms of major depressive disorder [122].	Forty-six serotonin-reuptake inhibitor (SRI) non-responders with MDD enrolled in a 6-week, double-blind, trial with SAME (DOSE) or placebo. Efficacy assessed with the self-rated cognitive and physical symptoms questionnaire (CPFQ), as well as physical symptoms of MDD, before and after treatment.	A greater improvement in the ability to recall information (P=0.04) and a trend towards statistical significance for greater improvement in word-finding (P=0.09) for patients who received adjunctive SAME than placebo.
A double-blind, randomized, placebo-	One hundred eighty-nine outpatients with DSM-IV-	Remission rates were 28% for SAME, 28% for escitalopram,

controlled clinical trial of S-adenosyl-L-methionine (SAME) versus escitalopram in major depressive disorder [123].	diagnosed major depressive disorder (MDD) were recruited. Subjects were randomized to either SAME (1600-3200mg), escitalopram (10-20mg) or placebo for 13-18 weeks.	and 17% for placebo. The results fail to support an advantage over placebo for either the investigational treatment SAME or the standard treatment escitalopram for MDD.
A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAME) versus imipramine in patients with major depressive disorder [124]	A total of 146 patients received SAME and 147 received IMI (an anti-depressive drug) for a period of 4 wk. The two main efficacy measures were endpoint HAMD score and percentage of responders to Clinical Global Impression (CGI) at week 4. SAME was injected intramuscularly.	These data show 400 mg/d i.m. SAME to be comparable to 150 mg/d oral IMI in terms of antidepressive efficacy, but significantly better tolerated.
S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial [125]	13 depressed patients with PD. SAME was administered in doses of 800 to 3600 mg per day for a period of 10 weeks. Eleven patients completed the study. Subjects had previously taken anti-depressives without effect.	10 of 13 showed at least 50% improvement in HDS. Although uncontrolled and preliminary, this study suggests that SAM is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease.
Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women [126]	80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAME 1,600 mg/day or placebo.	There was a significantly greater improvement in depressive symptoms in the group treated with SAME compared to the placebo group from day 10 of the study.
The antidepressant potential of oral S-adenosyl-L-methionine [101]	20 outpatients with major depression, including those with (n = 9) and without (n = 11) prior history of antidepressant nonresponse.	The group as a whole significantly improved with oral SAME: 7 of 11 non-treatment-resistant and 2 of 9 treatment-resistant patients experienced full antidepressant response.

Of the 22 interventional studies reported above, 15 showed significant improvements in depression with SAME supplementation.

Guidelines

Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytochemicals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian

Network for Mood and Anxiety Treatments (CANMAT) Taskforce is a publication providing guidelines on nutrient use for depression. The guideline has the following statement:

SAMe at 1600 mg–3200 mg is Weakly Recommended for Adjunctive use in MDD [9]. This position was held based on recent SAMe study data which did not reveal statistical significance over placebo. For note, there has been concerns raised over some studies having a very high placebo response rate, using too low a dose of SAMe, or stability issues.

5. Conclusions

The globally increasing prevalence of MDD, combined with the suboptimal response rates to standard antidepressant therapies, creates an urgent need for alternative and/or additional treatment options. Therefore, this review aimed to evaluate the efficacy of three evidence-based nutritional supplements (omega-3 fatty acids, methylfolate, and S-adenosylmethionine (SAMe)) in the management of depression, both as monotherapy and as adjuncts to conventional antidepressant treatments. Here, we have systematically presented findings from a broad range of study designs, including epidemiological research, clinical RCTs, meta-analyses, and clinical guidelines.

In doing this, we aimed to describe the theoretical rationale and empirical evidence around adjunctive use of these specific nutrients, for addressing both common nutritional deficiencies associated with MDD, and enhancing the efficacy of traditional antidepressants. Within this, a number of notable findings emerged, including (i) how omega-3 fatty acids may modulate inflammatory pathways and neurotransmitter functions (which are often dysregulated in MDD), (ii) the role of polymorphisms in the gene for folate metabolism in depression, (iii) methylfolate's role in the production of neurotransmitters and homocysteine metabolism, and (iii) SAMe's involvement in certain methylation processes implicated in the onset and treatment of depressive symptoms.

The efficacy of any nutrient for any health claim is dependent on product stability. In the case of omega-3 these lipids are readily oxidised due to their high level of desaturation. Typically, this is reduced by inclusion of anti-oxidants in the oil and the careful monitoring of primary and secondary oxidation during manufacturing. S-adenosylmethionine is notoriously unstable due to hydrolysis and commercially this is mitigated by tosylation. However, the compound remains unstable and studies that do not report stability have the limitation that lack of efficacy may result from lack of product.

The complementary but independent biological pathways of the nutrients reviewed also raises a clear possibility of additional benefit when using these nutrients in combination. Whilst combination studies have not been reported, the concept of a multicomponent approach is in keeping with the hypothesis that depression may have multiple-pathway aetiology. Such approaches align well with emerging trends in mental health research, which widely advocate for more use of “personalised medicine”, ideally through strategies that can cater to individual variation in dietary intake, nutrient metabolism and genetic factors which influence response.

Overall, this review identifies a body of evidence supportive of the role of omega-3 fatty acids, methylfolate, and SAMe as potentially useful compounds in the management of depression, while also noting where key research gaps exist. Continuing to investigate the mechanistic pathways and individual factors which determine the effectiveness of these nutraceuticals, either as standalone treatments or in unison with each other and other pharmaceutical options, will prove valuable for informing clinical and personal uses of nutrition for managing depression.

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Conflicts of Interest: DT and JS. are advisory board representatives for HedoniaUSA, which formulates and sells nutraceutical and medical food products. JS is employed and holds equity with Psychae Therapeutics. AV is a practicing psychiatric physician associated with McLean Hospital MA, in addition to being shareholder and founder of HedoniaUSA, Inc.

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