

Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments

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A literature review was conducted to examine the evidence for nutritional interventions in depression. It revealed a number of significant conclusions. Interestingly, more positive clinical trials were found to support adjuvant, rather than monotherapeutic, use of nutrients to treat depression. Much evidence exists in the area of adjuvant application of folic acid, S-adenosyl-methionine, omega-3, and L-tryptophan with antidepressants. Current evidence does not support omega-3 as an effective monotherapy to treat depression. However, this may be due, at least in part, to olive oil being used as the control intervention, some studies using docosahexaenoic acid alone or a higher docosahexaenoic acid to eicosapentaenoic acid ratio, and significant heterogeneity regarding depressive populations. Nevertheless, adjunctive prescription of omega-3 with antidepressants, or in people with dietary deficiency, may be beneficial. Inositol lacks evidence as an effective antidepressant and cannot be currently recommended. Evidence on the use of L-tryptophan for depression is inconclusive, and additional studies utilizing a more robust methodology are required.

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INTRODUCTION

Major depressive disorder (MDD) is characterized by either a low mood, or a loss of pleasure, in combination with changes in appetite, sleep, or energy, and is often accompanied by feelings of guilt or worthlessness or suicidal thoughts.¹ For a diagnosis of MDD to be reached, the episode's duration must be longer than two weeks and be uncomplicated by recent grief, substance abuse, or a medical condition.² MDD presents a significant socioeconomic burden, and is projected by the year 2020 to produce the second greatest impact on disability-adjusted life years, after cardiovascular disease.³ The lifetime prevalence of depressive disorders varies depending on country, age, sex and socioeconomic group, and approximates about one in six people.^{4,5} The sociological and financial impact of MDD is immense, and early, judicious, sustained treatment can improve outcomes and reduce overall costs

such as days of work or reduced productivity.⁶ Current medical treatments for MDD primarily involve synthetic antidepressants (e.g., tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors), and psychological interventions (e.g., cognitive behavioral therapy, interpersonal therapy).^{1,7} The main nutrients commonly prescribed as thymoleptic agents in clinical practice include omega-3 fish oils, S-adenosyl-methionine (SAME), L-tryptophan, and folic acid.⁸ Other nutrients with potential for mood modulation include magnesium, zinc, B_{1,3,5,6} vitamins, and inositol. Many nutrients function in biochemical reactions throughout the body in symphony with other factors. Attempting to create a physiological change via the prescription of a single nutrient is ambitious, given the complex nature of other nutritional intake and of internal biochemical mechanisms.

Depression does appear to be linked to poor nutritional status. Poor dietary intake and low serum levels of

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nutrients such as omega-3 and folate, increase risk of depressive symptoms.^{9–11} Human clinical trials on depression have been conducted using various nutrients as monotherapies, or adjuvant therapies, with synthetic antidepressants.¹² The aim of this review is to identify the current evidence for nutrients that are effective for the prevention or treatment of MDD. It describes the major clinical evidence, revealed via a systematic search of databases (Medline, Web of Science, and Cochrane Library), and it suggests potential avenues for further research.

Omega-3 fatty acids

A rise in depressive symptoms appears to be correlated with lower dietary omega-3 fish oil (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]),^{9,11,13,14} and people with depression have a tendency towards a higher ratio of serum arachidonic acid to essential fatty acid.^{15–17} Low erythrocyte and plasma concentrations of omega-3 have been correlated with a higher instance of depression compared to healthy controls.¹⁸ Urbanized Western cultures tend to have a far higher ratio of dietary omega-6 oils compared to omega-3 oils.¹⁴ The pathophysiology occurring from a pro-omega-6 diet may involve an increased promotion of inflammatory eicosanoids, a lessening of brain-derived neurotrophic factor, and a decrease in neuronal cell membrane fluidity and communication.^{11,19} Evidence currently suggests that omega-3 fatty acids exert antidepressant activity via beneficial effects on neurotransmission.²⁰ This may occur via modulation of neurotransmitter (norepinephrine, dopamine, and serotonin) re-uptake, degradation, synthesis, and receptor-binding.^{21,22} Animal models have demonstrated that omega-3 fatty acids increase serotonin and dopamine concentrations in the frontal cortex, and that a diet deficient in the nutrient decreases catecholamine synthesis.^{21,23,24} A recent human clinical trial demonstrated a significant increase in plasma concentrations of norepinephrine in healthy humans following supplementation with omega-3 fatty acid.²²

Several randomized controlled trials (RCTs) using omega-3 preparations have been conducted. A meta-analysis by Lin et al.²⁵ examined data from nine pooled studies. Omega-3 preparations demonstrated a positive benefit of omega-3 over placebo (*d*, a measure of the difference in standard deviation units, was 0.61). Appleton et al.¹³ found a similar effect size (*d* = 0.73) from pooled results of eight RCTs of n-3 long-chain polyunsaturated fatty acids on major depression. Effects of the studies were statistically heterogeneous, with publication bias appearing to be the main reason. Differences in methodology (e.g., dosage, length of study, blinding protocol, randomization), outcome measures used (e.g., different depression scales), types of preparation, and par-

ticipant characteristics were also seen between studies. A Cochrane review of omega-3 in the treatment of bipolar depression²⁶ included only one study (Frangou, 2006) due to very strict inclusion criteria. That study found a significant effect over placebo for depression, but a non-significant effect on mania.

Aside from adjuvant use of omega-3 with “treatment as usual” or antidepressants, there are several inconclusive studies using omega-3 monotherapy in samples of depressed human adults. While most reviews have included data from adjuvant omega-3 studies, recent human clinical trials of omega-3 (or fish oil) monotherapy in depressive disorders reveal no increased benefit over placebo.^{27–29} It should be noted, however, that in both the Rogers et al.²⁷ and Grenyer et al.²⁹ studies, olive oil was used as the “inert” control (in Mangarell et al.²⁸ the composition of the control was not stated). Olive oil plays a role in the maintenance of the physiochemical properties of membranes, via its ability to increase the delta-9 desaturase enzyme activity.^{30,31} As Stoll et al.³² argues, even though the use of such a small amount of olive oil may have minimal psychotropic effect, it should not be dismissed and needs further investigation. Also, the Marangell et al.²⁸ study used DHA alone, and the studies of Grenyer et al.²⁹ and Rogers et al.²⁷ used a higher ratio of DHA to EPA. As EPA is the fatty acid ester that exerts neuromodulation, its absence should be questioned.

Omega-3 studies of specific populations (children, pregnant women, and women with post-partum depression) have revealed positive results. A 16-week study conducted by Nemets et al.,³³ involving 28 children aged 6–12 years with diagnosed MDD, was conducted using a combination of EPA (400 mg/day) and DHA (200 mg/day). Results on the Childhood Depression Rating Scale³⁴ and Clinical Global Impression³⁵ revealed a significant reduction in depression in the omega-3 group (*n* = 10) compared to placebo (*n* = 10) after week 8. Seven of ten children in the active group were classified as responders to the treatment compared to none of ten in the placebo group. An 8-week clinical trial of 36 pregnant women with diagnosed MDD investigated the use of a preparation of omega-3 (3.4 g/day); the results showed a significantly greater reduction in depression on the Hamilton Rating Scale for Depression (HRSD)³⁶ and the Edinburgh Postnatal Depression Scale (EPDS)³⁷ at week 6 and week 8 (62% versus 27%).³⁸ The intervention was well tolerated, and no adverse effects occurred on the newborns. This pilot study encourages further research in this population. Omega-3 is required for optimal fetal development, and pregnancy may place the mother at greater risk of deficiency.

In an eight-week, open-label, three-arm pilot study using omega-3 fish oils (0.5 g/day, *n* = 6; 1.4 g/day, *n* = 3;

2.8 g/day, $n = 7$) to treat post-partum depression, all groups showed a significant decrease in depression on the EPDS and HRSD.³⁹ There were no dose-related differences. The small sample and absence of placebo control limit a confident interpretation of the results. A controlled study of 80 women (41 depressed, 39 healthy controls) conducted to examine the relationship between fish consumption, omega-3 polyunsaturated fatty acids, and depression found that neither prenatal fish consumption nor postnatal omega-3 status was prognostic of postnatal depression.⁴⁰

Adjuvant studies have been conducted using omega-3 fish oils with antidepressants to increase the therapeutic outcome. An eight-week, randomized, double-blind augmentation study using 20 mg of fluoxetine with 1 g of EPA in 60 depressed patients who were non-responsive to antidepressants, demonstrated a significantly greater reduction on HRSD than fluoxetine alone or placebo.⁴¹ The response rate from EPA (>50% decrease on HRSD) was 81% compared with 56% and 50% for fluoxetine and placebo, respectively. An eight-week clinical trial using 6.6 g/day of omega-3 concomitantly in 32 non-responders to established treatment, demonstrated a 13.6-point mean decrease on the HRSD, compared with 6.4 in the placebo group ($d = 1.85$).⁴² A four-week controlled study ($n = 20$) using 2 g daily of EPA in patients with non-response to stabilized antidepressants also showed significant benefit ($d = 2.92$).⁴³ One gram, or 4 g per day, of EPA was effective as an adjuvant agent in a 12-week study of 70 subjects with non-response to unspecified antidepressants.⁴⁴ These positive studies support recommending the adjuvant use of omega-3 (high EPA preparations) with synthetic antidepressants.

Folate

Deficiency of folate (as assessed via low dietary intake or low serum level) has been demonstrated consistently in depressive populations and in poor responders to antidepressants,^{10,45} with approximately one-third of people showing this deficiency suffering from depressive disorders.¹⁰ One hypothesis explaining the relationship between folate deficiency and a poor antidepressant response relates to the homocysteine hypothesis.^{46,47} Folate is involved with methylation pathways in the “one-carbon” cycle, and is responsible for the metabolism and synthesis of various monoamines. Folate is also most notably involved with synthesis of SAME (an endogenous antidepressant) from homocysteine.⁴⁶ In consequence, folate deficiency is associated with increased homocysteine levels. Increased homocysteine levels are seen in depressive groups compared with healthy controls.⁴⁶

Several studies have assessed the antidepressant effect in humans of folic acid with concomitant antide-

pressant use.⁴⁸⁻⁵⁰ All yielded positive results in regard to enhancing either antidepressant response rates or increasing the onset of response. An example study conducted by Coppen et al.⁴⁸ used 500 mcg of folic acid or placebo adjuvantly with 20 mg fluoxetine in 127 subjects with a HRSD score of ≥ 20 . There was a statistically significant reduction in HRSD scores after 10 weeks for women in the fluoxetine plus folic acid condition (-11.7 ± 6.7 ; $d = 0.73$) compared with fluoxetine plus placebo (-6.8 ± 4.1). However, a beneficial effect was not seen in the male sample.

The effect of folic acid supplementation on depression is currently being evaluated in a large UK-based RCT involving 730 human participants.⁵¹ The study “FolATED” will assess the effect of folic acid augmentation (5 mg/day) and will evaluate the cost-effectiveness of folic acid, whether baseline folate status can predict response to antidepressant response, and whether effects are moderated by specific genetic polymorphisms.

A potential confounding variable in some negative studies is the necessity of adequate vitamin B₁₂ status in order for the methylation reaction involving folate, SAME, and homocysteine to occur. During the remethylation of homocysteine, the methyl group is acquired from N-5-methyltetrahydrofolate, which is catalyzed by the B₁₂-containing enzyme N-5-methyltetrahydrofolate-homocysteine methyltransferase.⁵² These substances also function as methyl donors for a variety of brain compounds, including tetrahydrobiopterin (BH₄), which is an essential coenzyme in the activation of enzymes that manufacture monoamine neurotransmitters such as serotonin and dopamine from their corresponding amino acids.⁵³ Vitamin C is also necessary to produce BH₄. A study conducted by Hesecker et al.⁵⁴ administered ascorbic acid to over 1000 men aged 17–29 years with suboptimal status at baseline; the results showed that this led to less depression, along with decreased nervousness and emotional lability. Vitamin B₆ is also essential in the manufacture of all of the monoamine neurotransmitters; therefore, a B₆ deficiency may also negatively impact the depression outcomes in clinical trials of folic acid. In light of these issues, assessment of the adequacy of these nutrients in patients with MDD prior to the administration of drug therapy may be prudent. The use of synergistic formulations in future clinical trials using folic acid should be considered.

S-adenosyl-methionine

The sulphur-containing compound SAME has been studied for several decades in depression trials.⁵⁵ SAME serves as a necessary methyl donor of methyl groups involved with the metabolism and synthesis of neurotransmitters.^{50,56} SAME has demonstrated antidepres-

sant activity, with effects comparable to those of synthetic antidepressants.⁵⁵ Human clinical trials using SAME in subjects with MDD consistently demonstrate a beneficial effect,^{57–62} although the studies show heterogeneity in dosage and trial length, and many do not have adequate controls or blinding.

Studies of adjuvant therapy suggest that SAME can increase proportions of antidepressant responders, or improve the speed of response to antidepressants. An example of such a study was conducted by Alpert et al.⁵⁸ The six-week, open-label study gave 800–1600 mg/day of SAME to 30 non-responders to SSRIs or venlafaxine. An intention-to-treat analysis revealed that adjuvant use of SAME significantly reduced depression from baseline to week six, as measured on the HRSD. Intramuscularly administered SAME (200 mg/day) has demonstrated a significant increase in the onset of response to imipramine (150 mg/day).⁶¹ A significant effect became apparent by day four and remained until day 12, after which there was no difference between groups.

It should be noted that most clinical studies involve parenteral or intramuscular injections of SAME, rather than oral preparations.⁵⁶ Mode of administration should be considered when interpreting results of clinical studies (due to differing pharmacokinetic profiles affecting absorption, metabolism, and ability to cross the blood-brain barrier). SAME should be used with caution in patients with a history of (hypo)mania, due to concerns over potential switching from unipolar depression to mania. Furthermore, the therapeutic dosage of oral SAME has not been studied sufficiently to date. SAME is also expensive, and the cost may be prohibitive for some. Less expensive production of SAME and governmental subsidization could improve affordability.

Inositol

An initial positive pilot trial was conducted by Levine et al.⁶³ The double-blind, controlled, four-week study using 12 g/day of inositol in 28 participants demonstrated statistically significant antidepressant activity in comparison with placebo. However, two subsequent double-blind, controlled studies ($n = 27$, $n = 42$) using inositol as an augmenting agent with SSRIs^{64,65} demonstrated no significant difference between adjuvant use of inositol or placebo. Inositol augmentation was used in the STAR-D depression study (a large antidepressant augmentation trial), and revealed no significant effect on increasing antidepressant response.⁶⁶

Amino acids

Essential monoamine precursor amino acids are required for synthesis of dopamine, norepinephrine, and seroto-

nin.^{67,68} L-tryptophan has been studied extensively as an antidepressant.⁶⁹ Review of the literature revealed many studies had small sample sizes, poor outcome measures, and publication bias. Currently there are insufficient data to inform clinical practice. Only one RCT of sufficient merit was located. This trial involved 115 participants with depression and it compared L-tryptophan to placebo, L-tryptophan-amitriptyline combination, or amitriptyline.⁷⁰ It showed that the amino acid was equally as effective as the antidepressants and superior to the placebo. Eight controlled studies of adjuvant therapy were located in the current review. L-tryptophan augmentation was found to be effective in increasing the antidepressant response with phenazine sulphate,⁷¹ clomipramine,^{72,73} tranylcypromine,⁷⁴ and fluoxetine.⁷⁵ Earlier clinical studies using tricyclics showed no adjunctive benefit compared with placebo,^{76,77} although many of those studies were of weak methodological design.

The process to convert L-tryptophan into serotonin goes through an intermediary step to produce L-5-hydroxytryptophan (5-HTP), which has also been studied for use as an antidepressant agent and has been found to be more effective in improving depression than its precursor amino acid tryptophan.⁷⁸ One reason for this effect may be that L-tryptophan is metabolized through the kynurenine pathway to synthesize vitamin B₃; therefore, it may not be utilized for serotonin synthesis in the presence of vitamin B₃ deficiency because the body prioritizes niacin manufacture over serotonin. The enzyme needed for the conversion of L-tryptophan to 5-HTP is also dependent on adequate vitamin B₆, vitamin C, and BH₄.⁷⁹ As a result, a deficiency of any of these nutrients in subjects taking tryptophan would confound results. Another factor that needs consideration is the fact that the large, neutral amino acids (LNAAs) such as tryptophan, phenylalanine, and tyrosine, compete for common carrier molecules for transport into neurons. They should therefore be supplemented in the absence of protein-containing foods in order to maximize efficacy. Also, a carbohydrate-rich, low-protein meal can increase the ratio of L-tryptophan to other LNAAs and its subsequent availability to the brain; this is due to insulin stimulating the uptake of most of the LNAAs, other than tryptophan, into muscles.⁸⁰ Despite the potential of 5-HTP to be a superior thymoleptic agent in comparison to L-tryptophan, its final conversion to serotonin also requires adequate levels of zinc, magnesium, and vitamin B₆ for enzyme function.⁸¹ As a result, future studies should assess the efficacy of serotonin precursors, along with their synergistic nutrients, in order to optimize outcomes.

Amino acids DL-phenylalanine and L-tyrosine – precursors to dopamine and norepinephrine – may provide antidepressant activity, but no human clinical trial of sufficient methodological rigor could be located.

When considering these amino acids, their concomitant conversion enzyme cofactor nutrients need to also be considered. These include the iron- and BH₄-dependent enzyme tryptophan hydroxylase, which converts tyrosine to L-DOPA, and B⁶-dependent dopa decarboxylase, which converts L-DOPA to dopamine, as well as dopamine oxidase, which is next in line to convert dopamine to norepinephrine in a vitamin C-, copper- and iron-dependent reaction.⁸²

CONCLUSION

More positive clinical trials were found on the adjuvant, rather than monotherapeutic, use of nutrients for depression. In particular, the evidence does not currently support omega-3 as an effective monotherapy for depression. This conclusion is in conflict with some previous reviews and meta-analyses that cautiously advocated the use of omega-3 as an effective antidepressant monotherapy. Our conclusion, however, is moderated by the observation of substantial heterogeneity in methodology and results, use of DHA or higher DHA-to-EPA ratio, and potential confounding of olive oil as an inert control in many trials.

In contrast, the adjuvant application of folic acid, SAME, omega-3, and L-tryptophan with antidepressants appears to have substantial evidentiary support. Adjunctive prescription of nutritional supplements, such as omega-3, in people with deficient dietary intake may be especially beneficial.

Evidence indicating inositol is an effective antidepressant is lacking, so this treatment cannot be currently recommended. Evidence on the use of L-tryptophan for treating MDD is inconclusive, with no robust RCTs having been conducted on MDD to date. The use of 5-HTP in a synergistic formula with magnesium, zinc, and vitamin B₆ warrants further study. Other untested nutrients may have a role to play as primary or adjuvant interventions for MDD, and the promising results from folic acid and SAME should encourage further research.

Addressing deficiencies in clinical trials by using single nutrients may have limited value if other nutrient cofactors are required for its metabolism and biological activity. Further robust research is needed on the use of synergistic nutrient combinations, especially in cases of specific nutrient deficiency.

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