

Nutrients and herbal supplements for mental health

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SUMMARY

Some nutrient supplements and herbal medicines have supportive evidence for efficacy in some mental health disorders, other products do not.

Omega-3 fatty acids (eicosapentaenoic acid), St John's wort (high quality, standardised extracts), S-adenosyl-methionine and zinc may be beneficial in improving mood.

N-acetyl cysteine has shown some effects in bipolar depression and may be of benefit in obsessive compulsive disorder.

Kava is effective for reducing anxiety. However, there have been concerns about hepatotoxicity.

It is important to be aware of potential drug interactions between prescription drugs, herbal medicines and supplements. Patients should be asked which products they are taking.

Introduction

Mental health concerns are a major reason why people (especially middle-aged women) use nutrient or herbal-based supplements.¹ Due to increased community use, it is important to know which products have evidence of efficacy.

Another consideration for people using supplements is cost. While some products such as folic acid or omega-3 fish oils may be as little as \$5 per week, others such as S-adenosyl-methionine may cost up to \$70 per week. Quality is also an issue, with variations occurring between products, particularly herbal medicines.²

Diet, supplementation and mental health

There are a variety of relationships between diet, supplementation and mental health.

Poor diet as a risk for mental health symptoms

Some nutritional deficiencies, such as vitamin B and zinc, are associated with depression. A diet consisting of processed and 'junk' foods, as opposed to a wholefood diet of lean meats, fish, whole grains, fruit and vegetables, may be a risk factor for mental disorders. After confounding factors such as socioeconomic status were adjusted for, cross-sectional and longitudinal data revealed that poor diet is associated with increased depressive and anxiety symptoms.^{3,4}

Dietary supplementation to prevent mental health symptoms

Adding nutrient supplements to the diet has not been shown to prevent the development of psychiatric disorders.

Supplementation to treat mental health symptoms

Several supplements have evidence of therapeutic activity. However, there are some for which there is no consistent supportive evidence. Examples of these include valerian for insomnia, St John's wort in anxiety disorders or attention deficit hyperactivity disorder, N-acetyl cysteine or docosahexaenoic acid (DHA) fatty acids for unipolar depression, and omega-3 for mania. Interestingly, 'adjunctive' prescription of a range of nutrients – such as omega-3 fatty acids, folic acid, N-acetyl cysteine, S-adenosyl-methionine and zinc – with various medicines has been shown to have a beneficial effect in improving treatment beyond that of placebo.⁵⁻⁷

Supplements for mood

A number of supplements have been studied for improving general mood or treating major depression. Of these, omega-3 fatty acids, St John's wort, S-adenosyl-methionine, N-acetyl cysteine and zinc are the most researched and commonly used.

Omega-3 fatty acids

Epidemiological studies have shown that a lower dietary intake of omega-3 oils – eicosapentaenoic acid (EPA) and DHA – may be correlated with an increased risk of depressive symptoms.⁸ Dozens of clinical trials on major depression have assessed the efficacy of these fatty acids alone or in combination with selective serotonin reuptake inhibitors.^{9,10} Clinical trials have not commonly compared omega-3 fatty acids directly with selective serotonin reuptake inhibitors. A meta-analysis revealed that EPA (or higher ratio of EPA to DHA) supplementation may have a stronger

antidepressant effect than DHA.¹¹ The comparison found supplements containing more than 50% EPA were significantly better than placebo ($p=0.005$), whereas there was no significant difference with DHA monotherapy.

In bipolar depression, a meta-analysis of five pooled datasets from 291 patients found a significant effect in favour of omega-3 fatty acids ($p=0.029$) for reducing depression, with a moderate effect size.¹² The current weight of evidence supports EPA or EPA-rich omega-3 fatty acids as adjunctive treatment in bipolar depression.

S-adenosyl-methionine

Double-blind studies have shown that parenteral and oral preparations of S-adenosyl-methionine are as effective for treating depression as standard tricyclic antidepressants such as clomipramine, amitriptyline and imipramine, and tend to produce relatively fewer adverse effects.¹³ In a six-week randomised controlled trial involving 73 patients with major depression, S-adenosyl-methionine added to selective serotonin reuptake inhibitors (SSRIs) produced significantly greater clinical responses and remission rates compared to adding placebo.¹⁴ Aside from being expensive, S-adenosyl-methionine appears well tolerated with only mild adverse effects such as headaches, restlessness, insomnia and gastrointestinal upsets.¹⁵

St John's wort

St John's wort has been studied for treating depression in over 40 clinical trials of varying methodological quality. A Cochrane review of 29 trials (5489 patients) analysed 18 comparisons of St John's wort with placebo and 17 comparisons with antidepressants. It revealed that participants were significantly more likely to respond to St John's wort than to placebo (relative risk of 1.48, confidence interval 1.23–1.77), but results from the studies were very heterogeneous. In the same analysis, St John's wort had an equivalent effect to SSRIs (relative risk of response 1.00, CI 0.90–1.15).¹⁶

A long-term follow-up study of St John's wort (standardised European extract WS 5570) for mild to moderate depression assessed remission rates in 426 responders who either continued St John's wort or changed to placebo for 26 weeks.¹⁷ People continuing St John's wort had a significantly longer time in remission. Response to St John's wort was similar to that of SSRIs, with data indicating that an initial partial response is predictive of full response (which usually occurs within 2–4 weeks).¹⁸

Because of the risk of drug interactions (see Drug interactions with complementary medicines, Aust

Prescr 2010;33:177–80), people taking other medicines should only use St John's wort with low hyperforin (<4 mg per tablet). Products standardised for higher amounts of hypericin and flavonoids should not induce cytochrome enzymes.¹⁹ Amounts of hypericin are usually identified on St John's wort products, however hyperforin quantities are often not detailed. St John's wort should not be taken with antidepressants as serotonin syndrome can occur.

N-acetyl cysteine

N-acetyl cysteine is an amino acid with strong antioxidant properties and has a history of use in the management of paracetamol overdose. It has been found to significantly reduce depression in bipolar disorder. In a 24-week placebo-controlled trial of 75 people with bipolar disorder, 1 g of N-acetyl cysteine twice per day significantly reduced depression on the Montgomery-Asberg Depression Rating Scale ($p=0.002$).²⁰ N-acetyl cysteine appears to cause no common significant adverse effects. Currently, it is only available from compounding pharmacies or from overseas.

Zinc

There is emerging evidence that zinc improves depressed mood. A recent review of randomised controlled trials found four studies (pooled sample of 469 participants) that met inclusion criteria.⁶ In two of the studies that used zinc monotherapy (sample sizes of 60 and 20), zinc as an adjunct to antidepressants significantly lowered depression ($p<0.001$) at 12 weeks. Zinc can be safely prescribed up to 30 mg elemental per day, with amino acid or picolinate chelations being advised to improve absorption. Zinc may cause nausea on an empty stomach.

Multivitamins

Multivitamins (in particular formulations high in B vitamins) may provide an acute mood enhancement and decreased perceived stress. A meta-analysis of eight studies involving a pooled sample of 1292 people revealed that supplementation for a duration of at least 28 days reduced perceived stress ($p=0.001$), mild psychiatric symptoms such as low mood ($p=0.001$) and anxiety ($p<0.001$), but not depression ($p=0.089$).²¹ A recent 16-week randomised controlled trial of 182 participants found that while qualitative data revealed an improvement in mood and energy with multivitamins,²² the quantitative data did not support any effect beyond placebo.²³ The authors concluded that while an acute effect may occur directly after supplementation, this is diminished after the supplement is withdrawn, with no chronic effect occurring.

Supplements for anxiety

While several herbal medicines have been studied in anxiety, data are largely absent for nutrients. The most researched and used herbal medicine in the treatment of anxiety is kava. Other limited research indicates a possible beneficial effect for ginkgo, passionflower, chamomile, skullcap, lemon balm and bacopa.

Kava

Occasionally, patients may be taking kava. This is a perennial plant native to various regions of the South Pacific.²⁴ The roots are traditionally prepared as a water-based beverage which has medicinal and psychotropic properties.²⁵ Water-soluble extracts are available in Australia at maximum daily doses of 250 mg of kavalactones, approximately four to five tablets per day. While kava has been implicated in cases of abuse in the Northern Territory, commonly in combination with alcohol, research has shown it is not addictive when used at therapeutic doses.²⁶

A Cochrane review of kava for various anxiety disorders, involving seven studies with a pooled sample size of 380 participants, found a statistically significant mean reduction of 3.9 points on the Hamilton Anxiety Scale over placebo.²⁷ This result is comparable to antidepressant medicines. Another analysis of kava studies revealed a similar conclusion, with a positive result occurring in four out of six studies.²⁴ In a recent six-week placebo-controlled trial involving 75 participants with generalised anxiety disorder and no comorbid mood disorder, kava (120 mg titrated to a maximum of 240 mg of kavalactones per day after three weeks if the patient was not responding) reduced anxiety compared to the placebo, with a moderate effect size ($p=0.046$).²⁸ No other significant differences between groups occurred for any other adverse effects including liver function. Further research should compare kava to an established treatment for anxiety, such as cognitive behavioural therapy.

Kava was withdrawn from European and UK markets in 2002 due to concerns over reported hepatotoxicity. This may have been due to previous preparations being made using acetone or ethanol extractions from potentially contaminated or poorly stored material, or other parts of the plant.^{29,30} Use of only the peeled roots from noble cultivars using a water solute extraction method is advised (see the kava fact sheet by the Therapeutic Goods Administration www.tga.gov.au/safety/alerts-medicine-kava-050421.htm). Occasional liver function tests should be performed during regular use. Alcohol and benzodiazepines should be avoided.³¹ Currently

no safety data support or refute the use of kava concurrently with antidepressant drugs, and caution is urged.

N-acetyl cysteine

The role of glutamate dysfunction in obsessive compulsive disorder and related disorders, such as compulsive hair pulling³² or skin picking, has been established. N-acetyl cysteine, a glutamate modulator, has been studied as a treatment for these disorders.

A 12-week double-blind randomised controlled trial involving 48 patients with obsessive compulsive disorder was conducted in Iran.³³ N-acetyl cysteine was titrated from 600 mg/day to a maximum of 2400 mg/day. Symptom severity was assessed at four week intervals. N-acetyl cysteine was significantly better than placebo for ameliorating symptoms according to the Yale-Brown Obsessive Compulsive Disorder scale ($p=0.003$). N-acetyl cysteine has a good tolerability profile.

Supplements for cognition

Due to our ageing population, increasing research is being conducted on supplements that may have a beneficial role for cognition. Current data do not support this approach to prevent dementia. The greatest area of research concerns multivitamins, and the plant medicines ginkgo and bacopa. Other plants less well studied include lemon balm and sage, in addition to polyphenols from cocoa, pinebark and tea. Although adequate vitamin and nutrient concentrations are necessary for neurological functioning, there is no scientific agreement as to whether they prevent cognitive decline or enhance mental functioning. While a dietary deficit of omega-3 fatty acids may negatively affect cognition, supplementation appears to not exert any significant pro-cognitive effects.

Multivitamins

A meta-analysis of 10 randomised controlled trials (≥ 1 month) involving 3200 people found that oral multivitamins were effective in improving immediate free recall memory ($p<0.01$), but not verbal fluency ($p=0.26$) or delayed free recall memory ($p=0.33$).³⁴

Ginkgo

Ginkgo, in particular the standardised extract 761, has been studied for cognitive-enhancing properties for several decades. Initial research suggested it was superior to placebo in enhancing cognitive function and quality of life and reducing neuropsychiatric symptoms (such as low mood) in patients with mild to moderate dementia, and that it had additive effects with donepezil.³⁵ However, this appears not to be the

case. A recent randomised controlled trial involving 2854 adults aged 70 years or older, who had reported problems with their memory, found that ginkgo (120 mg extract 761 twice per day) did not reduce the risk of progression to Alzheimer's disease compared to placebo. After five years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (1.2 cases per 100 person-years) compared with 73 in the placebo group (1.4 cases per 100 person-years, $p=0.306$).³⁶

Ginkgo has several potential drug interactions.³⁷ It should not be used concurrently with anticoagulant and antiplatelet medicines, and should not be taken in the week before surgery.

Conclusion

Patients take a range of nutrient and herbal-based supplements for a number of mental health problems. While there is evidence of efficacy for some supplements, for many there are little or no data.² Prescribers should be mindful of differences between the quality and standardisation of supplements, and potential drug interactions.³⁷ ◀

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