This document has been written for clinicians. The content was developed by the Integrative Medicine Program, Department of Family Medicine, University of Wisconsin-Madison School of Medicine and Public Health in cooperation with Pacific Institute for Research and Evaluation, under contract to the Office of Patient Centered Care and Cultural Transformation, Veterans Health Administration.

Information is organized according to the diagram above, the Components of Proactive Health and Well-Being. While conventional treatments may be covered to some degree, the focus is on other areas of Whole Health that are less likely to be covered elsewhere and may be less familiar to most readers. There is no intention to dismiss what conventional care has to offer. Rather, you are encouraged to learn more about other approaches and how they may be used to complement conventional care. The ultimate decision to use a given approach should be based on many factors, including patient preferences, clinician comfort level, efficacy data, safety, and accessibility. No one approach is right for everyone; personalizing care is of fundamental importance.
WHOLE HEALTH: CHANGE THE CONVERSATION
Dietary Supplements and Mood
Clinical Tool

Dietary Supplements

**Note:** Please see the module on [Dietary Supplements](#) for more information about how to determine whether or not a specific supplement is appropriate for a given individual. Supplements are not regulated with the same degree of oversight as medications, and it is important that clinicians keep this in mind. Products vary greatly in terms of accuracy of labeling, presence of adulterants, and the legitimacy of claims made by the manufacturer.

What follows is summary of some of the key research regarding various dietary supplements for the treatment of depressive disorders. Please note that this covers the most-studied and most-used supplements in the U.S., but there are many more that your patients might be taking as well.

**Dietary Supplements: Non-botanicals**

Omega-3’s, folate, magnesium, and zinc are on the VA formulary. The others listed below are not; Veterans typically have to pay for them out of pocket.

**Folate**
Folate is known to be linked to serotonin metabolism,\(^1\) mostly due to its role in methylation reactions that form the rate-limiting step in the production of neurotransmitters like serotonin.\(^2\) Trials identified in a 2004 Cochrane review did not find evidence of adverse effects for folate. Limited evidence suggests folate may have a potential role as an adjunct to other treatments for depression.\(^3\)

**Inositol**
A Cochrane review identified two depression studies where inositol had marginally more responders in depression than placebo (\(p = 0.06\)). However, inositol also marginally caused gastrointestinal upset compared with placebo (\(p = 0.06\)). Inositol supplementation may have limited benefit for depression.\(^4\)

**Magnesium**
The use of magnesium to treat depression dates back 100 years ago, when magnesium sulfate was injected hypodermically and found to be helpful in patients with agitated depression.\(^5\) Magnesium’s mechanism of action is unknown, but it may be related to the glutamatergic mechanism, since magnesium acts as physiological NMDA receptor antagonist.\(^6\) Systematic reviews suggest that magnesium may be effective in the treatment of depression, but evidence is limited.
overall. Oral magnesium supplementation may prevent depression and might be used as an adjunctive therapy, but further research is needed.7

**Omega-3 fatty acids**
People with depression have been found to have a deficiency of omega-3 fatty acids or an imbalance in the ratio of omega-6 and omega-3 fatty acids.8 Synaptic membrane fluidity is significantly determined by cholesterol and dietary polyunsaturated fat levels. Therefore, optimal proportion of these elements is postulated to have an impact in depression.9 A clinically relevant antidepressant effect was demonstrated recently in a post hoc analysis of depressed patients who supplemented their diets with omega-3 fatty acids (DHA/EPA) in addition to taking their conventional antidepressants.10 Interestingly, in rat models, diets rich in omega-3 led to increased hippocampal neurogenesis.9 Furthermore, an elevated ratio of omega-6 to omega-3 fatty acids predicts depression development following interferon-alpha treatment.11 A low omega-3 index in late pregnancy was associated with a higher depression score three months postpartum.12

**Probiotics**
Taking probiotics daily may modulate immune function and mood. For mood benefits, *Bifidobacterium infantis* has been found especially useful.13,14 One billion colony forming units (CFUs) is a good starting point, and taking a variety of different species may be best. It is recommended that they be taken for at least two weeks and up to two months.

**S-adenosyl methionine (SAMe)**
Pronounced “Sammy,” S-adenosyl methionine is an amino acid derivative that is found in virtually all body tissues and fluids. It plays a role in over 100 biochemical reactions, most of which involve the transfer of methyl groups. SAMe is important for the synthesis and metabolism of proteins, nucleic acids, neurotransmitters, hormones, and many other compounds. Deficiencies of B12 and folate are linked to low levels of SAMe in the nervous system. SAMe’s mechanism of action is unknown, but higher SAMe levels have been linked to increased serotonin turnover and elevated dopamine and norepinephrine levels. Severely depressed patients often have low levels of SAMe in the spinal fluid, and SAMe supplementation can normalize them.15

SAMe is often used for treatment of both depression and also pain. Some people refer to it as the supplement equivalent of duloxetine (Cymbalta). SAMe significantly improves symptoms of depression.16 SAMe tends to have a more rapid onset than many antidepressants, so some clinicians may use it as a stopgap while waiting for drug therapies to take effect.17 It can significantly improve remission rates in depressed patients who do not respond to medications. Seven people with non-responsive depression need to be treated with SAMe (dose of 400-800 milligrams) to have one additional remission.
SAMe tends to be quite safe. Side effects can occur with high doses, such as nausea, vomiting, diarrhea, constipation, nervousness, dry mouth, and headache, but these tend to be minimal in comparison with side effects from antidepressants. Dosing ranges from 400 milligrams to 1600 milligrams daily divided into two doses. SAMe’s biggest drawback is that it can be quite expensive to purchase over the counter.

**Tryptophan and 5-hydroxytryptophan (5-HTP)**
A Cochrane review found that in 2 out of 108 trials, tryptophan and 5-HTP were better than placebo at alleviating depression. Further research is warranted to evaluate the efficacy and safety, as there is a possible association between these substances and the potentially fatal eosinophilia myalgia syndrome. Most authorities agree this was largely attributable to contamination of a specific batch of supplements made by one company.

**Zinc**
Research suggests potential benefits of zinc supplementation for depression, either as a stand-alone therapy or as an adjunct to drug therapy. However, a recent systematic review of randomized controlled trials found methodological limitations in existing studies and recommended further research.

**Dietary supplements: Botanicals**
Recently, there has been a 50% increase in the number of studies of botanicals for depression, including a number of epigenetic studies. Surveys indicate that 44% - 54% of depressed patients have used herbal remedies in the past 12 months. Most research to date has focused on the use of botanicals for mild to moderate depression.

Botanicals differ from medications, most notably because they are polyvalent. That is, they contain multiple chemicals that may contribute to therapeutic benefit that may work in synergy to bring about a therapeutic effect. This is thought to lead to a lower rate of side effects but also to difficulty in standardization. Since depressive disorders tend to be associated with comorbid anxiety and other psychiatric disorders, the use of polypharmacy in psychiatry is increasing; antipsychotics are often used along with antidepressants. Botanicals may, in some ways, have a similar effect; in both cases, the use of multiple different psychoactive compounds can be beneficial.

**St. John’s wort (Hypericum perforatum)**
This supplement is typically dosed at 300 milligrams three times a day standardized to between 3% and 6% hyperforin and not less than 6% flavonoids for depression. Outcomes in many studies include reduction in scores on the Hamilton Rating Scale for Depression (HAMD), lower relapse rate, and longer time to relapse compared
to placebo groups. Three studies showed an effect of St. John’s wort that was comparable with pharmaceuticals.

If anyone ever asks what botanical has the most interactions with medications, it is St. John’s wort. It alters the cytochrome P-450 3A4 detoxification pathway. Caution should be used with taking St. John’s wort with antiretrovirals, warfarin, cyclosporine, or oral contraceptives, among other medications. Because it is known to be a mild MAO-I, similar dietary and medication interaction precautions should be taken as with a MAO-I drug. St. John’s wort is not just an herbal SSRI; it seems to affect multiple different biochemical pathways.

**Roseroot (**_Rhodiola rosea_**)**
Roseroot significantly improved HAMD scores as well as insomnia, somatization, and emotional instability subscale outcome measures. The dose studied was 340 milligrams daily of standardized extracts.

**Saffron (**_Crocus sativus_**)**
Saffron demonstrated significant improvement for depression over placebo on the HAMD. Petals and stamens were used in doses of 30 milligrams daily. Equivalent therapeutic response was demonstrated for saffron, imipramine 100 milligrams daily, and fluoxetine at 20 milligrams twice daily on the HAMD.

**Lavender (**_Lavendula spp._**)**
Lavender showed a synergistic effect to imipramine; adding it to imipramine therapy led to a greater reduction on the HAMD than imipramine alone. It was dosed as a tincture (1:5 50% alcohol, 60 drops daily). Imipramine alone was more effective than lavender alone. Lavender’s mechanism of action is likely GABA modulation.

**Borage (**_Echium amoenum_**)**
Borage showed limited benefit for depression compared to placebo. There was an initial decrease in HAMD scores, but benefit was not maintained after week six of dosing at 375 milligrams daily.

**Ginkgo (**_Ginkgo biloba_**)**
Ginkgo has been found to be useful in treating older patients (51-78 years of age) with depression related to organic brain dysfunction, especially when they have proven to be unresponsive to standard drug treatment. Dosing used in depression studies was 40 milligrams to 80 milligrams three times daily of a 50:1 extract standardized to contain 24% ginkgo-flavone glycosides. Due to potential anticoagulation effects, ginkgo should not be used by anyone during the periods before or after surgery or labor and delivery, and it should be used with caution in people with bleeding problems. It may interact with blood thinners, calcium channel blockers, aminoglycoside antibiotics, anticonvulsants, and neuroleptics.
Many supplements show potential benefit, but they must be used with care. St. John’s wort, in particular, is involved in many supplement-drug interactions. In general, it is best not to recommend herbal remedies for depression at the same time as one is taking antidepressant medications.

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References


