Natural Products Used to Treat Depressed Mood as Monotherapies and Adjuvants to Antidepressants

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By James Lake, MD

Most persons who use CAM modalities to self-treat a mental health problem take prescription antidepressants concurrently. Combined use can result in serious supplement-drug interactions.

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Educational Objectives

After reading this article, you will be familiar with:

• Complementary and alternative medicine (CAM) modalities available for the treatment of depressed mood
• Indications for use of CAM
• Effectiveness and safety issues associated with the different CAM modalities

Every year one-third of the adults in the United States use 1 or more complementary and alternative medicine (CAM) modalities to treat a medical or psychiatric problem. It is estimated that 1 in 10 adults see CAM practitioners, and he or she does so primarily for a mental health problem. A large population survey found that receiving a diagnosis of a mood disorder is a strong predictor of CAM use. Another survey found that persons with major depressive disorder were significantly more likely to use CAM therapies than nondepressed persons. Almost two-thirds of psychiatrically hospitalized patients use at least 1 CAM modality before being hospitalized, and the majority self-treat depressed mood while failing to disclose CAM use to their psychiatrist or primary physician.

Most persons who use CAM modalities to self-treat a mental health problem take prescription antidepressants concurrently. Combined use can result in serious supplement-drug interactions. Because of the high prevalence of CAM use among patients with mental illness, and especially among persons with major depressive disorder, it is important to examine the efficacy and safety evidence of CAM modalities used as either monotherapies or in combination with conventional pharmacological agents to treat depressed mood. Select natural products used to treat depressed mood have been examined in well-designed, placebo-controlled, double-blind studies and in systematic reviews. Natural products used as stand-alone treatments of depressed mood include St John’s wort (Hypericum perforatum); S-adenosyl-L-methionine (SAMe); 5-hydroxytryptophan (5-HTP); folic acid; omega-3 essential fatty acids; and to a lesser extent, acetyl-L-carnitine (ALC) and dihydroepiandrosterone (DHEA). Some of these naturally occurring substances have also been evaluated in controlled trials for their potential role as adjuvants to conventional antidepressants. Two publications review the research evidence for natural products used to treat depressed mood.

This article is offered as a concise summary of research and clinical treatment issues pertaining to select natural products for which there is significant evidence. The Table presents natural products commonly used to treat depressed mood as both monotherapies and adjuvants in combination with antidepressants.

### Vitamins

Depressed mood is commonly seen in patients with folate deficiency, and refractory depressed mood is often associated with low serum levels of folate and vitamin B12. Low serum folate levels are associated with increased risk of relapse in patients who have successfully responded to fluoxetine or other antidepressants. Folate is an essential cofactor in the synthesis of SAMe, which has established antidepressant efficacy.

| Natural Product | Monotherapy | Adjuvant
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In a small randomized placebo-controlled trial, depressed patients treated with a combination of folic acid (0.5 mg) plus fluoxetine experienced significantly greater improvements in mood than the fluoxetine-only group. Significantly, only women experienced a differential beneficial response to folate augmentation. The researchers theorized that this gender difference may be caused by a relatively higher male requirement for folate to efficiently convert homocysteine back to SAMe. It has been suggested that the optimal form of folate for depressed mood is folic acid because it more readily crosses the blood-brain barrier. This is consistent with cases of patients with treatment-refractory depression who responded to antidepressants when folic acid was added to their regimen.

The authors of a systematic review of placebo-controlled studies of folate in depressed mood (N = 247) commented that folate may have a potential role as an adjuvant to pharmacological treatments of depressed mood. Sarris and colleagues have remarked that failure to take into account vitamins B12 (cobalamin) and B6 (pyridoxine) status may confound studies of folate or SAMe in patients with depressed mood in that remethylation of homocysteine to SAMe requires B12, and synthesis of all monoamine neurotransmitters requires B6. Depressed patients with relatively higher serum vitamin B12 levels have shown a more robust response with antidepressants than matched patients with lower B12 levels. On this basis, B12 supplementation (800 µg/d) has been suggested as adjuvant therapy for depressed patients with B12 deficiency. Case reports suggest that some depressed patients experience consistent improvements in mood and energy with 50 mg/d of thiamine.

A daily dose of 400 to 800 IU of vitamin D noticeably improved mood in patients with seasonal affective disorder after 5 days.

Omega-3 fatty acids

Several mechanisms of action underlie the putative antidepressant effects of omega-3 essential fatty acids—including increased CNS serotonin activity, anti-inflammatory effects, suppression of phosphatidyl-inositol second messenger activity, and increased heart rate variability. Blood cell membrane levels as well as serum levels of the omega-3 essential fatty acid docosahexaenoic acid (DHA) may be consistently lower in persons with depression. Preliminary findings suggest that the average dietary ratio of omega-6 to omega-3 essential fatty acids is correlated with the incidence of depressed mood. Lower dietary intake of foods rich in omega-3 fatty acids results in relatively higher ratios of arachidonic acid (AA) (an omega-6) to eicosapentaenoic acid (EPA) (an omega-3) in red blood cells, which in turn may be positively correlated with relatively greater severity of depressed mood. Food preferences that influence fatty acid consumption may be related to varying prevalence rates of depressed mood when industrialized countries are compared with more traditional cultures. Findings of epidemiological surveys suggest that risk of depressed mood and fish consumption are inversely related; however, the results of prospective trials are inconsistent. Countries in which fish is a central part of the average diet have significantly lower rates of depressed mood and suicide.

A large prospective study showed that the incidence of depressed mood declined as dietary intake of omega-3s increased relative to omega-6 fatty acids. What is significant is that relatively greater intake of omega-3 fatty acids was correlated with lower C-reactive protein levels, which suggests an overall reduction in inflammation. Equivocal findings from other studies obscure the relationship between a high-fish diet and the risk of depressed mood. In a large, prospective, 6-month trial (N = 452), men with histories of cardiovascular disease were randomized to a diet high in fatty fish or a diet without fish. There were no significant differences between the 2 groups in the number of new cases of depressed mood. Principal dietary sources of omega-3s include salmon, halibut, other deep-sea fish, certain algae products, and flaxseed oil.

Findings on purified omega-3s as stand-alone treatments of depressed mood are inconsistent. A study of 2 g of DHA daily for depressed mood found no benefit over placebo. However, a study that compared 3 regimens of DHA found greater antidepressant efficacy at 1 g daily than at 2 and 4 g daily.

Findings of controlled trials of omega-3s in pregnant and postpartum women with depression have been inconsistent. One small study found that in pregnant, depressed women who took a combined formula of EPA and DHA, symptoms improved more than in matched women who were given placebo. Nevertheless, 2 small placebo-controlled trials failed to confirm the beneficial effects of omega-3s in pregnant and postpartum depressed women. The results from meta-analyses of placebo-controlled trials confirm the efficacy of purified omega-3
supplement as adjuvant therapy in both unipolar and bipolar depressed mood. A placebo-controlled study of omega-3s as adjuvants to antidepressants failed to show benefit over placebo.

In a subsequent controlled trial (N = 60), unipolar depressed patients were randomized to omega-3s (1 g of EPA), to fluoxetine (20 mg/d), or to a combination of these agents. There were equivalent improvements in mood, but the group taking the combination improved more than the other 2 groups.

Research findings suggest that EPA is probably more beneficial than DHA and that lower doses of EPA (1 to 2 g/d) are as effective as higher doses and are associated with minimal adverse effects. Adverse effects associated with omega-3s are relatively minor. GI adverse effects have been reported. There has been 1 case report of increased bleeding risk when omega-3 fatty acids were used with warfarin.

**St John’s wort (Hypericum perforatum)**

In Western Europe and the United States, St John’s wort is the most widely used natural product to treat depressed mood. Discrete bioactive constituents of St John’s wort function as serotonin reuptake inhibitors; they decrease benzodiazepine receptor binding, weakly inhibit monoamine oxidase (MAO), and may have binding affinity to N-methyl-D-aspartate (NMDA) receptors. Hyperforin probably contributes more to the antidepressant effect of St John’s wort than hypericin, although many commercial preparations are standardized to 0.3% hypericin. Speculation about the primary antidepressant role of hyperforin has led to problems when comparing recent studies with early studies that did not control for that bioactive constituent. In response to these concerns, many St John’s wort preparations are now standardized to both hypericin and hyperforin.

More than 30 double-blind controlled trials on St John’s wort for depressed mood have been conducted. Ten placebo-controlled studies demonstrated equivalent efficacy of St John’s wort and tricyclic antidepressants, and 3 studies confirmed equivalent efficacy to SSRIs: fluoxetine, sertraline, and paroxetine.

A Cochrane review of 27 trials (N > 2200), 17 of which were placebo-controlled, concluded that St John’s wort is significantly more effective than placebo for mild to moderate symptoms of depressed mood. However, a meta-analysis that used more stringent inclusion criteria that controlled for publication bias and small study ef-fects found a significantly smaller antidepressant effect. Results from a large NIH-sponsored multicenter study suggest that St John’s wort and sertraline are equally ineffective against severe depressed mood, and neither treatment is more effective than placebo.

The validity of the NIH study findings has been criticized because of serious design flaws, including the use of subtherapeutic doses of both St John’s wort and sertraline, short duration, lack of statistical power, and selective recruitment of severely depressed patients who had previously been refractory to multiple antidepressants.

In a follow-up study to the NIH study, most nonresponders (n = 95) to a standardized St John’s wort preparation responded to conventional antidepressants with significant improvements in depressed mood. This suggests that antidepressants are more effective than St John’s wort in refractory depressed mood, and it reopens the question of a possibly significant placebo effect of St John’s wort.

Uncommon adverse effects of St John’s wort include upset stomach, feelings of restlessness, and mild sedation. There are no published cases of serotonin syndrome or other serious adverse effects when St John’s wort is used at recommended doses, but there are several case reports of possible serotonin syndrome when St John’s wort and a conventional antidepressant are used together. Caution pregnant women against using St John’s wort. Although no case reports have definitively linked St John’s wort to serious interactions with MAO inhibitors (MAOIs), their combined use should be avoided. Significant safety concerns exist when St John’s wort is used concurrently with protease inhibitors, immunosuppressive agents, warfarin, digoxin, and oral contraceptives.

**CASE VIGNETTE**

Michael is a fit 42-year-old insurance salesman with no medical problems who has experienced depressed mood of moderate severity since his mid-30s. Although his symptoms have responded to conventional antidepressants, he has gained 20 lb and he has had relationship problems because of diminished libido. On the advice of a naturopathic physician, Michael tapered and discontinued his SSRI over 2 weeks and then started a trial of a reputable brand of St John’s wort. After 2 weeks, he is taking 300 mg of St John’s wort 3 times a day without adverse effects. One month later his mood is stable, he has lost 10 lb, and his libido has improved.

**S-adenosyl-L-methionine**
SAME functions as a methyl donor and is required for synthesis of several important neurotransmitters. Antidepressant effects of SAME are probably achieved through increased CNS levels of serotonin, dopamine, and norepinephrine. The synthesis of all 3 neurotransmitters by SAME requires vitamin B12, folate, and vitamin B6. A meta-analysis of placebo-controlled trials on SAME in depressed mood (N = 1015) confirmed antidepressant efficacy equivalent or superior to synthetic antidepressants.\textsuperscript{51} It should be noted that most studies were based on parenteral or intramuscular administration of SAME, which are accepted forms of treatment in Europe. An effective dose is significantly smaller when SAME is administered parenterally, and few adverse effects have been reported.

A large multicenter, double-blind, randomized, placebo-controlled trial showed that oral SAME 1600 mg daily (in divided doses) and imipramine 150 mg daily had equivalent efficacy while SAME was associated with significantly fewer adverse effects.\textsuperscript{52} Two multicenter studies demonstrated equivalent efficacy between 400 mg of SAME administered by intramuscular injection and 150 mg of oral imipramine.\textsuperscript{53}

Findings of a small open trial suggest that 800 to 1600 mg of SAME daily in combination with an antidepressant improves overall response, is effective in patients who had previously been treatment-refractory to antidepressants, and accelerates the response rate.\textsuperscript{54} There is evidence that SAME is an effective adjuvant when taken with conventional antidepressants in the absence of serious safety issues (SAME should be avoided in bipolar depressed patients because of a small but significant risk of mania induction).\textsuperscript{55-58} Case reports of patients using this protocol suggest that antidepressant doses can be reduced by as much as 30%, with fewer adverse effects and improvements in medication adherence. Two large, placebo-controlled, NIMH-sponsored trials of SAME as monotherapy and as an adjuvant to antidepressants in treatment nonresponders are ongoing.

The advantages of SAME over synthetic antidepressants include relatively rapid onset of action—usually within 1 week of starting treatment—the absence of clinically significant interactions with drugs, and relatively few adverse effects compared with conventional antidepressants. The standard maintenance regimen for depressed mood is between 800 and 1600 mg in 2 to 4 divided doses. Absorption is improved when SAME is taken before meals. The butane-disulfonate form of SAME has significantly greater bioavailability than the tosylate form, and it is available as an enteric-coated tablet for longer shelf life.

SAME is generally well tolerated; however, transient anxiety, insomnia, GI adverse effects, dry mouth, and dizziness have been reported. Cases of hypomania have been reported in patients with bipolar disorder; therefore, patients with bipolar depression who take SAME should be carefully monitored.

**L-tryptophan and 5-hydroxytryptophan**

5-HTP and L-tryptophan are amino acid precursors required for serotonin synthesis. Both have been extensively evaluated for their antidepressant efficacy. 5-HTP is generally preferred because it crosses the blood-brain barrier at a higher rate, is converted into serotonin more efficiently than L-tryptophan, and has more marked antidepressant effects.

The use of L-tryptophan to treat depressed mood originated in response to findings that serum L-tryptophan levels are often low in depressed patients and tend to normalize following successful response to treatment.\textsuperscript{59} Two early, double-blind, placebo-controlled studies reported that 6 to 9 g of L-tryptophan and 150 mg of imipramine daily have equivalent antidepressant efficacy.\textsuperscript{60,61} However, research findings of controlled trials on L-tryptophan as monotherapy in depressed mood are inconsistent and limited by small study sizes and methodological problems.

Combining 2 g of L-tryptophan with 20 mg of fluoxetine resulted in a more rapid antidepressant response and improved sleep quality in depressed patients with chronic insomnia.\textsuperscript{62} L-tryptophan is typically used at night because of its sedating properties and is dose-dosed between 1500 and 5000 mg depending on therapeutic response.

Uncommon adverse effects of L-tryptophan include drowsiness, dry mouth, and blurred vision. In the late 1980s and early 1990s, 1500 cases of eosinophilia-myalgia syndrome and 37 deaths of patients taking L-tryptophan were reported. All cases of eosinophilia-myalgia syndrome were traced to contaminants in a single batch of an over-the-counter L-tryptophan preparation.\textsuperscript{63} The manufacturing problem that resulted in the contaminated batch was identified and rapidly corrected. There have been no subsequent reports of eosinophilia-myalgia syndrome associated with L-tryptophan.

5-HTP begins to have antidepressant effects at dosages between 100 and 300 mg/d. Early case reports suggest that treatment-refractory patients sometimes improve when 300 mg of 5-HTP is used as an adjuvant to carbidopa, tricyclic antidepressants, MAOIs, or SSRIs.\textsuperscript{64-69} But no
placebo-controlled trials have confirmed this. A Cochrane review of studies of 5-HTP or L-tryptophan in depressed mood identified 108 controlled trials, but analysis of findings was limited to only 2 studies (N = 64) because of small study size, heterogeneity of study designs, and methodological flaws. The reviewers remarked that 5-HTP is probably more effective than placebo for depressed mood but were unable to offer more definitive conclusions. Like L-tryptophan, 5-HTP is moderately sedating, and doses greater than 100 mg are typically taken at bedtime.

**Acetyl-L-carnitine**

ALC has general neuroprotective effects and is believed to improve mood and reduce the severity of cognitive impairments in normal aging, dementia, or traumatic brain injury. ALC enhances mitochondrial energy production and partially compensates for deficits in CNS cholinergic activity. ALC has been studied in placebo-controlled, double-blind trials in severely depressed patients, elderly depressed patients, and depressed patients with dementia. Most studies have evaluated ALC in elderly depressed patients and have demonstrated antidepressant effects after about 1 month of treatment at dosages between 1 and 3 g daily. In a 2-month, placebo-controlled trial, depressed patients with dementia who were randomized to 3 g of ALC daily, in divided doses, experienced significantly greater improvements in mood and global functioning than those who were given placebo. In a small, double-blind, cross-over study of hospitalized elderly patients who were depressed, ALC was shown to have superior antidepressant efficacy over placebo. In a small, double-blind, placebo-controlled study (N = 28) half of the elderly patients with severe depression who were treated with ALC, 500 mg 4 times a day, experienced full remission, and their previously elevated serum cortisol levels normalized.

Fewer studies have been done of ALC than of other natural products used to treat depressed mood, and no studies have been undertaken to compare ALC with antidepressants. A recent review of controlled studies of ALC in depressed mood found preliminary evidence for therapeutic benefits in elderly patients with depression, including possibly cognitive-enhancing effects. Most studies of ALC in depressed mood report few or no adverse effects. ALC may be safely used in combination with antidepressants, but studies have not been done to evaluate possible adjuvant benefits. In depressed patients who are elderly or have dementia, up to 2 g of ALC daily is a reasonable alternative in cases where antidepressants have been partially effective or have been discontinued because of adverse effects.

**CASE VIGNETTE**

Mr Jones is an 82-year-old retired stockbroker with chronic moderate depressed mood who has been taking therapeutic doses of several SSRIs for 10 years. He has not experienced significant adverse effects to conventional antidepressants and his symptoms have partially responded to conventional treatment. Recently, he has noticed short-term memory problems and is concerned that he may be in the early stages of Alzheimer disease. After reading an article on ALC, he consulted his family doctor who reviewed the evidence for ALC and advised Mr Jones that it was safe to take ALC in combination with his current antidepressant medication. After 8 weeks of taking 500 mg of ALC 3 times daily, Mr Jones has noticed improvements in both his mood and short-term memory problems in the absence of adverse effects. In consultation with his family physician, Mr Jones continues to take both the antidepressant and ALC.

**L-tyrosine**

The amino acid L-tyrosine plays many important roles in human physiology. It is obtained through diet or synthesized from phenylalanine and is a necessary precursor for synthesis of epinephrine, norepinephrine, and dopamine as well as nerve growth factor and thyroxin. Tyrosine deficiency is frequently associated with depressed mood. Beneficial dosages of L-tyrosine in depressed mood range from 500 to 1500 mg daily. Large doses of tyrosine may promote growth of malignant melanoma or other cancers.

**Inositol**

Inositol is a member of the vitamin B family that is synthesized into phosphatidyl inositol, a second messenger required for normal nerve cell function. Therapeutic effects of lithium in depressed mood and mania are believed to be mediated by the inhibition of the enzyme required for synthesis of phosphatidyl inositol in the hippocampus. In a small, 4-week, double-blind, placebo-controlled study (N = 28), depressed patients randomized to 12 g of inositol reported significantly greater improvements in mood than did placebo recipients. However, more recent placebo-controlled studies failed to show an adjuvant effect of inositol when combined with SSRIs in patients with major depressive disorder. A Cochrane review concluded that the basis for recommending inositol as a primary or adjuvant
treatment of depressed mood is insufficient. In contrast to its probable lack of efficacy in unipolar depressed mood, preliminary findings suggest that inositol has robust adjuvant effects when combined with mood stabilizers in the treatment of bipolar depressed mood. In a small, 6-week, double-blind trial, depressed patients with bipolar disorder (N = 24) were randomized to mood stabilizers plus 12 g of inositol daily and compared with those who were given placebo. By the end of the study half, 6 of the patients in the combined inositol–mood stabilizer group reported at least a 50% reduction in depressed mood symptoms, compared with only 3 patients in the placebo group. Large prospective studies are needed to evaluate possible adjuvant effects of inositol when used with antidepressants or mood stabilizers and to determine optimal dosing strategies. GI adverse effects associated with high doses used to treat depressed mood have resulted in limited use of inositol in spite of its therapeutic potential as an adjuvant.

**Dihydroepiandrosterone**

Antidepressant effects of DHEA are believed to be mediated by multiple endocrine systems, including both androgen and estrogen receptors, and indirect effects on neurotransmission involving serotonin, γ-aminobutyric acid, NMDA, and possibly norepinephrine. In a small, 6-week study (N = 22), DHEA administered in an escalating dose (30 mg daily for 2 weeks, followed by 30 mg twice a day for 2 weeks, and then 30 mg 3 times a day for 2 weeks) resulted in significant improvements in mood compared with placebo. Two-thirds of patients in both groups continued their antidepressants throughout the study. Mood scores in half of the patients in the DHEA group improved by 50% or more.

In a 6-week, double-blind, randomized, placebo-controlled, cross-over study (N = 46), moderately depressed adults were randomized to 90 mg of DHEA daily for 3 weeks followed by 150 mg of DHEA 3 times a day for 3 weeks or to placebo. A 50% or more reduction in symptom severity was observed in the DHEA group, which also reported improvements in baseline sexual functioning. Most patients who responded to DHEA remained asymptomatic at 12 months’ follow-up. HIV-positive patients with depression who took 200 to 500 mg of DHEA daily experienced significant improvements in mood and fatigue. Serum testosterone levels and CD4 T-cell counts were not affected.

Research findings suggest that DHEA improves negative psychotic symptoms in schizophrenic patients. In a small, double-blind, placebo-controlled study (N = 30), inpatients with schizophrenia who were treated with 100 mg of DHEA daily in addition to their antipsychotic medications experienced significant improvements in depressed mood, anxiety, and negative psychotic symptoms. Women improved more than men, and serum cortisol levels did not change during treatment.

Large prospective studies are needed to evaluate DHEA in severe depressed mood, clarify the mechanism underlying DHEA when used as an adjuvant or as monotherapy, and determine optimal dosing strategies. DHEA may promote cancer in women who have a history of estrogen receptor–positive breast cancer and should be avoided in this population. DHEA supplementation may increase the risk of prostate cancer in men with early or undetected prostate cancer. A metabolite of DHEA called 7-Keto DHEA is not converted into androgens or estrogens and can probably be safely used in this at-risk population.

**Rhodiola rosea**

*Rhodiola rosea* (Golden root) is a traditionally used Siberian herb that has been demonstrated to increase brain levels of 5-hydroxytryptophan and reportedly has antidepressant and cognitive enhancing effects. In vitro studies suggest that observed antidepressant effects of *R. rosea* are mediated by potent MAO-B inhibition. *R. rosea* can be safely taken with antidepressants and there is preliminary evidence of an augmentation effect. Typical dosages of standardized extracts range from 200 to 400 mg daily. Serious adverse effects have not been reported.

**Conclusion**

In the United States, Canada, the European Community, and other developed world regions, increasing numbers of patients are using nonconventional approaches to treat psychiatric disorders. Anyone in whom a psychiatric disorder has been diagnosed is significantly more likely to use a nonconventional treatment than the general population. Before prescribing an antidepressant, clinicians should ask the patient about any CAM use. Conventional medications used in conjunction with CAMs can result in potentially serious safety issues.

[Note: This article was originally published in the December 2009 issue of *Psychiatric Times*]
Table

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