Depression (Mild to Moderate)

En Español (Spanish Version)

Principal Proposed Natural Treatments

• Repetitive Transcranial Magnetic Stimulation (rTMS); St. John's Wort

Other Proposed Natural Treatments

• 5-Hydroxytryptophan (5-HTP); Acetyl-L-Carnitine; Acupuncture; Ayurveda; Beta-carotene; Chromium; Damiana; Dehydroepiandrosterone (DHEA); Exercise; Fish Oil; Folate; Ginkgo; Hatha Yoga; Inositol; Lavender; Massage; Multivitamins; Music Therapy; NADH; Phenylalanine; Phosphatidylserine; Pregnenolone; Rhodiola Rosea; S-Adenosylmethionine (SAMe); Saffron (*Crocus sativus*); Traditional Chinese Herbal Medicine; Tyrosine; Vitamin B6; Vitamin B12; Zinc

Depression is a common emotional illness that varies widely in its intensity. Many of the natural treatments described in this section have been evaluated in people with major depression of mild to moderate intensity. This apparently contradictory language indicates a level of clinical depression that is significantly more intense than simply feeling "blue," but not as disabling as major depression of severe intensity, which usually requires hospitalization.

Typical symptoms of major depression of mild to moderate severity include depressed mood, lack of energy, sleep problems, anxiety, appetite disturbance, difficulty concentrating, and poor stress tolerance. Irritability can also be a sign of depression.

More severe depression includes markedly depressed mood complicated by symptoms such as slowed speech, slowed (or agitated) responses, markedly impaired memory and concentration, excessive (or diminished) sleep, significant weight loss (or weight gain), intense feelings of worthlessness and guilt, recurrent thoughts of suicide, and lack of interest in pleasurable activities. This form of clinical depression is a dangerous and excruciating illness. The emotional structure of the brain has frozen into a pattern of misery that cannot be altered by willpower, a change of scenery, or the most earnest efforts of friends. In a sense, the brain has locked up like a crashed computer.

One of the earliest successful treatments for major depression was shock therapy. This technique is in some ways analogous to rebooting a computer, and in cases of major depression, its effects were revolutionary. For the first time, a reliable way was available to bring people out from the depths of major depression.

However, shock treatment was overused at first and became unpopular as a result. The accidental discovery of antidepressant drugs provided a route with fewer interventions. The original antidepressants, known as MAO inhibitors, could bring people out from the depths of major depression as successfully as shock treatment. However, MAO inhibitors can cause serious and even fatal side effects. No one would ever think of using MAO inhibitors to treat mild to moderate depression.

Subsequently, antidepressants with progressively fewer side effects came on the market, but most of them still caused significant fatigue. Since fatigue is one of the most characteristic symptoms of mild to moderate depression, such medications were seldom found useful for anything other than severe depression. With the appearance of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants, however, suddenly there was a practical option for depression that was less than catastrophic. Practically overnight, enormous numbers of people began taking Prozac and similar drugs for mild to moderate depression, as well as for the related, but more mild condition, known as dysthymia.
The big advantage of the SSRIs is that they usually don't cause severe fatigue. Many people find them to be entirely side effect-free. However, side effects are not uncommon and include sexual disturbances (such as impotence in men and the loss of the ability to experience an orgasm in women), insomnia, and nervousness. The antidepressant drug Wellbutrin is an option for people who have sexual side effects from SSRIs.

Principal Proposed Natural Treatments

Alternative medicine offers numerous options for treating depression, but only one has strong scientific evidence behind it: the herb St. John's wort.

What Is the Scientific Evidence for St. John's Wort?

Numerous double-blind, placebo-controlled studies have examined the effectiveness of St. John's wort for the treatment of mild to moderate major depression, and most have found the herb more effective than placebo. In addition, at least 8 studies have found that St. John's wort is at least as effective as standard antidepressants, including fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil). A 2008 detailed review of 29 randomized, placebo controlled trials found that St. John's wort was consistently more effective than placebo and equally effective to standard antidepressants. The total number of patients in these trials runs into the several thousands and compares favorably to the evidence-base for approved drugs. St. John's wort has also shown a bit of promise for severe major depression, but the evidence is quite limited.

Note: St. John's wort alone should never be relied on for the treatment of severe depression.

Much has been made of two double-blind, placebo-controlled trials performed in the United States that failed to find St. John’s wort more effective than placebo for mild to moderate depression. However, two studies cannot overturn a body of positive research. Approximately 35% of double-blind studies involving pharmaceutical antidepressants have also failed to find the active agent significantly more effective than placebo. As if to illustrate this, in the more recent of the two trials in which St. John’s wort failed to prove effective, the drug sertraline (Zoloft) also failed to prove effective. The reason for these negative outcomes is not that Zoloft (or Prozac, or any other drug) does not work. Rather, statistical effects can easily hide the benefits of a drug, especially in a condition like depression where there is a high placebo effect and no truly precise method for measuring symptoms.

St. John’s wort seldom causes immediate side effects. However, it interacts adversely with a large number of critical medications and may present other safety issues as well. For more information, see the full St. John’s Wort article.

Other Proposed Natural Treatments

There are a number of other herbs and supplements that may be helpful in depression, although the evidence for them is nowhere near as strong as that for St. John’s wort.

Folate

In the body, the vitamin folate works in tandem with SAMe. Observational studies have suggested that depressed people have reduced folate levels, and a bit of evidence hints that folate supplements may help alleviate depression. In addition, people with particularly low folate levels may respond poorly to antidepressants.
Based on these findings, a study examined the effects of combining folate with antidepressant treatment. This 10-week, double-blind, placebo-controlled trial of 127 people with severe major depression found that folate supplements at a dose of 500 mcg daily significantly improved the effectiveness of fluoxetine (Prozac) in female participants. Improvement in male participants was not significant, but blood tests conducted during the study suggest that higher intake of folate might be necessary for men.

Folate has also been paired with vitamin B₁₂. In one study, over 900 older adults with mild depression were randomized to different treatment groups. One of the groups took folate (400 mcg) and B₁₂ (100 mcg) daily for 2 years. Folate and vitamin B₁₂ were no better than placebo at improving their depressive symptoms. For more information, including dosage and safety issues, see the full Folate article.

**S-adenosylmethionine (SAMe)**

The supplement S-adenosylmethionine (SAMe) has been widely marketed for the treatment of depression, but the evidence to indicate that it works remains incomplete.

Several double-blind, placebo-controlled studies have found SAMe effective in relieving depression, however, most were small and poorly reported. In addition, many used injected SAMe rather than the oral supplement. Furthermore, a double-blind, placebo-controlled study of 133 depressed people, actually failed to find intravenous SAMe more effective than placebo. (Researchers managed to find some benefit to report by resorting to questionable statistical manipulation of the data.)

In addition to placebo-controlled studies, several trials have compared SAMe against antidepressant drugs in the tricyclic family. Again, many of these studies were poorly reported and designed, or they used injected SAMe rather than the oral supplement. Of the studies using oral SAMe, the best was a 6-week, double-blind trial of 281 people with mild depression. The results showed that SAMe was about as effective as the drug imipramine. However, the lack of a placebo group in this trial makes the results less than fully reliable. Other small studies have also compared the benefits of oral or intravenous SAMe to those of tricyclic antidepressants and have found generally equivalent results, although, again, poor reporting and inadequacies of study design (such as too limited a treatment interval) mar the meaningfulness of the outcomes.

Researchers have also studied the effectiveness of oral SAMe in combination with antidepressants. Seventy-three patients with treatment-resistant major depression were randomized to take SAMe (800 mg twice daily) or a placebo. Both groups continued to take their selective serotonin reuptake inhibitor (SSRI). Adding SAMe to the treatment increased the rate at which patients responded to their antidepressant medication.

For more information, including dosage and safety issues, see the full S-adenosylmethionine article.

**Ginkgo**

Ginkgo is used mainly for age-related mental decline such as that from Alzheimer's disease. However, during the studies on impaired mental function, researchers frequently observed improvements in mood and relief from symptoms of depression. This incidental discovery led scientists to investigate whether ginkgo might be useful as an antidepressant treatment.

One double-blind study, published in 1990, evaluated this effect in 60 people who suffered from depressive symptoms along with other signs of dementia. The results showed significant improvements among participants given ginkgo extract instead of placebo.

Another study followed 40 depressed people over the age of 50 who had not responded successfully to antidepressant treatment. Those who were given ginkgo showed an average drop of 50% in scores on the Hamilton Depression scale, whereas the placebo group showed only a 10% improvement.

In 1994 an interesting piece of research was reported that may shed light on the mechanism by which ginkgo may reduce depression. This study examined levels of serotonin receptors in rats of various ages. When older rats...
were given ginkgo, the level of serotonin-binding sites increased. However, the same effect was not observed in younger rats. The researchers theorized that ginkgo may block an age-related loss of serotonin receptors. Reduced receptors for serotonin may mean that the body needs more serotonin to produce a normal effect. Thus, ginkgo might improve the brain's ability to respond to serotonin (at least in older people). However, this is still highly speculative.

For more information, including dosage and safety issues, see the full Ginkgo article.

**Phenylalanine**

Phenylalanine is a naturally occurring amino acid that we all consume in our daily diets. There is some evidence that phenylalanine supplements may help reduce symptoms of depression.

Phenylalanine occurs in a right-hand and a left-hand form, known as D- and L-phenylalanine, respectively. Some studies have evaluated the D form, and others have evaluated a mixture of the D and L forms. Both formulations may provide some measure of relief for symptoms of depression. The mixed form (DLPA) is the one most commonly available in stores.

A 1978 study compared the effectiveness of D-phenylalanine against the antidepressant drug imipramine (taken in daily doses of 100 mg) and found them to be equally effective. A total of 60 people were randomly assigned to either one group or the other and followed for 30 days. D-phenylalanine worked more rapidly, producing significant improvement in only 15 days.

Another double-blind study followed 27 people, half of whom received DL-phenylalanine and the other half imipramine in higher doses of 150 mg to 200 mg daily. When the participants were reevaluated in 30 days, the two groups had improved by the same amount.

Unfortunately, there do not seem to have been any properly designed studies that compared phenylalanine to placebo. Until these are performed, phenylalanine cannot be considered a proven treatment for depression, but it is certainly promising.

For more information, including dosage and safety issues, see the full Phenylalanine article.

**5-hydroxytryptophan**

When the body sets about manufacturing serotonin, it first makes 5-hydroxytryptophan (5-HTP). The theory behind taking 5-HTP as a supplement is that providing the one-step-removed raw ingredient might raise serotonin levels.

There have been several preliminary studies of 5-HTP. The best of these trials was a 6-week study of 63 people given either 5-HTP (100 mg 3 times daily) or an antidepressant in the Prozac (fluvoxamine) family (50 mg 3 times daily). The results showed equal benefit between the supplement and the drug. Actually, 5-HTP worked a little better, but from a mathematical perspective, the difference was not statistically significant.

5-HTP caused fewer and less severe side effects than fluvoxamine. The only real complaint was occasional mild digestive distress.

For more information, including dosage and safety issues, see the full 5-hydroxytryptophan article.

**Fish Oil**

It has been suggested that fish oil or the related substance ethyl-EPA may be helpful for people with depression. For example, a 4-week, double-blind, placebo-controlled trial evaluated the potential benefits of fish oil in 20 individuals with depression. All but one of the participants were also taking standard antidepressants and had been for at least 3 months. By week 3 of the trial, the level of depression had improved to a significantly greater extent in the fish oil group than in placebo group. In addition, a double-blind,
placebo-controlled study of 70 people with depression that did not respond well to drug treatment found that the addition of ethyl-EPA (a modified form of a primary ingredient of fish oil) improved the response. Similarly, a double-blind study that evaluated the anti-depressant effect of EPA plus fluoxetine (a popular anti-depressant medication) found the combination to be more effective than fluoxetine or EPA alone after 4 weeks of treatment.

In another study, 40 people who had committed repeated acts of self-harm were given either fish oil or placebo for 12 weeks. The results indicated that fish oil supplementation markedly reduced measures of suicidality and well-being.

However, the best and most recent studies have failed to find benefit. A meta-analysis (formal statistical review of evidence) published in 2007 failed to find convincing evidence of benefit. The largest (77-participant) study in this review failed to find fish oil more effective than placebo for treatment of depression. Two subsequent studies enrolling a total of almost 300 people also failed to find benefit. And a third placebo-controlled study found no benefit for fish oil in improving “mental well-being” among 320 older adults without a diagnosis of depression.

For more information, including dosage and safety issues, see the full Fish Oil article.

**Exercise**

Exercise may be helpful for depression. In a review published in the journal *Sports Medicine*, researchers analyzed the published research on this subject. Their conclusion: a very qualified “yes.”

In seven out of eight studies reviewed, various forms of exercise proved beneficial for depression. Aerobic exercise, weight training, dancing, and racquetball all produced improvements in mood as compared to no exercise.

However, the findings of the one negative study reported in this review cast doubt on the others. In this trial, some participants exercised, while others took a course at school and didn't exercise at all. The results: equal benefits in both groups. This suggests that it may not be the exercise itself that is helping, but rather the general effects of participation in an organized activity.

Another feature of the positive studies also tends to cast doubt on the value of exercise per se in depression. You'd think that if it were exercise itself improving mood, the more effectively the participants exercised the greater the effect. However, no correlation was seen between how much participants increased their physical fitness and how significantly their depression improved.

**Repetitive Transcranial Magnetic Stimulation**

Repetitive transcranial magnetic stimulation (rTMS) involves the application of low-frequency magnetic pulses to the brain. A growing body of evidence suggests that rTMS is helpful for depression.

In a well-designed trial, for example, 70 people with major depression were given rTMS or sham rTMS in a double-blind setting over a period of 2 weeks. The results showed that participants who had received actual treatment experienced significantly greater improvement than did those receiving sham treatment. In a smaller trial involving 45 subjects, researchers found that rTMS is more effective than sham rTMS as an add-on treatment to anti-depressant medication in people with moderate to severe depression (including those with psychotic symptoms). In another trial involving 92 older patients whose depression has been linked to poor blood flow to the brain (so-called vascular depression), actual rTMS was significantly more effective than a sham rTMS. Benefits were more notable in younger patients.

In a particularly persuasive piece of evidence, researchers pooled the results of 30 double-blind trials involving 1,164 depressed patients and determined that real rTMS is significantly more effective than sham (fake) rTMS.

Studies suggest that rTMS may be an effective additional treatment for the 20%-30% of depressed people for
whom conventional drug therapy is not successful. Another group of researchers pooled the results of 24 studies involving 1,092 patients and found rTMS to be more effective than sham for treatment-resistant depression.\textsuperscript{178}

ECT (electroconvulsive therapy, or shock treatment) is often used for people who fall in this category, but rTMS may be an equally effective and less traumatic alternative.\textsuperscript{112,116,129}

**Other Herbs and Supplements**

Like gingko, the supplement phosphatidylyserine is used mainly for mental decline in the elderly, but it may also offer antidepressant benefits for seniors.\textsuperscript{68,69} Limited evidence hints that acetyl-L-carnitine may also offer benefits for seniors,\textsuperscript{108,109} as well as, potentially, for younger people.\textsuperscript{150}

Diets low in vitamin B\textsubscript{6} or vitamin B\textsubscript{12} have been associated with symptoms of depression.\textsuperscript{110,111} While there is little direct evidence that taking these supplements can help depression, deficiencies of B\textsubscript{6} are common, and B\textsubscript{12} deficiencies occur more often with advancing age, so it may be a good idea to take these vitamins on general principles. Nonetheless, a randomized trial involving 299 men over the age of 75 found that a daily supplement containing a combination of vitamins B\textsubscript{6}, B\textsubscript{12}, and folate was no better than placebo at preventing depression over a 2-year period.\textsuperscript{125} The same was true in another study in which older adults with mild depression took folate (400 mcg) and B\textsubscript{12} (100 mcg).\textsuperscript{184}

Other micronutrients are also commonly deficient in elderly populations. A small study among nursing home residents found that low levels of the mineral selenium was associated with depression. Moreover, 8 weeks of mineral supplementation tended to improve the mood of the most seriously depressed patients with low selenium levels.\textsuperscript{172}

In a small double-blind, placebo-controlled study, tincture of lavender enhanced the antidepressant effectiveness of the drug imipramine.\textsuperscript{129} The hormone DHEA has shown some promise for depression.\textsuperscript{113,151-152}

When depression is characterized by rapid mood changes, excessive sleeping and eating, a sense of leaden paralysis, and extreme sensitivity to negative life events, the condition is called atypical depression. A very small (15 participants) double-blind, placebo-controlled study found that chromium picolinate might be helpful for this form of depression;\textsuperscript{130} however, a much larger study failed to find convincing benefits.\textsuperscript{153}

One study found weak evidence that zinc supplements may enhance the effectiveness of standard antidepressants.\textsuperscript{142}

According to five preliminary double-blind studies, use of the herb saffron (\textit{Crocus sativus}) at 30 mg daily is more effective than placebo and equally effective as standard treatment for major depression.\textsuperscript{143,144,154,156,159} However, all these studies were small and were performed by a single research group in Iran. Larger studies and independent confirmation will be necessary to determine whether saffron truly is effective for depression.

Two studies of somewhat questionable validity reported benefit with an herbal combination used in Traditional Chinese Herbal Medicine ("Free and Easy Wanderer Plus").\textsuperscript{157,176} Beta-carotene, damiana, NADH, pregnenolone, and tyrosine are also sometimes recommended for depression, but there is no meaningful evidence as yet that they really work.

A double-blind study of 42 people with severe depression found no improvement with the supplement inositol.\textsuperscript{107} Similarly, use of multivitamin mixtures has failed to prove more effective than placebo.\textsuperscript{166}

The herb \textit{Rhodiola rosea} has also been studied as a treatment for depression.\textsuperscript{188} In a randomized trial, 89 people with mild to moderate depression received rhodiola extract 340 mg, rhodiola extract 680 mg, or a placebo for 6 weeks. Those in both rhodiola groups experienced an improvement in most of their depression symptoms, whereas those in the placebo group experienced no such benefit.
Alternative Therapies

Ayurveda, hatha yoga, massage and relaxation therapies have all been studied for their effectiveness against depression, but results to date have been largely unconvincing.

Music therapy, though, may have some promise. In one study, 79 people (aged 18-50) with depression were randomized to receive music therapy for 60 minutes, twice a day (plus standard care) or standard care alone. At 3 months, those in the music therapy group experienced an improvement in their depression, anxiety, and general ability to function.

One small trial involving 84 adults with major depression found that mindfulness-based cognitive therapy, a type of stress reduction program, was just as effective as antidepressants in reducing the chance of relapse. In addition, a 2011 systematic review that included 10 studies found evidence that mindfulness-based interventions may be beneficial for pain and depressive symptoms in patients suffering with chronic pain. The authors did highlight, though, the need for better quality studies.

Studies on acupuncture as a treatment for depression have shown mixed results. In a review of 20 trials involving 2,000 patients with major depression, researchers concluded that real acupuncture's effectiveness was comparable to that of anti-depressants, but was no more effective than sham acupuncture for this population. Other studies have not found this benefit, though. There is some suggestion that combining acupuncture with fluoxetine (Prozac) may hasten the effect of the antidepressants and allow for a lower dose.

Herbs and Supplements to Use Only With Caution

Various herbs and supplements may interact adversely with drugs used to treat depression. For more information on this potential risk, see the individual drug article in the Drug Interactions section of this database.

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