Well-studied treatments such as yoga, self-help books, and St. John's wort can be effective antidepressants

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How to negotiate CAM use with patients

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CAM for your depressed patient

6 recommended options

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Americans with depression turn to complementary and alternative medicine (CAM) more often than conventional psychotherapy or FDA-approved medication. In a nationally representative sample, 54% of respondents with self-reported "severe depression"—including two-thirds of those receiving conventional therapies—reported using CAM during the previous 12 months.[1]

Unfortunately, popular acceptance of CAM for depression is disproportionate to the evidence base, which—although growing—remains limited. As a result, your patients may be self-medicating with poorly supported treatments that are unlikely to help them recover from depression.

In reviewing CAM treatments for depression, we found some with enough evidence of positive effect that we feel comfortable recommending them as evidence-based options. These promising, short-term treatments are supported by level 1a or 1b evidence and at least 1 study that demonstrates an ability to induce remission (***Table 1, page 40***).[2]

For patients seeking "natural" or nonprescription treatments—or when you wish to augment standard treatments that are not working adequately—you might recommend fatty acids, St. John's wort, or S-adenosyl-L-methionine (SAMe). Similar recommendations can be made for yoga, exercise, and bibliotherapy, as we discuss here.

Reviewing CAM evidence

This article refers to as "alternative" any treatment other than a form of psychotherapy or an FDA-approved medication that substitutes for a standard psychiatric treatment. When used to augment

CAM for depression

Table 1

Evidence these authors required to recommend a CAM treatment

Minimum requirements	Level of evidence	Recommendation
Systematic review showing superiority to placebo or standard treatment	1a +	A
Plus		
1 study showing CAM treatment can induce remission	1b or 2b	
At least 2 RCTs showing superiority to placebo or standard treatment	1b	A–
Plus		
1 study showing CAM treatment can induce remission	1b or 2b	

CAM: complementary and alternative medicine; RCT: randomized controlled trial
Source: Reference 2

Clinical Point

Multiple RCTs have shown consistent superiority of some CAM treatments over comparison conditions

standard psychiatric treatments, these approaches are considered "complementary."

Our search for evidence on CAM treatments for depressive disorders raised questions about what constitutes acceptable and convincing methodology:

- Studies often had problems with blinding and suitable placebos. Many were small, with short duration and no long-term follow-up.
- Comparisons with active treatments that showed no differences were assumed to imply comparability, even though the studies were powered to detect only large differences.

On the other hand, multiple randomized controlled trials (RCTs) have shown consistent superiority of some CAM treatments over comparison conditions.

Applying the evidence. Because CAM use is widespread, be sure to ask psychiatric patients if they are using CAM treatments. If the answer is "yes," a risk-benefit assessment is needed. Inform patients who are using poorly supported CAM approaches that they could consider better-supported CAM options as well as standard effective antidepressants.

Monitor patients for an adequately prompt positive response to an evidence-based CAM approach that has shown efficacy for their level of depression. As with any treatment, consider other evidence-based options when CAM treatments are inadequate or unsuccessful in achieving remission of depressive symptoms.

Sufficient evidence of efficacy

Yoga. In their systematic review of yoga's effectiveness for depression, Pilkington et al[3] analyzed 5 RCTs that met 3 criteria:

- participants had mild to severe depression or depressive disorders
- yoga or yoga-based exercises alone were used for treatment
- depression rating scales were used as outcome measures.

They found evidence that yoga can reduce depressive symptoms and induce remission (***Table 2, page 43***). The studies were generally small and of short duration, and depression severity and interventions varied widely. Most participants were young and relatively fit, raising questions about yoga's applicability to older or less fit patients. Reporting of adverse events was limited, but no safety issues or adverse effects were identified.

Conclusion. Yoga has been studied primarily as an alternative treatment, but its physical health and group participation benefits and lack of side effects make it a suitable complementary treatment as well.

Exercise. Extensive literature has examined the relationship between exercise and depression. We identified 7 reviews published between 1993 and 2008 (***Table 3, page 44***). All supported positive effects of exercise except for patients age <20. In a later RCT, the efficacy of aerobic exercise and antidepressant medication did not differ significantly in 202 adults with major

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Table 2

5 RCTs of yoga's effectiveness in treating depression

RCT	Interventions	Conclusion
Broota and Dhir, 1990	Yoga and PMR vs control	Yoga and PMR were more effective than control, with yoga more effective than PMR
Khumar et al, 1993	Shavasana yoga vs no intervention	College students with severe depression improved during and after yoga treatment
Janakiramaiah et al, 2000	SKY vs ECT vs imipramine	Reductions in BDI scores for all 3 groups; ECT > SKY or imipramine, SKY = imipramine
Rohini et al, 2000	Full SKY vs partial SKY	30 individuals with MDD improved with either therapy, but results were not statistically significant
Woolery, 2004	Iyengar yoga vs wait list	28 mildly depressed individuals benefitted from yoga, as measured by BDI scores at midpoint and throughout treatment

BDI: Beck Depression Inventory; ECT: electroconvulsive therapy; MDD: major depressive disorder; PMR: progressive muscle relaxation; RCT: randomized controlled trial; SKY: Sudarshan Kriya yoga
Source: For references to studies described in Table 2, see this article at CurrentPsychiatry.com

depressive disorder (MDD). Remission rates were:

- 45% with supervised exercise
- 40% with home-based exercise
- 47% with sertraline, 50 to 200 mg/d
- 31% with placebo.[4]

Conclusion. Evidence supports exercise for short-term treatment of mild or moderate depression in adults. Studies tend to be small and brief, to enroll young physically-sound patients, and to include little follow-up. Studies of subjects age <20 are limited, of poor quality, and indicate no effect.

At least 2 studies suggest that high-energy exercise and aerobic or resistance training provide greater reductions in depressive symptoms than exercises such as walking.[5,6] Yoga's positive effects suggest, however, that an aerobic effect is not necessary for an antidepressant benefit.

Exercise has not been adequately tested as a complementary treatment but likely is safe for most psychiatric patients. Perspiration and dehydration might alter therapeutic blood levels of lithium or other medications. Advise patients to drink water before, during, and after exercise and to avoid outdoor exercise in extreme temperatures. More vigorous monitoring might be indicated in specific cases.

Tailor exercise programs to individual needs, considering the patient's age and health status. Refer a patient with a known heart problem or increased cardiovascular risk to his or her physician for selective exercise testing.

Bibliotherapy—reading self-help books, usually about cognitive-behavioral approaches to depressive disorders—has been relatively well studied. A recent meta-analysis examined 29 studies with pre-post designs. Group differences in the 17 controlled studies yielded a large effect size of 0.77. Participants who read the materials benefitted similarly whether they met in groups or applied the information on their own. Older adults tended to be less depressed at baseline and made smaller treatment gains.[7]

A study of 31 patients age >60 with mild-to-moderate depression[8] compared 16 sessions of professionally administered cognitive-behavioral therapy (CBT) with self-administered cognitive therapy learned from reading a book.[9] Both groups showed greater improvement in depressive symptoms compared with a control group. Subjects in the CBT group did somewhat better during the trial, but at 3-month follow-up most patients in both treatment groups no longer met diagnostic criteria for MDD.

Conclusion. Evidence supports bibliotherapy as an effective treatment for mild-to-moderate depression. No convincing data support its use as a complementary treatment, but it poses virtually no risk.

continued

Clinical Point

Yoga's positive effects suggest that exercise does not have to be aerobic to provide an antidepressant benefit

CAM for depression

Clinical Point

Self-administered CBT learned from reading books has been shown to be an effective treatment for mild-to-moderate depression

Table 3

Evidence of the antidepressant effect of exercise

Literature review	Methodology	Conclusion
Byrne and Byrne, 1993	13 studies, clinical samples, measured changes in depressed mood	90% of studies reported beneficial effects, especially in clinical populations
Scully et al, 1998	4 literature reviews, 1 monograph, 1 study	Positive relationship of physical activity and depression in healthy and clinical samples, increased over time
Lawlor and Hopker, 2001	14 RCTs from 1966 to 1999 with depression as an outcome	Significant methodologic weaknesses, but exercise effect > no treatment and = cognitive therapy
Dunn et al, 2001	Examined dose effect in 37 studies; subjects diagnosed with depressive disorders, mild-to-moderate symptoms, and no medical comorbidity	Only level B and C evidence; positive effects with exercise from light to heavy intensity; aerobic = nonaerobic; improvement may or may not be related to improved fitness
Brosse et al, 2002	12 RCTs from 1979 to 1999	Significant methodologic limitations, but authors concluded evidence supports a positive effect of exercise in healthy and clinical populations
Larun et al, 2006	4 RCTs in children and youth age <20	Exercise effect same as no intervention, low-intensity relaxation, or psychosocial intervention
Barbour et al, 2007	2 meta-analyses, 1 RCT, 2 studies	Positive effect; high-energy was optimal dose; aerobic = nonaerobic; improvement may or may not be related to improved fitness

RCT: randomized controlled trial
Source: For references to studies described in Table 3, see this article at CurrentPsychiatry.com

St. John's wort (*Hypericum perforatum*) has been extensively studied for depressive disorders, with 29 RCTs in a meta-analysis of MDD trials through July 2008.[10] Another meta-analysis compared St. John's wort with selective serotonin reuptake inhibitors (SSRIs) in 13 studies through June 2008.[11] These and most RCTs have found St. John's wort significantly more effective than placebo in reducing depressive symptoms.

Data selected from double-blind RCTs totaling 217 patients with mild depression [Hamilton Depression Rating Scale (HDRS) scores <20] showed that St. John's wort standardized extract WS5570 induced significantly higher remission rates than placebo.[12] Studies routinely show that treating MDD with St. John's wort is comparable to using tricyclic or SSRI antidepressants.

Side effects with St. John's wort generally are no different than with placebo and significantly less than with comparison treatments. Even so, using St. John's wort instead of SSRIs for MDD remains controversial.

Studies vs SSRIs. Many of the favorable St. John's wort trials were conducted in Europe, particularly in Germany. Two large RCTs conducted in the United States reported that the St. John's wort standardized extract LI-160 was not more effective than placebo, but neither could be clearly interpreted as negative for St. John's wort:

- In an 8-week trial, St. John's wort and placebo groups improved significantly but at unusually low rates. The remission rate with St. John's wort was small but significantly higher than with placebo.[13]
- A study sponsored by the National Institute of Mental Health compared St. John's wort, 900 to 1,500 mg/d; sertraline, 50 to 100 mg/d; and placebo in 340 adults with MDD. No positive effects were found for St. John's wort or sertraline.[14]

Side effects. St. John's wort can affect blood levels of circulating medications metabolized by the cytochrome P450 liver enzyme system, including tricyclic antidepressants. Case studies have reported pregnancy from oral contraceptive failure,

skin rashes, headache, and mania with St. John's wort use. Although these reports are disturbing, St. John's wort's side effects when compared with SSRIs have been less frequent (40% vs 49%) and milder (clinical trial dropout rate 2% vs 7%).[11]

Conclusion. Standardized extracts of St. John's wort—particularly WS5570, 300 mg tid, and ZE117, 250 mg bid—appear to be effective treatments, especially for mild-to-moderate MDD. Because St. John's wort is available without prescription and can interact with SSRIs or other antidepressants:

- care is required for its complementary use
- it is important to ask if patients are using St. John's wort on their own.

St. John's wort is used as a first-line depression treatment in Europe, but U.S. physicians may be less familiar with its potential interactions with other medications. We recommend that you consider St. John's wort:

- for first-line use only when you can adequately gauge its effects on your patient's other medications
- especially for depressed patients who cannot tolerate SSRIs.

SAMe is a metabolite involved in biosynthesis of norepinephrine, serotonin, and dopamine.[15] SAMe salts (such as 1,4-butanedisulfonate) are used as an over-the-counter supplement for depression treatment. Dozens of RCTs show SAMe has greater efficacy than placebo and positive effects comparable to those of standard antidepressants. In a meta-analysis of 28 RCTs by the Agency for Healthcare Quality and Research, SAMe produced significantly greater symptom improvement compared with placebo.[16]

SAMe has become a popular alternative treatment for depression since its introduction to the United States in the late 1990s, but it has been studied in only 2 U.S. open trials. One showed SAMe to be very effective in reducing depressive symptoms in patients with HIV/AIDS.[17] The other found a 50% response rate and 43% remission rate with adjunctive SAMe, 800 to 1,600 mg/d for 6 weeks, in 30 adults with MDD who failed to respond adequately to SSRIs or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. The most common side effects were gastrointestinal (GI) symptoms and headaches.[18] This open trial led to an ongoing National Institutes of Health-sponsored RCT on the safety and efficacy of SAMe for patients with treatment-resistant depression.

Conclusion. SAMe appears to have a faster onset of antidepressant effect than standard SSRIs or SNRIs and a favorable side-effect profile, which make the lack of rigorous trials in the United States striking. We recommend that you consider SAMe:

- as an adjunct in patients with incomplete response to standard treatments
- as a complementary treatment to speed onset of antidepressant effects.

Polyunsaturated fatty acids (PUFAs), usually from fish oils, have long been popular nutritional supplements because of their beneficial effects on cholesterol and cardiovascular health. Omega-3 and omega-6 fatty acids are the most common PUFAs. The omega-3 PUFAs include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Four meta-analyses independently looked at largely the same dozen RCTs through 2006 and found that 1 to 2 grams daily of omega-3 PUFAs was significantly more effective at reducing depressive symptoms than placebo.[19-22] Other data suggest that omega-3 PUFAs can induce depression remission in depressed Parkinson's disease patients[23] and depressed pregnant women.[24] Since 2006, however, findings have been inconsistent. Several trials have found PUFAs no more effective than placebo.[25-27]

An 8-week double-blind study compared EPA, 1 gram daily; fluoxetine, 20 mg/d; or both agents in 60 outpatients with MDD. Response rates—as measured by ≥50% reduction in baseline HDRS scores—were 50% with fluoxetine, 56% with EPA, and 81% with combination therapy.[28]

Conclusion. Questions remain about dosing, ratio of EPA to DHA, patient selection, and baseline blood levels of PUFAs compared with response. PUFAs have a benign side-effect profile, with occasional reports of diarrhea or GI upset. Although

Clinical Point

Consider St. John's wort for first-line use only when you can adequately gauge its effects on your patient's other medications

Clinical Point

SAMe could be useful as a complementary treatment to speed the onset of antidepressant effects

Table 4

Acupuncture: Insufficient evidence of antidepressant effect

Literature review	Methodology	Conclusion
Mukaino et al, 2005	Systematic review of 7 RCTs including 509 patients; compared either manual or electroacupuncture with any control procedure	Inconsistent evidence of manual acupuncture's effectiveness vs sham; electroacupuncture's effect may be similar to that of antidepressant medication and merits further study
Leo and Ligot, 2007	Systematic review of 9 RCTs, 5 considered low quality; some focused on very specific populations (ie, hospitalized stroke patients or pregnant depressed patients)	Evidence inconclusive because of study designs and methodologies
Smith and Hay, 2005	Meta-analysis of 7 trials including 517 adults with mild-to-moderate depression; 5 trials (409 participants) compared acupuncture with medication; 2 trials compared acupuncture with wait list or sham acupuncture	No difference between acupuncture and medication; study quality too poor to support acupuncture's efficacy
Wang et al, 2008	Meta-analysis of 8 small RCTs totalling 477 subjects (256 received active acupuncture, remainder received sham acupuncture); sham acupuncture design, number of acupuncture sessions, and duration varied among studies	Significant reduction in HRSD or BDI scores for acupuncture vs sham, but no significant effect of acupuncture on response or remission rates

BDI: Beck Depression Inventory; HRSD: Hamilton Rating Scale for Depression; RCT: randomized controlled trial
Source: For references to studies described in Table 4, see this article at CurrentPsychiatry.com

their therapeutic effects are being clarified, PUFAs appear safe to recommend as an adjunct treatment if standard care is not satisfactory.

Insufficient evidence

L-tryptophan. It seems reasonable to expect a serotonin precursor to increase serotonin in the CNS and improve depressive symptoms. Of 111 trials on L-tryptophan for depression, however, only 2 met the quality criteria for inclusion in a recent meta-analysis.[29] Combining the 2 trials showed L-tryptophan alone and in combination with a tricyclic antidepressant was more effective than placebo for treating depressive disorders in adults.

Conclusion. Very little research continues to test L-tryptophan as a viable CAM for depressive disorder. Its serious side effect of eosinophilia-myalgia syndrome makes clinical use of this agent unlikely.

Acupuncture. Numerous small studies with questionable controls, different needling placements, and poor allocation concealment and blinding limit the ability to draw conclusions about acupuncture for treating depression (***Table 4***). A recent meta-analysis by Wang et al[30] added 2 Chinese trials not included in an earlier review[31] and found acupuncture significantly reduced depressive symptoms. No consistent differences were detected in response or remission rates, however.

Conclusion. Evidence is methodologically weak, and the use of acupuncture as an alternative or complementary treatment of depression is questionable.

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Related Resources

- National Center for Complementary and Alternative Medicine, National Institutes of Health. http://nccam.nih.gov.
- Journal of Alternative and Complementary Medicine. www.liebertpub.com/products/product.aspx?pid=26.
- Complementary and alternative medicine. www.nlm.nih.gov/medlineplus/complementaryandalternativemedicine.html.

Drug Brand Names

Fluoxetine • Prozac
Imipramine • Tofranil
Lithium • Eskalith, Lithobid
Sertraline • Zoloft
Venlafaxine • Effexor

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

CAM interventions' popularity for depressive disorders is disproportionate to the limited evidence base. Ask patients about CAM use, and assess with them the risks and benefits based on the best available evidence. Yoga, exercise, bibliotherapy, St. John's wort, SAMe, and omega-3 fatty acids have been shown capable of inducing remission of depressive symptoms in randomized controlled trials.

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Clinical Point

Although PUFAs' therapeutic effects remain unclear, they appear safe to use as adjuncts if standard treatment is not satisfactory