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# Treating depression: What works besides meds?

How effective are cognitive behavioral therapy, prescribed exercise, dietary supplements, and other nonpharmacologic options for alleviating depression? Here's what the evidence tells us.

## **PRACTICE RECOMMENDATIONS**

- › *Recommend cognitive behavioral therapy, interpersonal therapy, or problem-solving therapy for the treatment of depression in patients of all ages. (A)*
- › *Consider prescribing exercise as a stand-alone or adjunctive treatment for patients with depression. (B)*
- › *Advise patients who ask about omega-3 fatty acid supplements that formulations with a high eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio (2:1) may be a useful "add-on" to their current regimen. (B)*

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

**CASE 1** ▶ Steve J, age 43, comes to your clinic looking uncharacteristically glum. He was recently downsized from his job and misses his former colleagues. His job loss has caused a financial strain for his family, and he admits to crying in the shower when he thinks about how his life has turned out. Mr. J tells you that he's gotten a part-time job, but he's already called in sick several times. On those sick days he "stayed in bed all day and slept." He says that when he does go to work, he rarely interacts with his coworkers and his concentration is poor. He tells you he wakes up early in the morning on most days and cannot return to sleep, despite being "tired all the time." He denies suicidal ideation. Mr. J has never felt this way before, which is what prompted his visit today, but he thinks it is "weak to take a pill to feel better."

What nonpharmacologic options can you offer him?

**CASE 2** ▶ Kerri S is a 27-year-old mother of 2 who comes to your clinic to establish care. She tells you about a recent recurrence of depressed mood, which she feels is due to the stress of moving to the area. She is experiencing sleep-onset insomnia and concentration lapses. Her appetite is poor (self-reported 8-lb weight loss in 2 months) and she lacks the motivation to engage in her daily activities, saying, "I wouldn't even get out of bed if my kids didn't need me." She notes that she is constantly irritable and has completely lost her sex drive. Unlike her prior depressive episode, she has not had any suicidal thoughts. Mrs. S was previously successfully treated with paroxetine, 20 mg/d, but she is not interested in restarting her medication because she is still breastfeeding her toddler.

Are there evidence-based options for her care that do not include medication?

**M**ajor depressive disorder (MDD) is widespread and often disabling, affecting nearly 8% of people ages 12 and older at any given time.<sup>1</sup> Thus, it's crucial to

be familiar with the diverse array of evidence-based treatment options from which patients can choose. Although medications are an essential treatment option for patients with severe depression, their value for patients with mild to moderate depression is often limited.<sup>2</sup> In addition, when antidepressants aren't combined with psychosocial interventions, discontinuing them is associated with relapse.<sup>3</sup>

Fortunately, research has found that certain nonpharmacologic interventions—including psychotherapies, somatic therapies, and dietary supplements—can have either therapeutic or adjunctive benefits for treating depression, and can be provided in ways that are time- and cost-effective. This article reviews the evidence supporting several options in each of these treatment categories.

### Evidence backs several types of psychotherapy

Several recent meta-analyses suggest that a variety of psychotherapeutic treatments may hold promise for your patients with depression.<sup>4,5</sup> When analyses were limited to larger studies in order to decrease the risk of bias, cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and problem-solving therapy (PST) all resulted in moderate to large improvement in depressive symptoms when compared to wait-list controls.<sup>4</sup> These findings were echoed in a recent systematic review/meta-analysis that focused on depressed primary care patients. Linde et al<sup>5</sup> found that the number needed to treat (NNT) to achieve one response (≥50% reduction in score on a depression scale) using any type of psychotherapy was 10, and the NNT to achieve one remission (scoring below a pre-defined score on a depression scale) was 15.

Psychotherapy can be effective when provided in individual and group settings,<sup>6</sup> as well as via telephone, the Internet, or software programs.<sup>7</sup> (For a list of self-help, computerized, and Internet-based resources, see **TABLE W1** at the end of this article at [jfonline.com](http://jfonline.com).)

■ **CBT** has been studied for several decades and there's strong evidence for its efficacy.<sup>6</sup> Recent investigations have suggested that CBT delivered in less resource-intensive modes (such as via computer program, In-

ternet, telephone, or videoconferencing) can be as effective as face-to-face CBT.<sup>6,8</sup> CBT has been shown to be helpful for a wide range of patients,<sup>6</sup> improves outcomes over standard primary care treatment,<sup>9</sup> and provides a useful adjunct to medication in treatment-resistant severe depression.<sup>10</sup>

■ **Behavioral activation (BA)**, which generally is included as a component of CBT, has received support as an independent treatment, and may produce therapeutic results similar to CBT<sup>11</sup> and PST (which we'll discuss in a bit).<sup>12</sup> The core components of BA are scheduling pleasant activities and increasing the patient's positive interactions with his or her environment by decreasing avoidance, withdrawal, and inactivity.<sup>11</sup> Compared to CBT, BA is easier for clinicians to learn and incorporate into primary care visits, and it may be especially useful as an adjunctive or first-step intervention in outpatient clinics.<sup>11</sup> Like CBT, BA can be effective in diverse patient groups<sup>13,14</sup> and can be provided using novel delivery modes, such as via the Internet.<sup>15</sup>

■ **IPT** is a supportive, structured, brief therapy (12-16 visits) that focuses on helping patients identify and solve current situation- and relationship-based problems that stem from or contribute to their depression.<sup>16</sup> Enhancing the patient's interpersonal communication—including improving social skills, assertiveness, and appropriate expression of anger—is typically a component of IPT. Like CBT, IPT has been found to be effective for treating depression when administered in person, in group therapy, or via the phone or Internet, and across a broad age range.<sup>17-19</sup>

■ **PST** involves teaching patients a structured problem-solving process to decrease interpersonal strain and improve positive life experiences.<sup>20</sup> Patients are taught to define their problem, generate and evaluate multiple solutions for it, implement a plan for the solution, and evaluate the results. In addition to being used to successfully treat adults,<sup>4,5</sup> PST has been adapted effectively to treat adolescents<sup>16</sup> and older adults.<sup>18</sup>

### Somatic therapies are also an option

**Exercise** has long been considered a possible depression treatment due to its activity on en-



Compared to cognitive behavioral therapy, behavioral activation is easier for clinicians to learn and incorporate into primary care visits.

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More than half of patients receiving electroconvulsive therapy respond to treatment by the end of the first week.

dorphin, monoamine, and cortisol levels and via increased social and general activity. A 2013 Cochrane review of 39 randomized control trials (RCTs; N=2326) assessed whether exercise was effective for treating depression in adults.<sup>21</sup> Thirty-five trials found a moderate effect size when specifically comparing exercise to no treatment or control interventions. The effect size was reduced, however, when analyses were restricted to trials with the highest methodological quality. There was no statistically significant difference when exercise was compared to pharmacologic treatment or psychotherapy.

Although the amount of research is meager, small but statistically significant improvements have also been found for older adults<sup>22</sup> and children/adolescents.<sup>23</sup> There is no consensus on the type, frequency, or intensity of exercise needed to achieve benefit. However, because nearly all studies for all age groups have found that exercise has no adverse psychological effects and substantial positive physical effects, exercise should be recommended to all patients with depression unless contraindicated.

■ **Yoga** (both exercise-based and meditation-based) has been evaluated both as a sole treatment and as an adjunctive treatment for depression. Several studies have supported the impact of yoga, particularly in pregnant women,<sup>24</sup> although the evidence for its efficacy is inconsistent, with yoga frequently failing to improve upon the outcome of waitlist control.<sup>25</sup> The evidence for meditation and mindfulness is more consistently positive, with these interventions equaling or exceeding “treatment as usual,” other psychotherapies, and antidepressants in numerous RCTs.<sup>25</sup>

■ **Electroconvulsive therapy (ECT)** has a substantial evidence base supporting its efficacy.<sup>26</sup> ECT has been used for decades, although stigma, cardiac and memory risks, and risks of anesthesia often limit its use. Benefits of ECT include a rapid response relative to pharmacotherapy (>50% of patients respond by the end of the first week of ECT)<sup>27</sup> and a strong response in older patients.<sup>28</sup>

■ **In repetitive transcranial magnetic stimulation (rTMS)**, electromagnetic coils are placed on a patient’s head to deliver electromagnetic pulses that stimulate areas of

the brain that regulate mood. Although rTMS is not widely available, a growing body of evidence supports its use for treating depression, including a meta-analysis of 34 RCTs that included 1383 patients.<sup>29</sup> A multisite RCT (N=190) that was not industry-funded reported a 15% response rate and 60% maintenance of remission at 3 months (NNT=12).<sup>30</sup> Although ECT is more effective than rTMS, rTMS appears useful for treatment-resistant depression, and can be used as an adjunctive treatment.<sup>29,31</sup>

### Dietary supplements may be best used as adjuncts

■ **St. John’s wort** (*Hypericum perforatum*), which contains 2 bioactive ingredients (hyperforin and hypericin), has been effectively used to treat depression.<sup>32</sup> A 2008 Cochrane review that was limited to high-quality trials involving patients meeting *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* criteria for depression identified 29 trials (N=5489), of which 18 involved comparisons with placebo and 17 with standard antidepressants.<sup>33</sup> Patients’ depression was rated mild to moderate in 19 studies and moderate to severe in 9 studies. Trials examined 4 to 12 weeks of treatment with *Hypericum* extracts. This study (and several published since) provides strong clinical evidence supporting the efficacy of St. John’s wort for mild to moderate depression. There is insufficient evidence for its use for severe major depression.<sup>33</sup> TABLE 1 contains dosing information for St. John’s wort and other supplements used to treat depression.<sup>34-36</sup>

■ **S-adenosyl-L-methionine (SAME)**. In a 2003 systematic review,<sup>37</sup> 1600 mg/d of oral SAME was found to significantly benefit patients with depression in 4 of 5 studies, as did parenteral SAME (7 of 7 trials). Another review of 48 studies found SAME was safe and effective for depression.<sup>38</sup> SAME has been proposed for use alone or in combination with an antidepressant.

■ **Folate and folic acid.** Low folate levels have been associated with a less robust response to antidepressants in patients with MDD,<sup>39</sup> and higher folate levels appear to be associated with better antidepressant re-

TABLE 1

Dietary supplements used to treat depression\*<sup>34-36</sup>

Herb/supplement	Dosage	Comments	Safety in special populations
Folate	Folate: .5-5 mg/d, or L-methylfolate: 7.5 mg/d, or folinic acid: 15-30 mg/d	L-methylfolate may be the preferred formulation.  Individuals with the polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene may have an increased need for folate.	Likely safe in children/adolescents and women who are pregnant or breastfeeding
Omega-3 fatty acids	1-6 g/d  Use formulations with an eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio of 2:1	Although increased bleeding is a theoretical risk, several large trials have failed to identify any clinically significant increased risk of bleeding with omega-3 use.  Recommend monitoring when used by patients taking anticoagulant or antiplatelet medications.	Children/adolescents: safe  Pregnancy: safe; may provide neurodevelopmental benefits  Breastfeeding: likely safe
S-adenosyl-L-methionine (SAME)	Initial: 400-1600 mg/d  Maintenance: up to 3000 mg/d	Can worsen underlying agitation, panic, or anxiety. Possibly induces swings toward mania. May be cost-prohibitive.	Children/adolescents: insufficient evidence of safety  Pregnancy: likely safe  Breastfeeding: insufficient evidence of safety
St. John's wort	300-600 mg 3 times a day  Symptom improvement can occur quickly (as early as 10 days) or can take up to several weeks.  If there is no response after 4 weeks, dose may be increased by 200 to 400 mg/d every 1 to 2 weeks up to 1800 mg/d.	Induces cytochrome P450 3A4 and intestinal P-glycoprotein.  Risk of drug interactions. May lead to symptoms of serotonin syndrome when combined with selective serotonin reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors.	Children/adolescents: safe for short-term use; insufficient evidence for long-term use  Pregnancy: category C  Breastfeeding: not recommended

\* Encourage patients to purchase United States Pharmacopeia-verified products to be assured of accurate, verified ingredient labeling and the absence of harmful contaminants.

sponse.<sup>40</sup> A 2003 Cochrane review suggested folate might have a role in treating depression.<sup>39</sup> A 2009 study found folate supplementation could reduce depressive symptoms for patients with normal baseline folate levels as well as those with low levels.<sup>41</sup> Although the evidence is equivocal, folate augmentation may enhance antidepressant efficacy or improve response/remission rates.<sup>41,42</sup>

It seems reasonable to check folate levels in depressed patients, and address deficiencies by instructing patients to increase their dietary intake of folate or to take supplements. Augmenting antidepressants with folate appears to be low-risk and possibly helpful in maintaining remission.

■ **Omega-3 fatty acids.** There is substantial evidence that omega-3 fatty acids can prevent and treat depression.<sup>43,44</sup> Recent meta-analyses support the use of omega-3 fatty acids as monotherapy and augmentation, but only formulations that contain a high eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio (EPA/DHA 2:1).<sup>45,46</sup> Omega-3 supplementation has been used with positive results in older adults, children,<sup>47</sup> pregnant women,<sup>48</sup> and women with postpartum depression.<sup>49</sup> Although initial research into omega-3 treatment of depression appears promising, augmentation of standard antidepressant therapy may be a good conservative option.

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**Low folate levels have been associated with a less robust response to antidepressants in patients with major depressive disorder.**

### Use a validated tool to monitor response to treatment

You can enhance outcomes for your patients with depression if you schedule routine follow-up visits with them to gauge adherence to recommendations, monitor response to treatment, and increase the intensity of care when response is inadequate.<sup>50</sup> The most important aspect of monitoring response is to use a standardized instrument that quantifies symptoms at every visit.

The Patient Health Questionnaire 9-item depression assessment (PHQ-9)—which is free—has been validated for depression screening and monitoring of treatment response in primary care patients.<sup>51</sup> A decrease of 5 points on the PHQ-9 is the minimum considered to be clinically significant.<sup>52</sup> Other well-validated, although lengthier, self-report depression assessment and monitoring instruments include the Beck Depression Inventory-revised and the Zung Depression Scale.

**CASE 1** ▶ Mr. J is not enjoying his new job or engaging with new coworkers to replace the positive social experiences he had at his previous job. Together, you set a goal of increasing social involvement by having him make plans to see at least one friend per weekend. Because he indicates that he is unlikely to follow through with a therapy referral, you encourage him to try an online CBT program, start an exercise regimen, or take a SAME supplement. Mr. Jackson agrees to try the CBT and exercise (moderate intensity, 30 minutes 3-4 times per week), but does not want to take SAME. He agrees to an assessment of his folate levels, which are normal.

Mr. J starts the online CBT program, which reinforces the exercise and social activity prescription you provided. He establishes a regular exercise routine with a good friend. After one month, his mood has started to im-

prove and he has added regular participation in a hobby (woodworking), as well as volunteer work, which he finds fulfilling. You plan to continue monitoring his depression and his adherence to the treatment plan.

**CASE 2** ▶ The recent move has decreased Mrs. S's interactions with family and long-time friends. Because she had previously expressed interest in exercise, you encourage her to join a local "Mommy and Me" exercise and support group for mothers of toddlers. She is willing to participate in psychotherapy, so you provide a referral to a local therapist with expertise in IPT. You also discuss with Mrs. S the possible benefits of omega-3 fatty acid supplementation, which appears to be safe during breastfeeding.<sup>34</sup>

Mrs. S begins therapy and exercise classes, but can't motivate herself to continue either of these activities. She becomes discouraged because she's unable to easily find an omega-3 fatty acid supplement with the ratio you specified (EPA/DHA 2:1). When you see her 2 weeks later, her depression has worsened.

Because you are concerned her suicidality will return, you revisit the pros and cons of taking an antidepressant. Although small amounts of antidepressants can be passed from mother to infant via breastmilk, the amount varies by specific medication, as do the potential risks. Mrs. S decides to resume taking paroxetine 20 mg/d and eventually, once her motivation improves, she's able to add psychotherapy and exercise to her maintenance/relapse prevention regimen. After you discuss with her the possibility that B vitamin supplementation may assist in maintenance of remission, she adds L-methylfolate 7.5 mg/day to her regimen. **JFP**


#### CORRESPONDENCE

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 The PHQ-9— which is free—has been validated for depression screening and monitoring of treatment response in primary care patients.

**TABLE W1**

## Self-help, computerized, and Internet-based therapeutic options for combating depression

### For patients

Living Life to the Full ([www.lttf.com](http://www.lttf.com))

*Free online CBT program for depression; DVDs and books also available for purchase*

MoodGym (<https://moodgym.anu.edu.au/welcome>)

*Free online CBT program for depression*

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*IPT for depression*

Otto MW, Smits JAJ. *Exercise for Mood and Anxiety: Proven Strategies for Overcoming Depression and Enhancing Well-being*. Oxford, England: Oxford University Press; 2011

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*CBT manual; includes information on depression, anxiety, anger, and other mood difficulties*

Burns D. *Feeling Good: The New Mood Therapy*. New York, NY: Harper; 2008

*Classic CBT book for depression*

Williams C. *Overcoming Depression and Low Mood*. Oxon, UK: Hodder; 2009

*Self-help guidance based on problem-solving therapy*

Robinson PJ, Strosahl KD. *The Mindfulness and Acceptance Workbook for Depression: Using Acceptance and Commitment Therapy to Move Through Depression and Create a Life Worth Living*. Oakland, CA: New Harbinger; 2008

*Mindfulness and meditation incorporated into CBT strategies*

### For clinicians

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*Training DVDs for healthcare providers available at <http://www.10minutecbt.co.uk>*

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Beating the Blues ([http://u2interactive.com/b\\_over.html](http://u2interactive.com/b_over.html))

*Research-supported computerized CBT program for depression and anxiety; US providers can contract with Beating The Blues to allow patients access to the system*

Association for Behavioral and Cognitive Therapies (<http://www.abctcentral.org/xFAT/>)

*Directory of therapists who provide CBT*

CBT, cognitive behavioral therapy; IPT, interpersonal therapy.