



# CATEGORY

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## Integrative Treatment of Bipolar Disorder: A Review of the Evidence and Recommendations

by James Lake, MD

**C**omplementary and alternative medicine (CAM) therapies—which include many natural products—are widely used alone or in combination with psychotropic drugs to treat or self-treat mental illness. It has been estimated that up to half of all

individuals with a diagnosed mood disorder use 1 or more CAMs.<sup>1,2</sup> A significant percentage of this population combines conventional pharmacological treatments with CAMs.<sup>3</sup>

In bipolar disorder, however, there is relatively little evidence for the safety and efficacy of most CAM or integrative treatments.<sup>4,5</sup> A recent survey of older patients with a diagnosed major

depressive disorder (n = 50) or bipolar disorder (n = 50) found that 44% of those with bipolar disorder use herbal and other natural products compared with only 16% of those who were depressed.<sup>6</sup> Another significant finding of the survey was that up to 20% of older patients with a mood disorder preferred to use herbal or other natural products over prescription medications,



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### FACULTY

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### FACULTY DISCLOSURES

Dr Lake reports no conflicts of interest concerning the subject matter of this article.  
This activity has been independently reviewed for balance.

### TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, nurse practitioners, and other health care professionals who seek to improve their care for patients with bipolar disorder.

### GOAL STATEMENT

This activity will provide participants with an understanding of the most commonly used alternative and integrative treatments of bipolar disorder and how such nonconventional therapies can most benefit patients with this disorder. In addition, participants will be able to assess when caution is warranted in using natural product treatments.

### ESTIMATED TIME TO COMPLETE

The activity in its entirety should take approximately 90 minutes to complete.

### LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Appreciate the usefulness of complementary and alternative medicine (CAM) and integrative therapies for the nonacute treatment of bipolar disorder
- Identify the most common types of CAM and integrative treatments, eg, omega-3 fatty acids, magnesium, amino acids, and herbal compounds or combinations of natural products and conventional pharmacological treatments
- Recognize the indications and uses for select natural products in bipolar disorder
- Understand efficacy and safety issues for CAM and integrative treatment options in bipolar disorder

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and that more than 40% of older adults believed that natural products were regulated by the FDA for treatment of depressed mood and bipolar disorder. The majority of older adults with a diagnosis of any mood disorder (64%) had not discussed use of herbals or other natural products with their physicians.

I briefly review the limitations of conventional pharmacological therapies in this article. My goal is to identify factors that lead increasing numbers of patients with bipolar disorder to use CAMs alone or in combination with conventional pharmacotherapy (ie, as integrative treatments). I then examine the evidence base for select CAM and integrative modalities currently used to treat or self-treat bipolar disorder. Finally, I offer provisional guidelines for the safe, judicious use of select CAM therapies as adjuvants in both phases of bipolar disorder.

Where study findings permitted statistical analysis, effect sizes are presented as Cohen's *d* by finding the difference between the intervention and placebo scores on the scale used (eg, Hamilton Rating Scale for Depression [HAM-D], Young Mania Rating Scale [YMRS]) and dividing this by the pooled standard deviation at baseline.<sup>7</sup>

### Limitations of conventional treatment approaches

To provide the best clinical advice to patients with bipolar disorder about the range of available treatment choices, psychiatrists and other mental health professionals should be knowledgeable about the evidence that supports conventional pharmacological treatments as well as promising CAM and integrative treatment strategies. While conventional pharmacological treatment is necessary for patients in the acute phase of bipolar illness, medications alone do not make up an adequate maintenance strategy for stable bipolar patients. For example, regular exercise, adequate sleep, good nutrition, a strong social support network, and a predictable low-stress environment are known to significantly reduce relapse risk in bipolar patients who are being treated with mood stabilizers.<sup>8,9</sup> Integrative mental health care embraces the perspective that tailoring an individualized treatment plan to each patient's unique history, symptoms, preferences, and financial constraints increases the patient's motivation to stay in treatment, which improves adherence and results in better outcomes.

Widely prescribed pharmacological treatments of both the depressive and manic phases of bipolar disorder have a mixed record of success because of their limited effectiveness and high rates of discontinuation.<sup>10</sup> One study showed that fewer than half of the patients who were treated with a conventional mood stabilizer or other psychotropic medications after an initial manic episode reported sustained control of their symptoms.<sup>11</sup> Furthermore, as many as half of all patients with bipolar disorder who take maintenance mood stabilizers do not experience good control of their symptoms or they refuse to take medications, and approximately half eventually discontinue their medications because of adverse effects that include tremor, weight gain, and elevated liver enzyme levels.<sup>12</sup>

A significant percentage of patients with bipolar disorder rely on maintenance antidepressant therapy to control depressive mood swings, which significantly increase the risk of mania. Commonly prescribed pharmacological regimens used to treat bipolar disorder combine mood stabilizers with antidepressants or atypical antipsychotics; however, a systematic review found only modest improvements in outcomes when such combination therapy was used.<sup>13</sup>

The limited effectiveness and safety issues associated with conventional psychotropics in the management of bipolar disorder have resulted in high relapse rates in individuals taking mood stabilizers and other psychotropic medications, with associated impairment in social, academic, and occupational functioning, and increased risk of suicide.<sup>14</sup> These issues underscore the urgent need to identify more effective, better-tolerated treatments for bipolar disorder and invite rigorous and open-minded consideration of emerging research findings for promising CAM and integrative treatments.

**Table 1** summarizes significant findings and comments on unresolved research and treatment issues for the natural products reviewed in this article.

### Omega-3 essential fatty acids ( $\omega$ -3s)

Placebo-controlled trials have evaluated  $\omega$ -3s in bipolar disorder as both a monotherapy and an adjuvant to mood stabilizers. In an early controlled trial of 44 patients with stable bipolar disorder who were treated with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (9.6 g/d) in combination with mood stabilizers, significant improvements were seen in depressed mood on the HAM-D (*d* = 1.40); however, changes in symptoms of mania by the YMRS were not significant.<sup>15</sup>

In a 12-week, 3-arm, placebo-controlled study, patients with stable bipolar disorder were treated with EPA 1 g/d (*n* = 24), EPA 2 g/d (*n* = 25), or placebo (*n* = 26) and their usual maintenance regimen; patients in the groups that received EPA experienced small but significant improvements in measures of depressed mood on the HAM-D (1 g: *d* = 0.90; 2 g: *d* = 0.50), compared with those in the placebo group, but a significant effect on mania was not achieved on the YMRS.<sup>16</sup> In a subsequent larger study (*N* = 121), patients with rapid cycling bipolar disorder did not experience improvements in the frequency or severity of manic symptoms on the YMRS while taking purified EPA (6 g/d) in combination with at least 1 mood stabilizer.<sup>17</sup>

A systematic review identified 5 placebo-controlled trials for  $\omega$ -3s in bipolar disorder that met strict inclusion criteria for methodological quality. Only 1 study included in the review in which  $\omega$ -3s were taken as an adjunct to a mood stabilizer showed a significant differential beneficial effect on depressive but not manic symptoms.<sup>18</sup> The reviewers commented on the uneven quality of published studies and cautioned that it is premature to draw conclusions about the effectiveness of  $\omega$ -3s for bipolar disorder pending large, well-designed, placebo-controlled studies.

Results of 2 small open-label studies have re-

cently been published that suggest beneficial effects of  $\omega$ -3s in both phases of pediatric bipolar disorder. In a small open-label study, 20 children and adolescents who met DSM-IV-TR criteria for bipolar disorder and had a YMRS score of greater than 15 were given 1290 to 4300 mg of fish oil. There were significant reductions on the YMRS (*d* = 0.90) and the brief psychiatric rating scale (BPRS; *d* = 0.83) compared with baseline.<sup>19</sup>

In a 6-week open-label study, 18 children and adolescents with bipolar I or II disorder were treated with purified  $\omega$ -3s (DHA 1560 mg/d and EPA 360 mg/d). The results showed significant reductions in clinician-rated mania and depression relative to baseline.<sup>20</sup> While large placebo-controlled studies are needed to confirm these findings, preliminary data suggest that  $\omega$ -3s may be effective when combined with mood stabilizers in the depressive phase of bipolar illness but may not significantly improve symptoms of mania or rapid cycling.

Although  $\omega$ -3s are generally well tolerated, some patients report nausea, loose stools, and fishy-smelling "burps." GI adverse effects may be reduced by taking  $\omega$ -3s with meals. Cod liver oil contains high levels of vitamins A and D, and long-term use or inappropriate high doses can result in vitamin toxicity. Mild anticoagulant effects may occur with use of  $\omega$ -3s. Rare cases of increased bleeding time but not increased bleeding have occurred when  $\omega$ -3s were used concurrently with aspirin or anticoagulants.<sup>21</sup> Patients treated with  $\omega$ -3s should be advised to use pharmaceutical-grade preparations to avoid contamination from heavy metals, polychlorinated biphenyls, and organochlorines.

### Magnesium

Preliminary findings suggest that oral or intravenous magnesium may be an effective adjuvant to mood stabilizers in patients with acute mania or rapid cycling bipolar disorder. In an early open-label trial lasting 32 weeks, 4 of 9 rapid cycling bipolar patients who took oral magnesium (40 mEq/d) experienced improvement similar to that seen in patients who received maintenance lithium therapy.<sup>22</sup>

In a subsequent case series, 10 patients with severe treatment-resistant agitated manic bipolar disorder who received a continuous intravenous magnesium sulfate infusion (200 mg/h) for 7 to 23 days while continuing to take psychotropic medications (lithium, haloperidol, and clonazepam) showed significant improvement in functioning on the clinical global impression (CGI) scale.<sup>23</sup> Several of these patients remained stable while taking lower doses of conventional medications. Five patients experienced bradycardia that promptly resolved when magnesium flow was reduced.

There is evidence that oral magnesium augmentation may improve the antimanic effectiveness of mood stabilizers in patients with stable bipolar disorder. In a small controlled trial, 20 men with bipolar disorder were randomized to verapamil (80 mg qid) plus oral magnesium oxide (320 mg/d) or to verapamil and a placebo. Results showed that patients treated with verapamil and magnesium oxide had significant im-

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provement on the BPRS from baseline compared with patients who were treated with verapamil and a placebo ( $P = .015$ ).<sup>24</sup>

Large placebo-controlled studies are needed to confirm the safety and efficacy of intravenous and oral magnesium before either therapy can be recommended for bipolar patients.

### Amino acids

Emerging evidence suggests that some bipolar patients may be genetically susceptible to mood swings when select amino acids are not present in the diet.<sup>25</sup> The results of 2 small placebo-controlled trials suggest that certain branched-chain amino acids (leucine, isoleucine, and valine) may provide rapid improvement in patients with acute

mania—possibly by interrupting synthesis of norepinephrine and dopamine.<sup>26,27</sup> In one study, 25 patients with bipolar disorder were randomized to a special tyrosine-free amino acid drink (60 g/d) or to placebo. Compared with patients who had received placebo, the patients in the active-treatment group experienced significant reductions in mania within 6 hours that were sustained with repeated administration of the amino acid drink and lasted at least 1 week after the study ended.<sup>27</sup> Improvements in mania were not observed in the placebo group.

Preliminary findings suggest that restricting or excluding L-tryptophan from the diet may increase the susceptibility to depressive mood swings in bipolar patients. Rapid tryptophan depletion has been shown to induce transient depressive symptoms in patients with major depressive disorder whose symptoms are in remission.

A rapid reduction of up to 80% in plasma tryptophan level can be accomplished by administering an oral tryptophan-free amino acid solution.

In a small, 7-day, double-blind, placebo-controlled, pilot study, 23 acutely manic bipolar patients who were given sodium valproate (starting at 1000 mg/d) were randomized to receive either a daily tryptophan-free amino acid drink or a placebo drink.<sup>28</sup> Compared with patients in the placebo group, patients who received the amino acid drink had better scores on the YMRS and CGI scale on days 3, 5, and 7. However, there was a high intolerance rate and only 17 patients completed the study (23% drop-out rate). Larger studies are needed to replicate these preliminary findings and address intolerance issues.

*N*-acetylcysteine (NAC) is an amino acid with strong antioxidant properties that has been used to treat a range of inflammatory disorders.<sup>29</sup>

Table 1

### Summary of significant research findings for CAMs

Treatment	Summary of findings	Comments
Omega-3 essential fatty acids	Effective adjuvants in combination with mood stabilizers in the depressive phase of bipolar illness but do not significantly improve symptoms of mania or rapid cycling	Large placebo-controlled studies needed; increased risk of vitamin A and D toxicity with long-term or high-dose use of cod liver oil; nausea and loose stools at higher doses; fishy-smelling “burps” common; GI adverse effects may be minimized by taking with meals; mild anticoagulant activity but no increased bleeding risk when used alone or with aspirin or warfarin; advise patients to use pharmaceutical-grade products to avoid contamination from heavy metals, PCBs, organochlorines
Magnesium	Oral or intravenous magnesium may be an effective adjuvant to mood stabilizers in acutely manic or rapid cycling bipolar patients, possibly permitting reduction in dosing of mood stabilizers	Large placebo-controlled studies needed
Branched-chain amino acids	A drink containing branched-chain amino acids may result in rapid improvement in acute manic symptoms	Large placebo-controlled studies needed
<i>N</i> -acetylcysteine	May reduce symptoms of depressed mood but not mania in stable bipolar patients when combined with mood stabilizers	Large placebo-controlled trials needed
Choline and phosphatidylcholine	May reduce the severity of both mania and depressed mood in bipolar patients	Large placebo-controlled trials needed
Folate	Abnormally low tissue and CNS levels in both depressed mood and mania; may be effective adjuvant when combined with lithium carbonate in both depressive and manic phase	Large placebo-controlled trials needed
Proprietary nutrient formula <sup>a</sup>	May significantly reduce symptoms in some cases of mania, depressed mood, and psychosis when used adjunctively with mood stabilizers	Large placebo-controlled studies needed; reports of GI adverse effects, including nausea and diarrhea; avoid use in women who are pregnant or breast-feeding because of high vitamin A content
St John's wort ( <i>Hypericum perforatum</i> ) <sup>b</sup>	May be effective adjuvant to mood stabilizers in seasonal affective disorder	No studies done on bipolar disorder; should be avoided in bipolar patients because of mania-induction risk; photosensitive rash; induces CYP3A4, causing increased metabolism and decreased serum levels of some widely used drugs, including antiretrovirals, digoxin, oral contraceptives, cyclosporine, warfarin, and statins
<i>Rauwolfia serpentina</i>	May be effective in treatment-refractory psychosis, including bipolar mania	

CAM, complementary and alternative medicine; PCBs, polychlorinated biphenyls; CYP3A4, cytochrome P-450 3A4.

<sup>a</sup> Serious safety problems reported when taken with a mood stabilizer; may result in toxic drug levels and associated adverse effects.

<sup>b</sup> Restricted use in Western countries because of safety concerns (nausea, vomiting, gastric ulceration, GI distress, erectile dysfunction, hypotension, bradycardia) and increased suicide risk.

Emerging findings suggest that NAC may reduce symptoms of depressed mood but not mania in patients with stable bipolar disorder when it is combined with mood stabilizers.

In a 24-week, placebo-controlled trial, 75 patients with stable bipolar I or bipolar II disorder received 1 g of NAC twice daily as an adjunct to their usual medication. Compared with patients who received placebo in combination with their regular mood stabilizer regimen, patients in the NAC group had significant improvements in bipolar depression on the Montgomery Asberg Depression Rating Scale and the Bipolar Depression Rating Scale, with strong effect sizes of 1.04 and 0.83, respectively. Nonsignificant improvements were found over baseline for symptoms of mania.<sup>30</sup>

### Phosphatidylcholine

Choline is a necessary precursor for synthesis of acetylcholine (ACh); abnormally low CNS ACh levels may underlie some cases of mania.<sup>31</sup> Findings of a small controlled trial suggest that phosphatidylcholine (15 to 30 g/d) may reduce the severity of mania and depressed mood in bipolar patients.<sup>32</sup>

### Folic acid

Folic acid may be an effective adjuvant therapy when combined with lithium carbonate in unipolar and bipolar depression. In an early 1-year placebo-controlled study, 102 patients with unipolar or bipolar depression receiving maintenance lithium therapy were randomized to folate 200  $\mu$ g/d or placebo.<sup>33</sup> Patients in the folic acid group ( $n = 41$ ) had significantly lower Beck Depression Inventory scores than those in the control group, with a strong effect size of 1.07.

At the start of the trial, a significant percentage of patients had low serum folate levels. In those whose plasma folate levels increased to 13 ng/mL (roughly twice the mean of pretrial levels), there was a significant decrease in symptom severity during the trial year. The researchers speculated that the therapeutic benefits of folate supplementation in folate-deficient individuals with affective disorders might be related to the essential

role of folate in serotonin synthesis. Abnormally low levels of folate are also associated with mania. Forty-five inpatients with acute mania had significantly lower red blood cell folate levels than socioeconomically matched controls, but there was no significant difference in serum folate levels.<sup>34</sup> Pending replication by larger studies, these preliminary findings suggest that reduced tissue and CNS levels of folate may be associated with bipolar illness and not dietary deficiency or reduced absorption.

### Proprietary multnutrient formula

A proprietary nutrient formula containing 36 separate constituents, including chelated minerals, vitamins, and trace elements, may reduce symptoms of mania, depressed mood, and psychosis in bipolar patients when taken alone or used as an adjunct to conventional mood-stabilizing medications.<sup>35-39</sup> Beneficial clinical outcomes in bipolar disorder may result from correction of hereditary metabolic errors in genetically predisposed individuals when select micronutrients are deficient or absent in the diet.<sup>37</sup>

In one case series, 11 patients with bipolar disorder who completed a 6-month protocol consisting of 32 capsules daily in 4 divided doses had clinical response with strong effect sizes (HAM-D: 1.70; YMRS: 0.83) and were able to reduce their conventional mood stabilizers by half and improve clinically.<sup>37</sup> In another case series, 13 of 19 bipolar patients who continued taking the nutrient formula remained stable after they discontinued conventional mood stabilizers.<sup>40</sup> Some patients stopped taking the formula because of nausea and diarrhea, and 3 patients resumed conventional mood stabilizers because of recurring manic symptoms. An analysis of self-reported data from 682 adults with bipolar disorder who were taking the proprietary nutrient formula reported significant and sustained clinical improvements over a 6-month period.<sup>41</sup> Serious safety concerns have been reported when the nutrient formula is taken with conventional medications, including toxic levels of certain mood stabilizers.<sup>38</sup> Pregnant women and women who are breast-feeding should avoid use of this formula

because of its potentially toxic high vitamin A content.

### Herbal supplements

St John's wort (*Hypericum perforatum*) has been evaluated extensively as the treatment of major depressive disorder, with mixed results.<sup>42</sup> To date, no studies have been conducted on St John's wort in the depression phase of bipolar disorder. Emerging findings suggest that St John's wort may be effective adjunctive treatment in combination with mood stabilizers in patients with the seasonal variant of bipolar disorder (ie, seasonal affective disorder). In an open study, 169 self-referred patients with a history of seasonal mood changes but without a formal DSM-IV diagnosis of bipolar disorder were randomized to a standardized St John's wort preparation or to St John's wort plus early morning bright light exposure.<sup>43</sup> Both groups experienced significant reductions in anxiety and insomnia; however, the group that received both St John's wort and bright light therapy experienced greater diminution of insomnia.

Adverse effects with St John's wort are infrequent and include mild GI distress, rashes, and fatigue. St John's wort can result in a photosensitive rash and should not be used by patients who are likely to experience prolonged exposure to sunlight. There are case reports of serotonin syndrome with the concurrent use of St John's wort and an SSRI; therefore, this combination should be avoided.<sup>44</sup>

Case reports of mania induction with St John's wort have resulted in limited use of this herbal for the treatment of both major depressive disorder and bipolar disorder.<sup>45,46</sup> Interactions between St John's wort and conventional drugs are mediated by the induction of cytochrome P-450 3A4, which results in increased metabolism and decreased absorption of widely used drugs, including digoxin, anticoagulants, antiretrovirals, oral contraceptives, statins, and cyclosporine.<sup>47</sup>

Reserpine, an alkaloid derivative of *Rauwolfia serpentina*, is used in ayurvedic medicine to treat hypertension and symptoms that resemble the Western diagnoses of psychotic disorders and bipolar disorder. Early studies suggested that reserpine may be an effective adjunctive treatment in severe refractory cases of bipolar disorder or schizoaffective disorder.

In one case series, 6 acutely manic inpatients with bipolar disorder or schizoaffective disorder who had previously been refractory to lithium and an antipsychotic improved significantly when reserpine was substituted for the antipsychotic; in some cases, the lithium dosage was reduced. The results showed improved tolerance to conventional pharmacological treatment, and the patients remained stable on this combination regimen. None of the patients became depressed and none reported significant adverse effects.<sup>48</sup> Preliminary findings suggest that *R serpentina* may be an effective and safe adjuvant to lithium in the treatment of acute mania.

In a retrospective review of treatment-refractory, acutely psychotic, agitated inpatients, 50% of 36 patients who received reserpine (0.5 to 5.5

Table 2

### Suggested provisional guidelines for integrative treatment of bipolar disorder

#### Manic phase

Use of select natural products as adjuvants to conventional mood stabilizers

Use of magnesium, choline, and branched-chain amino acids as adjuvants in acute manic phase

Use of folate as adjuvant to lithium carbonate in acute manic phase

Use of proprietary nutrient formula as adjuvant to mood stabilizers in mania

Use of *Rauwolfia serpentina* for treatment-refractory bipolar mania with psychosis; adjuvant to lithium for acute manic phase

#### Depressed phase<sup>a</sup>

Use of omega-3 essential fatty acids as adjuvant to mood stabilizers

Use of *N*-acetylcysteine in stable bipolar disorder as adjuvant to mood stabilizers

<sup>a</sup> Bipolar patients being treated with any conventional or complementary and alternative medicine (CAM) antidepressant should be monitored closely for warning signs of mania; if a patient becomes manic, the conventional or CAM antidepressant should be discontinued immediately.

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mg/d) following a nonblinded protocol in combination with antipsychotics or antipsychotics plus lithium experienced moderate to dramatic improvement.<sup>49</sup> Three of the responders had full clinical symptom remission, and 8 patients were evaluated as having no psychosis at the time of maximum response. These early findings have not been replicated by large placebo-controlled studies.

Reserpine has relatively few and minor adverse effects when used at dosages of less than 0.2 mg/d; the main adverse effect is nasal congestion.<sup>50</sup> However, use of reserpine in the United States and other Western countries is restricted because of safety concerns that include nausea, vomiting, gastric ulceration, cramps and diarrhea, erectile dysfunction, hypotension, and bradycardia. Western-trained psychiatrists are also cautious about reserpine because of the increased risk of depressed mood and suicide, although most reports of suicide have come from early uncontrolled studies with dosages as high as 0.5 mg/d.<sup>51</sup>

### Conclusions and caveats

Conventional pharmacological treatments of bipolar disorder have limited effectiveness and a record of significant unresolved safety issues. These factors have resulted in high rates of non-response, partial response, and nonadherence. In this context, many patients with bipolar disorder use CAM therapies alone or in combination with prescription medications in the absence of FDA approval and in spite of a paucity of research evidence for the majority of nonconventional treatments—often without disclosing this information to their physician. These trends underscore the urgent need to objectively evaluate the research evidence so that psychiatrists and other mental health professionals can knowledgeably advise patients about appropriate, safe uses of CAM and integrative therapies.

The use of CAM therapies as stand-alone treatments for mania or depressed mood in bipolar disorder is not supported by strong evidence (see **Table 2** for provisional guidelines). Questions remain about the appropriate off-label use of select CAM treatments in bipolar disorder. Thus, decisions on whether to recommend CAM or integrative therapies to patients should be based on reviews of available data on efficacy and safety of these products.

While acknowledging the limited efficacy and unresolved safety issues of mood stabilizers and atypical antipsychotics, it is my view that conventional pharmacological therapies should be considered as first-line treatments of severe symptoms of mania and depressed mood in bipolar patients. By the same token, current limited evidence for CAM and integrative modalities used to treat bipolar disorder argues for a conservative treatment philosophy employing nonconventional therapies, pending additional findings needed to further substantiate both safety and efficacy. Well-documented limitations and benefits of both conventional and CAM therapies suggest it is prudent and reasonable to take a middle-

ground approach when treating bipolar patients; in other words, to follow a conservative treatment philosophy that emphasizes conventional pharmacological management while remaining rigorously open-minded to the use of select natural products as adjuvants when appropriate on a case-by-case basis (**Table 2**).

Psychiatrists and other mental health professionals should stay abreast of current research findings on natural products and other CAM therapies (eg, exercise, biofeedback, yoga, mind-body therapies) in order to judiciously and appropriately educate and advise patients regarding safety and efficacy findings. Integrative treatments using select natural products reviewed in this article add to the established armamentarium of conventional treatments of bipolar disorder and should be considered when formulating a treatment plan for bipolar disorder.

When recommending any conventional, alternative, or integrative treatment for bipolar disorder (or any psychiatric disorder), the clinician's first task is to carefully examine the evidence supporting all available treatment choices. Conventional, alternative, and integrative therapies whose safety and efficacy are not supported by strong research evidence should not be recommended as first-line treatments of severe symptoms of bipolar mania or depressed mood.

Because of the potentially serious consequences of inappropriate treatment or undertreatment of bipolar disorder, patients should be discouraged from self-medicating with over-the-counter natural products or combinations of natural products and mood stabilizers for which safety and efficacy are not supported by solid research evidence. Keep in mind that all natural products reviewed in this article should be regarded as "off-label" because they are not currently endorsed by the FDA for the treatment of bipolar disorder or other psychiatric disorders. Therefore, it is important to review potential risks and benefits of any natural product therapies and to obtain and fully document informed consent when recommending these therapies.

To minimize safety issues, it is incumbent on the clinician to advise all bipolar patients who elect to use a natural product to use *only quality brands of select natural products* following a critical appraisal of the evidence and *only under the supervision of a medical or naturopathic physician*. When discussing CAM treatment options with patients, it is important to keep in mind that the literature is incomplete with regard to safety of most natural product supplements in young children, pregnant and breast-feeding women, and patients with significant liver or kidney disease. Maximum safe dosages have not been clearly established for these populations, and conservative dosing strategies should be used with close monitoring for treatment-emergent adverse effects. Before recommending any natural product to a patient with bipolar disorder, the clinician should be familiar with important safety considerations summarized in **Table 1**.

With these general comments and caveats in mind, **Table 2** summarizes provisional guidelines for the use of CAM and integrative therapies in patients with bipolar disorder. Emerging evidence supports the use of select natural products

as safe and efficacious adjuvants to conventional mood stabilizers in treating the manic phase of bipolar illness. In contrast to the manic phase of bipolar illness, there is less evidence for CAM or integrative therapies for bipolar depressed mood.

Large placebo-controlled studies on all CAM and integrative treatments discussed in this article are needed to establish safety, efficacy, and optimal dosing strategies before general treatment recommendations in bipolar disorder can be strongly endorsed. However, pending further research, there is sufficient evidence for provisional treatment guidelines for using select natural products reviewed in this article as adjuvant therapies in combination with mood stabilizers.

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## Category 1 Posttest

- Therapies that are useful in combination with conventional mood stabilizers in bipolar disorder include:
  - Regular exercise
  - Complementary and alternative medications (CAMs)
  - A strong social support system
  - All of the above
  - None of the above
- Pharmacological treatments of bipolar disorder may be unsuccessful because of their limited efficacy and high rates of nonadherence.
  - True
  - False
- What percentage of patients with bipolar disorder eventually discontinue their medications?
  - Fewer than 25%
  - 25%
  - 50%
  - More than 50%
- The best practice for treating bipolar disorder is a combination of a mood stabilizer and an antidepressant or atypical antipsychotic.
  - True
  - False
- Which of the following can be used as adjuvants to conventional mood stabilizers in the manic phase of bipolar disorder?
  - Folate, branched-chain amino acids, proprietary nutrient formula
  - Omega-3 essential fatty acids ( $\omega$ -3s)
  - N*-acetylcysteine
  - All of the above
  - None of the above
- Intravenous magnesium can be used as an adjuvant to conventional mood stabilizers for which phase of bipolar disorder?
  - Depression
  - Stable
  - Acutely manic or rapid cycling
  - All of the above
  - None of the above
- Branched-chain amino acids may provide rapid improvement in acutely manic patients by interrupting synthesis of norepinephrine and dopamine.
  - True
  - False
- Which of the following adverse effects are associated with the use of  $\omega$ -3s as adjuvants to mood stabilizers in the depressed phase of bipolar disorder?
  - GI effects, including nausea and loose stools
  - Increased bleeding risk
  - Erectile dysfunction
  - All of the above
  - None of the above
- St John's wort may be safely used as an adjuvant to mood stabilizers in the depressed phase of bipolar disorder.
  - True
  - False
- Which of the following statements is true regarding the use of CAM therapies as adjuvants to conventional pharmacotherapy for bipolar disorder?
  - When used appropriately, CAMs can be effective and are well tolerated
  - A middle-ground approach should be used when considering the use of CAMs as adjuvant therapy for bipolar disorder
  - Further studies are needed to replicate findings of safety and efficacy
  - All of the above
  - None of the above