

# Omega-3 Fatty Acids in Psychiatry

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## KEYWORDS

- Omega-3 • n-3 • Depression • Bipolar disorder
- Complementary and alternative medicine • Ethyl-eicosapentaenoate
- Docosahexaenoic acid

## KEY POINTS

- Omega-3 fatty acids (n-3FAs) are widely used for the treatment of various psychiatric conditions, particularly major depressive disorder and bipolar disorder.
- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived from fish oil, are the n-3FAs that seem to be most important in terms of psychiatric disorders and in other fields of medicine.
- Recommended doses for depressive disorders are typically 1000–2000 mg/day of an EPA/DHA combination, preferably at an EPA:DHA ratio of 3:2 or greater.
- Dosing recommendations for other psychiatric disorders are less clear, due to limited and conflicting data.
- Adverse effects from n-3FAs may include minor gastrointestinal upset, cycling in bipolar patients, and a theoretical risk of bleeding when combined with anticoagulant drugs such as warfarin or aspirin.

## OVERVIEW

Dietary intake of omega-3 fatty acids (n-3FAs) in Western society has decreased dramatically over the past century while the intake of processed foods rich in vegetable oils containing omega-6 (n-6) has increased. This dietary shift has resulted in a higher physiologic ratio of n-6:n-3 fatty acids in Western countries compared with countries with higher fish and n-3 consumption.<sup>1–5</sup> The modern Western diet, coupled with the increasingly stressful twenty-first century life, have been postulated to create a proinflammatory state in humans that is thought to contribute to cardiovascular and psychiatric illness.<sup>6</sup> Administration of n-3FA supplements may potentially reverse this

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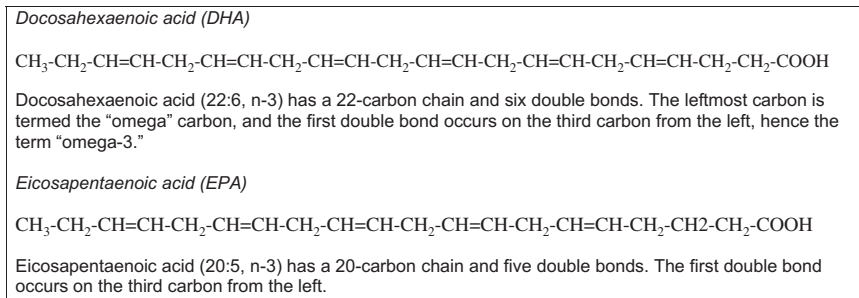
proinflammatory state by correcting the n-6FA:n-3FA ratio, thus providing beneficial cardiovascular and psychiatric effects.

Over the past 2 decades, research on n-3FAs in psychiatry has included many treatment studies with encouraging evidence of clinical efficacy for n-3 in mood disorders (unipolar depression and bipolar disorder), and more preliminary data on conditions such as psychotic disorders and personality disorders. The 2 n-3 fatty acids most relevant to psychiatry are eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6), both of which are found primarily in fish oil and other marine sources (**Fig. 1**). Other important fatty acids include the shorter-chain n-3FAs such as  $\alpha$ -linolenic acid (ALA; 18:3), obtained from flaxseed and other plants, although the evidence for ALA as a psychotropic is scant.<sup>7</sup> Linoleic acid (LA; 18:2) and the n-6 arachidonic acid (AA; 20:4) are also of interest; for example, the proinflammatory AA is reported to be displaced by EPA and DHA supplementation, suggesting a competitive dynamic between them that may account for some of the beneficial effects of n-3FAs.<sup>8</sup> As of this writing, most clinical investigations of psychotropic efficacy have examined EPA and DHA separately and in combination with each other, with a paucity of research on other essential fatty acids.

### PROPOSED MECHANISMS OF PSYCHOTROPIC ACTION

n-3FAs may exert antidepressant effects through a variety of possible mechanisms of action. Proposed mechanisms of n-3FAs for the amelioration of mood disorders include an effect on membrane-bound receptors and enzymes involved in the regulation of neurotransmitter signaling, including increased serotonergic neurotransmission<sup>9,10</sup> and alterations in dopaminergic function,<sup>11,12</sup> as well as regulation of calcium-ion influx through calcium channels.<sup>6</sup> This process may contribute to stabilization and fluidity of neuronal membranes. Interaction with nuclear receptors has also been proposed.<sup>6</sup> Hamazaki and colleagues<sup>13</sup> found that administration of a combination of EPA and DHA to healthy subjects resulted in a lowering of plasma norepinephrine levels in comparison with placebo, suggesting that n-3FAs could exert their effect by interaction with catecholamines.

Omega-3 administration may counter the impact of n-6FA-derived eicosanoids and inhibit secretion of inflammatory cytokines, resulting in decreased corticosteroid release from the adrenal gland and dampening of the mood-altering effects associated with cortisol.<sup>6,14</sup> For example, EPA inhibits the synthesis of prostaglandin E<sub>2</sub>, thus reducing the synthesis of P-glycoprotein, the latter of which may be involved in



**Fig. 1.** Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). (From Mischoulon D. Update and critique of natural remedies as antidepressant treatments. *Obstet Gynecol Clin North Am* 2009;36:789–807. Box 2; with permission.)

antidepressant resistance.<sup>14</sup> In this regard EPA resembles amitriptyline, which also inhibits P-glycoprotein and is generally considered useful for depression, particularly for treatment-resistant depression.

## CLINICAL EFFICACY IN PSYCHIATRIC DISORDERS

Within psychiatry, n-3FAs have been studied most often in mood disorders and, to a lesser degree, in schizophrenia. More than 30 controlled trials and a few open studies in the United States with EPA and/or DHA suggest that supplementation with n-3FAs at doses about 5 or more times the standard dietary intake may yield antidepressant and/or mood-stabilizing effects. Most studies have used EPA monotherapy or a combination of EPA and DHA; few studies have examined DHA alone. Various reviews and meta-analyses of depression studies with n-3 fatty acids<sup>15,16,17,18,19</sup> generally support the efficacy of n-3FAs, but are limited by mixed studies of augmentation and monotherapy, small sample sizes, inclusion of bipolar subjects, different preparations of n-3FAs with varied ratios of EPA/DHA, and doses ranging from 1 to 10 g/d. A few representative studies are highlighted here.

### ***EPA and EPA/DHA Combinations for Unipolar Major Depressive Disorder***

Peet and Horrobin<sup>20</sup> conducted a randomized, placebo-controlled, dose-finding study of ethyl-eicosapentaenoate (ethyl-EPA) as adjunctive therapy for 70 adults with unipolar major depressive disorder (MDD) who were not responsive to standard antidepressants. A dose of 1 g/d ethyl-EPA for 12 weeks yielded significantly higher response rates (53%) than placebo (29%), with notable improvement of depressed mood, anxiety, sleep disturbance, libido, and suicidality. The 2 g/d group showed no significant separation between drug and placebo, and the 4 g/d group showed a nonsignificant trend toward improvement. These results suggested a therapeutic window for n-3FA required for maximum benefit, and it is possible that an “overcorrection” of the n-6FA:n-3FA ratio with higher n-3FA doses may limit the antidepressant effect of ethyl-EPA.

Su and colleagues<sup>21</sup> conducted an 8-week, double-blind, randomized, placebo-controlled trial comparing adjunctive n-3 (6.6 g/d EPA + DHA) with placebo in 28 depressed patients. Patients in the n-3FA group had a significant decrease in Hamilton-D (HAM-D) depression scores compared with placebo. In 20 subjects with MDD on antidepressant medication, Nemets and colleagues<sup>22</sup> found a statistically significant benefit of 1 g/d adjunctive EPA and a clinically important difference in mean reduction on the 24-item HAM-D scores by the study end point after 4 weeks, compared with placebo (12.4 vs 1.6 points). Overall response rates were 60% for EPA and 10% for placebo.

Frangou and colleagues<sup>23</sup> randomized 75 depressed subjects in a double-blind trial to receive 1 g/d ethyl-EPA, 2 g/d ethyl-EPA, or placebo for 12 weeks. EPA outperformed placebo significantly at both ethyl-EPA doses, based on HAM-D scores; the higher dose of ethyl-EPA seemed to confer no added benefit in comparison with 1 g/d. A recent randomized controlled study examining EPA monotherapy for depression found an advantage for EPA compared with placebo, although the study was limited by a smaller than projected sample size.<sup>24</sup> A double-blind study was carried out by Grenyer and colleagues<sup>25</sup> with a sample of 83 depressed outpatients randomized to tuna fish oil or placebo in addition to conventional treatment for 4 months. Results suggested good compliance and robust improvement in depressive symptoms but no significant differences between treatment groups at any time point. In all the aforementioned studies, EPA was well tolerated.

### ***DHA for Unipolar MDD***

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Marangell and colleagues<sup>26</sup> performed a 12-week placebo-controlled study with 36 subjects that showed lack of efficacy of DHA (2 g/d) monotherapy for depression. Response rates were 27.8% for DHA and 23.5% for placebo, although DHA showed a modest advantage in mean improvement in the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), and Global Assessment of Functioning (GAF) scales. On the other hand, a double-blind 3-armed dose-finding study of DHA monotherapy<sup>27</sup> demonstrated greater efficacy for DHA doses of 1 g/d in comparison with 2 g/d and 4 g/d. A therapeutic window for DHA similar to that seen for EPA may exist.<sup>20</sup> The DHA dose-finding study was limited by the lack of a placebo arm. Nonetheless, these studies suggest that DHA may work better at lower doses, and there may be an “overcorrection effect” if n-3FAs are dosed too high.

A recent meta-analysis by Sublette and colleagues<sup>19</sup> found that EPA, rather than DHA, appeared to have the main antidepressant effect. Their conclusion was based on the fact that all the significant positive omega-3 studies on depression in their review had at least 60% EPA, whereas all studies with less than 60% EPA were negative. As it stands, the evidence as a whole is more supportive of EPA than of DHA, or at least formulations whereby the ratio of EPA to DHA is higher than 3:2.

### ***Omega-3 Fatty Acids in Perinatal Depression***

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Freeman and colleagues<sup>28</sup> performed a double-blind dose-finding trial of omega-3 in 16 women with postpartum depression. Subjects received 0.5 g/d, 1.4 g/d, or 2.8 g/d. HAM-D and Edinburgh Post Natal Depression Scale scores both decreased by approximately 50% for all groups, and there seemed to be no dose-response effect. Marangell and colleagues<sup>29</sup> found no preventive effect for postpartum depression in an open study with 2960 mg/d of an EPA/DHA mix in a small sample of pregnant women. A more recent prospective large-scale study<sup>30</sup> found no association between fish intake or n-3FA intake and risk of postpartum depression. Various lines of investigation have demonstrated benefit from n-3FAs for expectant mothers, in whom fish intake is often restricted during pregnancy, and for unborn children and infants, particularly with regard to neural development<sup>31,32</sup> and allergy prevention.<sup>33</sup> In fact, many prenatal vitamins now include an n-3FA supplement.

To date there have been 3 placebo-controlled trials of n-3FAs for the treatment of perinatal depression. In one study, Su and colleagues<sup>34</sup> found a significant benefit of n-3FA for the treatment of depression during pregnancy; however, 2 other studies have not shown a benefit of n-3FA over placebo in pregnant and postpartum women with MDD.<sup>35,36</sup> Therefore, at present it is premature to recommend n-3FAs as a primary treatment for perinatal depression. Nevertheless, for many pregnant and postpartum women n-3FA supplementation may be a reasonable augmentation strategy, considering the benefits of n-3FAs for both maternal and infant health. Despite the apparent safety of n-3FAs, the safe upper limit of these supplements during pregnancy is not known.<sup>32</sup> Pregnant women who are depressed and are considering omega-3 therapy should therefore discuss the matter with their physician. Patients should use only products whose labels indicate that they are free from mercury, polychlorinated biphenyls, or other contaminants, though recent evidence suggests that capsules generally do not contain these. Moreover, n-3FAs should be refrigerated to prevent oils from becoming rancid.

### ***Omega-3 Fatty Acids in Bipolar Disorder***

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In the first clinical trial of omega-3 for bipolar illness, Stoll and colleagues<sup>37</sup> administered high doses of an n-3FA mix (6.2 g/d EPA plus 3.4 g/d DHA) to 30 patients with

bipolar disorder I or II in a comparison with placebo over a 4-month period. Kaplan-Meier survival analysis revealed a significantly longer duration of remission for those receiving the adjunctive n-3FA mix versus placebo along with their current mood-stabilizing regimen. However, Keck and colleagues<sup>38</sup> were unable to replicate these results in a larger-scale study. In their double-blind, placebo-controlled trial of adjunctive EPA, 6 g/d, for 4 months in patients who had bipolar depression (n = 57) or rapid cycling (n = 59), outcomes with EPA did not differ from those with placebo. It should be noted that the differences in outcomes could be due to patient selection and to the forms of n-3FAs administered. For instance, the bipolar-depression or rapid-cycling group may not respond as well as the bipolar I or II group based on the Kaplan-Meier curve. Rapid-cycling subjects would also be less likely to have a longer duration of remission. Finally, the first study used EPA plus DHA, whereas the second study used EPA only.

Osher and colleagues<sup>39</sup> found benefit in a small study of 12 bipolar I patients in the depressed phase of the illness. Patients received 1.5 to 2 g/d open adjunctive EPA for up to 6 months. Ten patients completed at least 1 month of follow-up, and 8 achieved a 50% or greater reduction in HAM-D scores. No cycling occurred with any patients. In a study of 75 patients with bipolar depression, Frangou and colleagues<sup>23</sup> compared ethyl-EPA at 1 g/d or 2 g/d, versus placebo for 12 weeks. EPA outperformed placebo significantly in both EPA treatment arms, based on HAM-D scores. Higher doses of EPA appeared to confer no added benefit compared with 1 g/d.

Sarris and colleagues<sup>40</sup> have performed a recent meta-analysis of 6 selected studies, with one analysis focusing on bipolar depression and the other on bipolar mania. With regard to bipolar depression the investigators observed a significant but moderate effect in favor of n-3FAs (Hedges  $g = 0.34$ ;  $P = .029$ ). In bipolar mania, there was a nonsignificant trend in favor of n-3FAs (Hedges  $g = 0.20$ ;  $P = .099$ ). These meta-analyses, as well as other systematic reviews, have suggested that most of the benefit in bipolar subjects is probably related to depressive rather than manic symptoms.<sup>41,42,43</sup> Finally, there is preliminary evidence that n-3FAs may reduce anger and irritability in bipolar disorder.<sup>44,45</sup>

## OMEGA-3 FATTY ACIDS IN OTHER PSYCHIATRIC DISORDERS

In other psychiatric syndromes, n-3FAs have been studied to a lesser extent than in mood disorders. Conditions investigated in small studies include borderline personality disorder, schizophrenia, attention-deficit disorder (ADD), obsessive-compulsive disorder (OCD), and Tourette disorder. These investigations tend to consist of smaller patient samples, and their conflicting results reflect this limitation. Selected studies from this body of work are reviewed here.

### *Omega-3 Fatty Acids in Psychotic Disorders*

Fenton and colleagues<sup>46</sup> compared EPA, 3 g/d with placebo in 87 subjects with schizophrenia and schizoaffective disorder. After 16 weeks of treatment, no significant advantage was found for EPA over placebo. Of note, subjects in this study had been ill for longer than in previous case reports and case series that had suggested potential benefits in psychotic disorders.

Peet and Horrobin<sup>47</sup> performed a 12-week multicenter dose-finding study comparing EPA (1, 2, and 4 g/d) with placebo in 115 subjects with schizophrenia. Doses of 2 g/d and 4 g/d decreased triglyceride levels in patients taking clozapine. Doses of 2 g/d improved scores on the Positive and Negative Syndrome Scale, but the high placebo response rate resulted in a nonsignificant difference compared with

placebo. The clozapine-treated patients showed little placebo effect in comparison with the rest of the sample, and EPA had a significant effect on all outcome scales.

### ***Omega-3 Fatty Acids in Borderline Personality Disorder***

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Zanarini and Frankenburg<sup>48</sup> compared EPA, 1 g/d versus placebo in 30 women with borderline personality disorder. EPA significantly outperformed placebo in reduction of aggressive and depressive symptoms, although improvement also occurred in the placebo group. EPA resulted in a drop from 22.7 to 7.2 in the Modified Overt Aggression Scale (MOAS) score, and a change from 17.7 to 6.2 in the MADRS score. Scores in the placebo group dropped from 27.6 to 12.9 in the MOAS and from 18.0 to 8.0 in the MADRS. Comparison between the two treatment groups showed a significant advantage for EPA over placebo on both outcome measures.

### ***Omega-3 Fatty Acids for Obsessive-Compulsive Disorder***

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Fux and colleagues<sup>49</sup> performed a placebo-controlled crossover trial of adjunctive EPA for OCD in a sample of 11 patients with inadequate response to selective serotonin uptake inhibitors (SSRIs). Subjects remained on their SSRI and were randomized to 6 weeks of placebo followed by 6 weeks of EPA, 2 g/d, or vice versa. Outcome measures included the Yale-Brown Obsessive-Compulsive Scale (YBOCS), and the HAM-D and HAM-A scales. No treatment-related effects were observed, although YBOCS scores improved in both treatment arms. Because treatment of OCD with all psychotropics usually requires 9 to 12 weeks for improvement, the observed lack of response may be due to the short duration of the treatment period.

### ***Omega-3 Fatty Acids and Self-Harm***

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In a 12-week randomized controlled trial by Hallahan and colleagues,<sup>50</sup> 49 patients presenting after acts of repeated self-harm were randomized to receive, in addition to standard psychiatric care, a combination of 1.2 g EPA + 0.9 g DHA or placebo. At 12 weeks, the n-3FA group had significantly greater improvements in scores for depression, suicidality, and daily stresses. Scores for impulsivity, aggression, and hostility did not differ between treatment arms.

Lewis and colleagues<sup>51</sup> published a case-control study of suicide deaths among active-duty military, in which higher serum DHA appeared to have a protective effect against suicide, whereas EPA conferred only a trend to significance regarding protective effects. This result was especially intriguing in view of the body of evidence that seemed to favor the antidepressant benefit of EPA over DHA in the meta-analysis by Sublette and colleagues<sup>19</sup> (discussed in Ref.<sup>52</sup>).

## **OMEGA-3 FATTY ACIDS IN PEDIATRIC POPULATIONS**

n-3FAs may be especially well suited to pediatric populations, in that they are considered important in brain development (especially DHA). There are some preliminary data in mood and developmental disorders. An exhaustive discussion of the various pediatric studies is beyond the scope of this review, although a few key data are highlighted.

### ***Omega-3 Fatty Acids for Developmental Disorders***

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A recent review and meta-analysis of n-3FA supplementation for children with symptoms of attention-deficit/hyperactivity disorder (ADHD)<sup>53</sup> examined 10 clinical trials with a total of 699 children. Results suggested a modest but significant benefit regarding ADHD symptoms, particularly when the supplement was rich in EPA. The investigators cautioned that n-3FAs overall did not have the same degree of benefit

as registered pharmacotherapies, but suggested that n-3FAs might be useful as an adjunct to these agents, given their safety and tolerability coupled with modest efficacy. Other studies have examined n-3FA therapy for childhood aggression,<sup>54</sup> autism,<sup>55</sup> and Tourette disorder,<sup>56</sup> with generally modest or mixed results.

### ***Omega-3 Fatty Acids for Childhood Mood Disorders***

Nemets and colleagues<sup>57</sup> performed a 16-week double-blind randomized controlled trial with 26 children of ages 6 to 12 years. Subjects were randomized to an omega-3 mix or placebo. Significant improvements were found using the Children's Depression Rating Scale, Children's Depression Inventory, and Clinical Global Impression.

Wozniak and colleagues<sup>58</sup> performed an 8-week open-label study with 20 children aged 6 to 17 years with bipolar disorder. Monotherapy with 1290 mg to 4300 mg combined EPA and DHA yielded a significant but modest reduction of  $8.9 \pm 2.9$  points on the Young Mania Rating Scale (YMRS). Only 35% had a response by the usual criteria of a greater than 50% decrease on the YMRS. A more recent study suggested possible benefit from flax oil (ALA) in pediatric bipolar disorder.<sup>7</sup>

Overall, the results in pediatric populations are encouraging but should be considered preliminary.

### **SAFETY AND TOLERABILITY**

The omega-3s have been shown to be very safe and well tolerated. Most complaints of side effects, such as gastrointestinal upset and fishy aftertaste, tend to occur with higher doses (greater than 5 g/d) and with less pure preparations. At the more typical doses of 1 g/d with highly purified omega-3 preparations, these adverse effects are less common.<sup>15</sup> There has been some concern about the possibility of bleeding with doses greater than 3 g/d, although this risk seems to be minimal, except in patients who are taking other agents that also affect platelet function.

Rare cases of increased bleeding times have been reported in patients taking aspirin or anticoagulants together with n-3FAs,<sup>59,60</sup> and platelet-function effects from n-3FAs have been demonstrated.<sup>61</sup> Individuals with bleeding disorders or who are taking anticoagulants such as warfarin or aspirin need to be carefully monitored for changes in serum International Normalization Ratios under physician supervision,<sup>15</sup> which may alert the clinician to the risk of bleeding. Although the clinical trials of n-3FAs in bipolar samples have generally supported safety, there have been a few reported cases of cycling in bipolar patients,<sup>15</sup> although direct causation can be hard to prove. Considering this along with the more modest evidence as a monotherapy for bipolar disorder, n-3FAs should be used with care in this population, perhaps with a concomitant mood stabilizer.

### **RECOMMENDATIONS**

Given the apparent safety and tolerability of n-3FAs, their psychotropic effectiveness, particularly in mood disorders, deserves continued investigation. The data supporting use of n-3FAs for depression are the most encouraging, especially with regard to EPA. Low doses of n-3FA appear to be an effective and well-tolerated monotherapy or adjunctive therapy for depressed adults, although most clinical trials thus far have used n-3FAs as adjunctive agents. A recent review by Freeman and colleagues<sup>15</sup> recommends that depressed individuals may safely use approximately 1 g/d of an EPA/DHA mixture but should not substitute n-3FAs for conventional antidepressants at present. Likewise, individuals who take more than 3 g/d of an omega-3 preparation should do so under a physician's supervision.<sup>15</sup> This warning may be especially



relevant for bipolar populations, in whom higher doses (6–10 g/d) have been used and in whom there may be a risk of cycling.<sup>15</sup>

The n-3FAs may be particularly well suited for the treatment of specific patient populations for whom antidepressants must be used with caution.<sup>62</sup> Such patients may include pregnant or lactating women, elderly people who may not tolerate side effects of conventional antidepressants, and people with cardiovascular disease or autoimmune conditions for which there may be dual benefits. There is some evidence that n-3FAs may be better suited to cases of more severe MDD, but the results are heterogeneous.<sup>62</sup>

Despite the mostly encouraging data, the authors cannot yet say whether the n-3FAs (and which ones) are truly effective antidepressants and/or mood stabilizers. This statement is even more tentative for psychotic disorders, OCD, and ADD, which have much more limited data, most of which is not encouraging. Controlled trials of n-3FA monotherapy are still limited, as are comparisons against standard agents in depression and the other aforementioned psychiatric conditions. Likewise, the issue of whether EPA, DHA, or a combination of the two is more effective in the treatment of depression remains to be clarified. Finally, the mechanism of action of the n-3FAs, particularly their interplay with the immune system, merits further investigation. Findings are under analysis from a study recently completed at Massachusetts General Hospital and Emory University, addressing the comparative efficacy of EPA and/or DHA as well as the role of lipid levels and immune biomarkers as moderators and mediators of response. It is hoped that these and other future investigations will help to clarify some of the unanswered questions about this exciting and potentially valuable treatment.

#### APPENDIX: REFERENCES

The complete reference list is online at <http://www.psych.theclinics.com/dx.doi.org/10.1016/j.psc.2012.12.002>.

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