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# Omega-3 fatty acids for major depressive disorder associated with the menopausal transition: a preliminary open trial

**Marlene P. Freeman, MD**[1], **Joseph R. Hibbeln, MD**[2], **Michael Silver, MS**[3], **April M. Hirschberg, MD**[3], **Betty Wang, MD**[1], **Amy M. Yule, MD**[1], **Laura F. Petrillo, MD**[1], **Erica Pascuillo, BS**[3], **Nicole I. Economou, BS**[3], **Hadine Joffe, MD, MSc**[1,*], and **Lee S. Cohen, MD**[1,*]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD and [3]Department of Psychiatry, Massachusetts General Hospital, Boston, MA

## Abstract

**Objectives—**We sought to obtain preliminary data regarding the efficacy of omega-3 fatty acids for major depressive disorder associated with the menopausal transition. Secondary outcomes were assessed for vasomotor symptoms (or hot flashes).

**Methods—**After a single-blind placebo lead-in, participants received 8 weeks of treatment with open-label omega-3 fatty acid capsules (eicosapentaenoic acid and docosahexaenoic acid, 2 g/d). The Montgomery-Asberg Depression Rating Scale (MADRS) was the primary outcome measure. Hot flashes were monitored prospectively using daily diaries and the Hot Flash Related Daily Interference Scale. Blood samples for plasma pretreatment and post treatment essential fatty acid assays were obtained. Because of the small sample size, data were analyzed using nonparametric techniques.

**Results—**Of 20 participants treated with omega-3 fatty acids, 19 (95%) completed the study. None discontinued because of adverse effects. The pretreatment and final mean MADRS scores were 24.2 and 10.7, respectively, reflecting a significant decrease in MADRS scores (P G 0.0001). The response rate was 70% (MADRS score decrease of Q50%), and the remission rate was 45% (final MADRS score of e7). Responders had significantly lower pretreatment docosahexaenoic acid levels than nonresponders did (P = 0.03). Hot flashes were present in 15 (75%) participants. Among those with hot flashes at baseline, the number of hot flashes per day improved significantly from baseline (P = 0.02) and Hot Flash Related Daily Interference Scale scores decreased significantly (P = 0.006).

**Conclusions—**These data support further study of omega-3 fatty acids for major depressive disorder and hot flashes in women during the menopausal transition.

Address correspondence to: Marlene P. Freeman, MD, Massachusetts General Hospital, Perinatal and Reproductive Psychiatry Program, 185 Cambridge Street, Boston, MA 02114., mfreeman@partners.org.
*Shared last author.

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**Keywords**

Depression; Major depressive disorder; Omega-3 fatty acids; Menopause; Eicosapentaenoic acid; Docosahexaenoic acid

## Introduction

A significant number of women have major depressive disorder (MDD) and hot flashes associated with the menopausal transition. The lifetime prevalence of MDD in women is greater than 20%, and hot flashes affect up to 80% of women during the menopausal transition.1, 2 Prospective studies have demonstrated an increased risk of onset of MDD during the menopausal transition,3, 4 and persistent mood symptoms have been demonstrated to affect 15% to18% of perimenopausal women, compared with 8% to 12% of premenopausal women.5 Depression and hot flashes commonly co-occur during the menopausal transition, and women with hot flashes are at increased risk for MDD.6 Many women prefer nonhormonal therapies to treat menopause-related symptoms in light of the demonstrated or perceived risks of hormone therapy. Interest in other treatments has increased since the publication of the results of the Women's Health Initiative study, which failed to demonstrate some of the preventive medical benefits thought to be associated with hormone therapy and also suggested some risks associated with these treatments.7 Standard antidepressants have also been studied as a treatment for both the mood and vasomotor symptoms (VMS) in perimenopausal and postmenopausal women, but many women are reluctant to use these because of their adverse effectprofiles.8 Complementary and alternative medicine (CAM) treatments are widely used and often easily accessible. Most remain understudied in the treatment of MDD and menopausal symptoms. The use of CAM therapies has increased over the past several decades. A recent report from the National Center for Complementary and Alternative Medicine demonstrated that more than 40% of the adult population in the United States used at least one CAM treatment over the previous year, with women more likely than men to use CAM.9,10 CAM use is most prevalent among adults aged 30 to 69 years.9 In 2007, US adults spent more than $33.9 billion as out-of-pocket medical costs on CAM therapies, with 44% of that amount (almost $15 billion) spent on nonvitamin, nonmineral, natural products like omega-3 fatty acids.11 This pattern of utilization highlights the need for CAM treatment research for depression in women, as women are both more likely than men to have MDD and to use CAM treatments,9 especially midlife women with depression. Omega-3 fatty acids are a CAM therapy worthy of further systematic study in perimenopausal and postmenopausal women who have MDD. Omega-3 fatty acids are among the most widely used CAM therapies and are associated with well established health benefits. Omega-3 fatty acids are polyunsaturated fatty acids, and as essential fatty acids, they are an important dietary component, because they must be consumed and cannot be made by the human body. The typical American diet is composed of a relative excess amount of omega-6 fatty acids compared with omega-3 fatty acids.12 Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids found in fish and marine sources. A significant benefit for omega-3 fatty acids has been found compared with placebo in several independent meta-analyses, although omega-3 fatty acids have been used as an adjunctive therapy in most published randomized controlled trials.13–15 There have been few systematic controlled trials of CAM therapies for hot flashes. In a recent double-blind, placebo-controlled study comparing black cohosh, multibotanicals, soy, and estrogen therapy for the treatment of VMS, none of the CAM therapies showed any benefit over placebo, whereas hormone therapy did demonstrate more benefits for VMS.16 Preclinical data suggest a role for omega-3 fatty acids in the treatment of VMS. Omega-3 fatty acids seem to affect serotonergic transmission, as do antidepressants, which have been demonstrated to diminish VMS.17–19 One placebo-

controlled study has been published suggesting that omega-3 fatty acids are efficacious in the treatment of hot flashes in women 40 to 55 years old who were experiencing psychological distress at baseline.20 In an 8-week study, 120 women were enrolled and received 1,200 mg/day of EPA and DHA (1,050 mg EPA and 150 mg DHA per day). There was significantly greater benefit on hot flashes in the omega-3 fatty acids group compared with the placebo group. For depressive symptoms, women had depressive symptoms at baseline, although only 24% met the criteria for MDD. Both the omega-3 fatty acid and placebo groups experienced improved quality-of-life scores throughout the study, without demonstrated benefit of the omega-3 fatty acids over placebo.20 In the present study, we sought to determine if an 8-week intervention with omega-3 fatty acids significantly reduces (1) depressive symptoms and (2) VMS in perimenopausal and postmenopausal women with MDD.

## METHODS

We conducted an open-label study of omega-3 fatty acids for the treatment of MDD in women who were perimenopausal or postmenopausal. After a 1-week single-blind placebo lead-in, participants received 8 weeks of treatment with open-label omega-3 fatty acids. The study was approved by the institutional review board at Massachusetts General Hospital. An Investigational New Drug exemption from the US Food and Drug Administration was obtained before the use of this omega-3 fatty acid preparation for the treatment of MDD in perimenopausal and postmenopausal women. All participants provided written informed consent forms. In total, 24 eligible women provided informed consent forms and were enrolled between November 2008 and April 2009.

### Participants

Women were eligible to participate if they met all of the following criteria: (1) 40 years or older, (2) met perimenopause or postmenopause status as defined by the standardized Stages of Reproductive Aging Workshop criteria,21 (3) met criteria for MDD, verified by the Mini-International Neuropsychiatric Interview (MINI), and (4) had a minimum score of 19 on the Montgomery-Asberg Depression Rating Scale (MADRS) at the screening visit.22 Women were ineligible if any of the following criteria were present: (1) currently pregnant (urine human chorionic gonadotropin obtained at the screening visit), breast-feeding, or trying to conceive, (2) currently being treated with an antidepressant, hormone treatment (hormone therapies, hormonal contraceptives), or omega-3 fatty acid supplements or recently treated with one of the preceding treatments within 1 month of study entry, (3) acute suicidal ideation, (4) current or recent (past month) diagnosis of panic disorder or obsessive compulsive disorder or any lifetime history of psychosis, mania, or hypomania, as assessed by the MINI, (5) diagnosis of treatment-resistant MDD, defined as treatment with two or more therapeutic courses of antidepressant medication without remission of symptoms for the current episode of depression, and (6) presence of a known allergy to fish or fish oil. Women who responded to placebo (950% decrease in MADRS) were withdrawn from the study.

### Treatment

Participants received open-label Lovaza 2 g/day (given as 2 capsules per day). Lovaza (GlaxoSmithKline, Philadelphia, PA, and Research Triangle Park, NC) is a brand of omega-3 fatty acids with Food and Drug Administration indication for hypertriglyceridemia, supplied as 1-g transparent soft gelatin capsules. Each 1-g capsule of Lovaza (omega-3 acid ethyl esters) contains 840 mg of the ethyl esters of omega-3 fatty acids, provided as a combination of ethyl esters of EPA (approximately 465 mg per capsule) and DHA (approximately 375 mg per capsule). Small amounts of other omega-3 fatty acids composed

the remaining 160 mg in each capsule, including docosapentaenoic acid, stearidonic acid, heneicosapentaenoic acid, eicosatetraenoic acid, and α-linolenic acid.

### Measures

Before inclusion in the study, women were assessed with the MINI to verify a diagnosis of MDD and to exclude diagnoses that would determine ineligibility. Medical symptom rating scales were completed at each of the six visits throughout the study to measure depressive symptoms and VMS. The instrument used to measure mood at each visit was the MADRS. 22 VMS (hot flashes) were not required at baseline but were experienced by most of the participants and were monitored throughout the study. VMS were tracked and quantified prospectively using a daily hot flash diary, completed throughout the study, as well as a self-report Hot Flash Related Daily Interference Scale (HFRDIS), completed every other visit. Hot flash diaries were completed daily by participants prospectively throughout the study. The diary used was adapted from the 7-day North Central Cancer Treatment Group Diary, a self-report tool for VMS.23 The diary was adapted so that nocturnal and daytime hot flashes could be recorded both together and separately. Scores were calculated to incorporate frequency and severity.23 The HFRDIS is a 10-item self-report questionnaire that measures the degree to which hot flashes interfere with daily activities and quality of life during the prior week.24 Blood was drawn to measure essential fatty acid assays before treatment and after 8 weeks of open-label omega-3 fatty acid treatment. Each participant's intake of additional omega-3 fatty acids, including food containing omega-3 fatty acids, was monitored starting at baseline using a food questionnaire modified from the National Health and Nutrition Examination Survey study.25 Participants were asked to continue their fish and seafood intake as usual throughout the study. No significant changes in fish and/or seafood consumption were noted in any of the participants.

### Biostatistical analysis

Our primary objective was to determine if an 8-week treatment intervention with omega-3 fatty acids would decrease depressive symptoms in perimenopausal and postmenopausal women with MDD. Depressive symptoms were measured using MADRS. The secondary outcome was change in hot flashes from beginning to end of the study, as measured by hot flash diary and HFRDIS scores. We also sought to determine if baseline DHA or EPA levels or changes in their levels across the study were associated with response to treatment. This was a completers' analysis using a nonparametric approach. The primary outcome measure (changes in MADRS scores from screening to end of study) was assessed with the Wilcoxon signed rank test. The same nonparametric procedure was used to examine differences in HFRDIS scores and hot flash diary from baseline to end of study. Statistical significance was established at the > = 0.05 level for all analyses.

## RESULTS

Of 30 women who consented to participate, 24 were eligible. Three women withdrew during the placebo run-in (two were no longer interested, one began disallowed medication). Another woman was a placebo responder after the 1-weekplacebo lead-in. Of the 20 participants who started omega-3fatty acids, 19 (95%) completed the 8-week study. None discontinued the study because of adverse effects or adverse events. The participant who began open-label omega-3 fatty acids but did not complete withdrew because of scheduling difficulties. The mean (SD) age of the participants was 52.5 (4.9) years (range, 42–64 y). The majority were white (66.7%), non-Hispanic (87.5%), and employed (62.5%). Their menopause status included a mixture of perimenopausal (37.5%), naturally postmenopausal (54.2%), and surgically postmenopausal (8.3%) women. See Table 1 for additional demographic characteristics.

### Depression outcomes

Table 2 presents the mean MADRS scores at baseline, pretreatment, and posttreatment. There was a significant effect of treatment on depression symptoms. Mean MADRS scores decreased from 22.4 to 10.7 after 8 weeks of treatment. The MADRS scores improved significantly from pretreatment to study end (P G 0.0001). The response rate was 70% (14/20), and the remission rate was 45% (9/20). Hot flash symptom outcomes Table 2 also shows baseline, pretreatment, and posttreatment hot flash measures and changes in hot flashes. Hot flashes improved significantly with treatment, as evident in hot flash diary scores and HFRDIS scores. On the diary, there was a significant improvement in the mean frequency of hot flashes reported over a 24-hour period (P = 0.02) and when separated by day (P = 0.05) and night (P = 0.002). The HFRDIS scores also decreased significantly (P = 0.006). Comparisons of hot flash outcomes between MDD treatment responders and nonresponders Participants who were responders to treatment on depression measures were significantly more likely to have decreased hot flash diary scores than were nonresponders (P = 0.029). This association was also observed when VMS were analyzed separately on the diary by night time symptoms (P = 0.02), with a weaker association for daytime symptoms (P = 0.11). Participants who experienced remission of MDD had a significant decrease on the HFRDIS compared with those who did not experience remission (P = 0.04), although the difference between depression treatment responders and nonresponders on the HFRDIS was not significant (P = 0.37).

### Biological measures predicting MDD treatment response

There was a significant increase in both plasma DHA and EPA levels from baseline to endpoint (P = 0.0005 and P <0.0001, respectively). MDD treatment responders had significantly lower pretreatment DHA plasma levels (P = 0.03) compared with nonresponders. No other fatty acid measures were associated with response to treatment. There was a trend for MDD treatment responders having a greater increase in plasma EPA levels than nonresponders (P = 0.08). The changes in DHA levels were not significant between MDD treatment responders and nonresponders (P = 0.9).

### Adverse events

No serious adverse events occurred during the study. All adverse effects were mild in severity, and no one withdrew because of adverse events. While taking single-blind placebo, one participant reported an increase in hot flashes, one participant reported experiencing gastrointestinal discomfort, and one participant reported diarrhea. In the open treatment phase with omega-3 fatty acids, the following were reported: gas and/or bloating (n = 3), mild rash (n = 2), puffiness in her face (n = 1), and flulike symptoms (n = 1), which were assessed by the investigator to be unrelated to the study medication.

## DISCUSSION

More data are needed to inform the treatment of women who experience MDD and hot flashes during the menopausal transition. Given the significant number of perimenopausal and postmenopausal women who experience MDD, the potential risks of hormone therapy and antidepressants, and the broad acceptability of CAM therapies, omega-3 fatty acids are an important potential treatment alternative. These preliminary data support further study of omega-3 fatty acids for MDD and VMS during the menopausal transition. In this open trial, we found promising evidence that omega-3 fatty acids may be efficacious for the treatment of MDD and hot flashes. Our finding of reduced hot flashes is consistent with the findings of Lucas et al,20,26 who observed improvement in hot flashes in a randomized placebo controlled trial of omega-3 fatty acids. However, Lucas et al did not observe a significantly greater decrease in depressive symptoms with omega-3 fatty acids compared with placebo

among their participants who were recruited with psychological distress, although only a minority of their participants had diagnoses of MDD. It may be that a lack of improvement in mood between groups in that study was due to the fact that the population included participants with mild to moderate depressive symptoms, who may have been less likely to respond significantly to treatment, and that nonspecific effects of study participation attributed to a placebo response. Several different putative mechanisms of action have been proposed for central nervous system effects of omega-3 fatty acids.14,15,27 The fluctuating and intermittently lowered levels of estrogen may contribute to the increased prevalence of depression in perimenopause.28 Treatment with estrogen compounds, such as oral estrogen therapy or oral contraceptive pills, has been shown to increase levels of DHA in women, theoretically from the up-regulation of DHA synthesis from dietary precursors.29 Hormone therapy has been demonstrated to increased EPA and DHA in plasma and has been hypothesized to contribute to a role in antidepressant effects.30 If a decline in endogenous estrogen levels were found to lower the amount of omega-3 fatty acids available to the brain, increased consumption of omega-3 fatty acids during the menopausal transition may be of particular importance in the treatment of MDD in perimenopausal and postmenopausal women.

The strengths of the current trial include validated diagnoses of MDD at baseline, specified severity at baseline, and clear outcome criteria for depressive symptoms in terms of validated ratings and remission and response criteria. In addition, we monitored VMS frequency and severity. This study also had important limitations. These included the small sample size and the lack of a placebo control group. A randomized, well-powered, placebo-controlled trial of omega-3 fatty acids will be important to ascertain a definitive role of omega-3 fatty acids in perimenopausal and postmenopausal women with MDD. In addition, the potential role of omega-3 fatty acids as an adjunct to hormonal therapies and antidepressant medications would be important to elucidate. The favorable tolerability and risk-benefit profile of omega-3 fatty acids make them a clinically important treatment option warranting further study.

## CONCLUSIONS

In this preliminary study, omega-3 fatty acids seemed to reduce depressive symptoms and VMS in women who presented with MDD related to the menopausal transition. These data suggest that larger controlled trials are justified to more definitively assess the role of omega-3 fatty acids in the treatment of MDD in women during the menopausal transition.

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**Table 1**

Demographics of enrolled subjects (n=24)

| Variable | Value |
|---|---|
| Age, mean ± SD | 52.5 ± 4.9 |
| Marital Status | |
| Married/living with partner | 8 (33.3%) |
| Single (never married) | 6 (25.0%) |
| Widowed/divorced | 10 (41.7%) |
| Employment Status | |
| Full time | 12 (50.0%) |
| Part time | 3 (12.5%) |
| Home maker | 2 (8.3%) |
| Student | 1 (0.2%) |
| Disabled | 1 (4.2%) |
| Unemployed | 3 (12.5%) |
| Retired | 1 (4.2%) |
| Other | 1 (4.2%) |
| Education | |
| Attended graduate school | 5 (20.8%) |
| College graduate | 5 (20.8%) |
| Attended some college | 11 (45.8%) |
| High school diploma or GED | 2 (8.3%) |
| Ethnicity | |
| Hispanic/Latina | 2 (8.3%) |
| Non-Hispanic/Non-Latina | 21 (87.5%) |
| Decline to Answer | 1 (4.2%) |
| Race | |
| White/Caucasian | 16 (66.7%) |
| Black/African American | 5 (20.8%) |
| Asian/Pacific Islander | 1 (4.2%) |
| Other | 2 (8.3%) |
| Menopausal Status | |
| Perimenopausal | 9 (37.5%) |
| Naturally Postmenopausal | 13 (54.2%) |
| Surgically Postmenopausal | 2 (8.3%) |
| History of previous major depressive episode* | |
| Yes | 8 (33.3%) |
| No | 15 (62.5%) |
| No answer | 1 (4.2%) |

**Table 2**

Changes in depression and hot flash scores from baseline to end point

| variable change from baseline to end of study | n* | Mean Pre-Treatment Score | Mean Post-Treatment Score | Mean Change Score | Standard Deviation of Mean Change Score | Median of the Change Score | IQR of the Change Score | pvalue |
|---|---|---|---|---|---|---|---|---|
| MADRS | 20 | 24.2 ± 3.9 | 10.7 ± 8.5 | 13.5 | 7.9 | 13.5 | 7.0 | <0.0001* |
| Hot Flash Scores: 24-hour score | 15 | 9.0 ± 10.3 | 2.5 ± 4.0 | 5.1 | 9.70 | 2.1 | 5.4 | 0.02* |
| Daytime hot flash score | 15 | 4.3 ± 4.8 | 1.8 ± 3.6 | 2.0 | 5.0 | 0.9 | 2.9 | 0.05* |
| Nighttime hot flash score | 15 | 4.6 ± 5.5 | 0.7 ± 0.8 | 3.2 | 4.9 | 1.1 | 3.1 | 0.002* |
| HFRDIS | 15 | 36.9 ± 27.7 | 14.1 ± 24.2 | 22.9 | 27.5 | 20.0 | 44.0 | 0.37 |

* indicates significant change from baseline to endpoint (with alpha ≤ 0.05)

N=20, number of participants who started omega-3 fatty acids after the one-week placebo lead in N=15, number of participants who had hot flashes at baseline and could be included in the hot flash analyses