NATIONAL DEFENSE RESEARCH INSTITUTE

Omega-3 Fatty Acids for Major Depressive Disorder

A Systematic Review

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Preface

The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury is interested in determining the efficacy and comparative effectiveness of integrative medicine approaches for psychological health conditions. This document is a systematic review of the effectiveness of omega-3 fatty acids for the treatment of major depressive disorder, conducted during year two of a two-year project on integrative medicine approaches for psychological health conditions. The review will be of interest to military health policymakers and practitioners, civilian health care providers, and policymakers, payers, and patients.

A version of this report was provided to the committee for review in May 2015; we reproduce that version here, with minor editorial updates. None of the authors has any conflict of interest to declare.

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Abstract

Major depressive disorder (MDD) is a prevalent condition that accounts for considerable suffering and lost productivity. Epidemiological evidence supports a potential role for dietary and/or supplemental omega-3 (n-3) fatty acids in the management of depression. We conducted a systematic review of randomized controlled trials (RCTs) that assessed the efficacy and safety of n-3 fatty acids for treating depression.

We searched the electronic databases PubMed, PsycINFO, CINAHL, Embase, and AMED and screened recent existing reviews to identify English-language reports of randomized placebo-controlled or head-to-head trials testing the efficacy and safety of n-3 fatty acids as a monotherapy or adjunctive therapy to treat adults with MDD. Standard systematic review methods were used to screen the literature against a predetermined set of inclusion and exclusion criteria, abstract the study-level details and outcomes of interest, and assess the methodological quality of the studies. Effectiveness outcomes were pooled using the Hartung-Knapp-Sidik-Jonkman method for random-effects models. The quality of evidence for each conclusion was assessed using the GRADE approach.

We identified 24 RCTs that met inclusion criteria; 20 studies reported efficacy outcomes for placebo comparisons. All studies combined showed a small but significant effect of n-3 fatty acids compared with placebo on depression scale scores (standardized mean difference [SMD] 0.42; 95% confidence interval [CI] 0.11, 0.73; 20 RCTs; I^2 77%; low quality of evidence) and on the proportion of treatment responders (odds ratio [OR] 2.09; CI 1.25, 3.49; 13 RCTs; I^2 38%; moderate quality of evidence), but there was evidence of publication bias. No statistically significant effect was found for the proportion of patients in remission compared with placebo (OR 2.19; CI 0.74, 6.51; 6 RCTs; I^2 52%; low quality of evidence). Benefits compared with placebo were primarily based on monotherapy studies. Only two studies compared eicosapentaenoic acid (EPA) with docosahexaenoic acid (DHA) head to head. Pooling studies of EPA alone with high EPA:DHA ratio studies revealed a significant effect on depression scale scores (SMD 0.62; CI 0.25, 0.98; 15 RCTs; I^2 77%; low quality of evidence) and on the proportion of treatment responders (OR 2.31; CI 1.09, 4.88; I^2 51%; low quality of evidence) compared with placebo, but studies that administered DHA or a high DHA:EPA ratio showed no effect (SMD –0.06; CI –0.61, 0.49; 6 RCTs; I^2 68%; moderate quality of evidence). Very few studies specified depression severity. Few studies assessed effects on quality of life. N-3 fatty acids were associated with an increased risk for mild gastrointestinal symptoms compared with placebo (OR 2.58; CI 1.73, 3.91; 17 RCTs; moderate quality of evidence) but not with other categories of minor adverse events or serious adverse events.

In conclusion, the n-3 fatty acid EPA may have a small benefit in improving depression symptoms compared with placebo, with relatively minor gastrointestinal adverse events for adults with MDD, but the existing evidence base is weak.

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Summary

Introduction

Major depressive disorder (MDD) is a prevalent condition that accounts for considerable suffering and lost productivity. Effective pharmacological therapies exist but are not without side effects. Epidemiological evidence supports a potential role for dietary and/or supplemental omega-3 (n-3) fatty acids in the management of depression. A number of randomized controlled trials (RCTs) have assessed the efficacy and safety of n-3 fatty acids for treating MDD. We conducted a systematic review of the literature reporting the outcomes of these trials.

Key Questions

The following key questions (KQs) guide this systematic review:

- KQ 1: What are the efficacy and safety of n-3 fatty acid supplements for depressive symptoms and quality of life in adults with MDD compared with placebo or active comparator?
  - KQ 1a: Are n-3 fatty acids more effective as monotherapy than as an adjunctive therapy?
  - KQ 1b: Does efficacy differ depending on the type—eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or alpha-linolenic acid (ALA)—and amount of n-3 fatty acid used?
  - KQ 1c: Does the efficacy of n-3 fatty acids differ depending on the type of MDD (i.e., mild, moderate, severe, recurrent, postpartum)?
  - KQ 1d: What is the safety (e.g., adverse effects, drug-nutrient interactions) of n-3 use in individuals with MDD compared with standard antidepressant therapy or placebo?
  - KQ 1e: How does the efficacy of n-3 fatty acids compare with that of standard antidepressant therapy?

Methods

We searched the electronic databases PubMed, PsycINFO, CINAHL (Cochrane Central Register of Controlled Trials), Embase, and AMED (Allied and Complementary Health Database) and screened recent existing reviews to identify English-language reports of randomized placebo-controlled or head-to-head trials testing the efficacy and safety of n-3 fatty acids (as fortified foods or dietary supplements) as a monotherapy or adjunctive therapy to treat adults with MDD. Two independent reviewers screened identified citations for inclusion, abstracted study-level information, and assessed the quality of included studies. Outcomes of interest included changes in depressive symptomatology, quality of life, and adverse effects.

Efficacy meta-analyses used the Hartung-Knapp-Sidik-Jonkman method for random-effects models. Quality of evidence was assessed using a modification of the Grades of Recommendation, Assessment, Development, and Evaluation (or GRADE) approach.

Results

Key Question 1

We identified 24 studies that met the inclusion criteria and assessed the efficacy of n-3 fatty acids for MDD. The pooled effect size (standardized mean difference [SMD] 0.42; 95% confidence interval [CI] 0.11, 0.73; 20 RCTs; I^2 77%; N=1,603) indicated a statistically significant effect of n-3 fatty acid treatment on depressive symptoms compared with placebo. Study quality was mixed. Tests suggested the likelihood of publication bias, and a sensitivity analysis using the trim-and-fill method to adjust for potential publication bias indicated a smaller and not statistically significant treatment effect (SMD 0.23; CI −0.03, 0.48). The quality of evidence for this conclusion is low, meaning that additional studies could be likely to change this finding.

Thirteen studies (N=765) assessed the effects of n-3 fatty acids on clinical response (improvement of 50 percent or more in a depression scale score), identifying a significant positive response for n-3 fatty acids compared with placebo (odds ratio [OR] 2.09; CI 1.25, 3.49; 13 RCTs; I^2 38%). There was indication of publication bias, and a sensitivity analysis using the trim-and-fill method indicated a smaller and not statistically significant effect (OR 1.22; CI 0.89, 1.65). The quality of evidence for this conclusion was moderate, meaning that additional studies might change this finding.

Six studies (N=503) assessed the effects of n-3 fatty acids on remission (change in depression score to within the normal range). The number of participants who achieved remission was small, and the pooled effect size showed a non-significant difference between n-3-treated and placebo participants (OR 2.19; CI 0.74, 6.51; 6 RCTs; I^2 52%). There was some evidence for publication bias, and the trim-and-fill sensitivity analysis estimated a smaller effect size (OR 1.18; CI 0.49, 2.85).The quality of evidence for the lack of efficacy of n-3 fatty acids for remission was low, as additional studies are likely to change the effect estimate.

Two studies, one of fair quality and one of poor quality, assessed effects on quality of life using the mental and physical functioning composites of the RAND 36-Item Short Form Health Survey, or SF-36. The SMD for mental functioning showed significant difference compared with placebo in both studies (SMD −0.68; CI −1.27, −0.08; and SMD −1.11; CI −1.83, −0.39). The SMD for physical functioning showed positive results for one study (−0.8; CI −1.4, −0.2) but not for the other study (SMD −0.63; CI −1.32, 0.06). The quality of evidence for a conclusion regarding the efficacy of n-3 fatty acids for quality of life is very low because of the very small number of studies and inconsistency among studies.

Key Question 1a

Only one small study was designed to compare n-3 fatty acids as a monotherapy with those systematically given as adjunctive therapy to antidepressants. The study showed a significantly greater efficacy for adjunctive therapy combining n-3 fatty acids and antidepressants compared with n-3 fatty acids alone or antidepressants alone, but because the study was poor quality, the quality of evidence is very low.

Subgroup analyses showed statistically significant effects on depression scores compared with placebo in monotherapy studies but not adjunctive therapy studies where standard depression treatment was given to all patients. A meta-regression comparing the subgroups was suggestive of a systematic difference but was not statistically significant (p=0.09).

Key Question 1b

Two good quality RCTs compared EPA and DHA head to head. One showed higher efficacy for EPA than DHA for depression scale scores and a non-significant increase in the proportion of treatment responders and patients in remission, whereas the other showed no difference in depression scale scores, proportion of treatment responders, or patients in remission. The quality of evidence is very low because of the small number of studies.

Fifteen RCTs of mixed quality comparing EPA alone or an EPA:DHA ratio of 1 or greater showed a significant effect on depression scale scores compared with placebo (SMD 0.62; CI 0.25, 0.98; 15 RCTs; I^2 77%). Evidence for publication bias was found, and the trim-and-fill effect estimate was lower (SMD 0.33; CI 0.02, 0.64). The quality of evidence for the effect estimate is low because of the high heterogeneity and publication bias.

Nine studies of mixed quality comparing EPA alone or higher EPA showed a significantly greater effect for EPA on the number of treatment responders (OR 2.31; CI 1.09, 4.88; 9 RCTs; I^2 51%). Evidence for publication bias was found and the trim-and-fill effect estimate was lower and not statistically significant (OR 1.38; CI 0.71, 2.68). The quality of evidence for this finding was low because of heterogeneity and evidence for publication bias.

Six good and fair quality studies compared EPA alone or a higher EPA:DHA ratio with placebo and did not find a statistically significant difference (OR 2.19; CI 0.74, 6.51; 6 RCTs; I^2 52%).

Six RCTs of mixed quality comparing DHA alone or a DHA:EPA ratio of 1 or higher showed no difference in depression scale scores (SMD –0.06; CI –0.61, 0.49; 6 RCTs; I^2 68%) compared with placebo. Evidence for publication bias was not found (Egger test p=0.790, Begg test p=0.817). The quality of evidence for this finding is moderate because of the high heterogeneity. The RCTs also showed no effect on the percentage of responders (OR 0.97; CI 0.61, 1.56; 3 RCTs; I^2 0; high quality of evidence), and there was no evidence of publication bias. There was no statistically significant difference between DHA alone or DHA:EPA ratio of

1 or higher on the outcome remission (OR 0.81; CI 0.42, 1.56; 2 RCTs; low quality of evidence); there was no evidence of publication bias, but only two RCTs reported on this outcome.

A meta-regression indicated a significant difference in efficacy between the studies of EPA or higher EPA:DHA ratio and the studies of DHA or higher DHA:EPA ratio (p=0.008).

One study each compared high- to low-dose EPA (fair quality) and high- to low-dose DHA (good quality); both favored the lowest dose. The quality of evidence for these findings is very low, given the small numbers of studies.

We found no studies that met our inclusion criteria that assessed the efficacy of supplemental ALA.

Key Question 1c

No studies explicitly assessed the effects of n-3 fatty acids on participants with moderate and severe depression. Two studies assessed the effects of n-3 fatty acids in participants with "mild-to-moderate" depression (by the studies' own description), and one study assessed effects in participants with mild depression. Twenty-one studies did not state the severity of depression among participants. A meta-regression showed no difference in efficacy between these studies and other studies (p=0.79). Four (mixed quality) studies of women with peripartum depression showed no significant difference in efficacy of n-3 fatty acids compared with that of placebo (SMD 0.47; CI –0.44, 1.34; I^2 78%), but a meta-regression did not indicate that effects are systematically different from other studies (p=0.863).

The evidence base is insufficient to determine whether the efficacy of n-3 fatty acids differs depending on the type of MDD.

Key Question 1d

Of 24 studies that met inclusion criteria, 21 assessed and reported adverse events: 19 placebo controlled trials and two head-to-head trials. Only one study compared the safety of n-3 fatty acids with that of standard antidepressant therapy. No studies reported serious adverse events. Only one category of adverse events, gastrointestinal events, was significantly increased in n-3-treated participants compared with placebo-treated groups (17 studies of varying quality) (OR 2.58; CI 1.73, 3.91). The quality of evidence for this finding is moderate, based on the quality of reporting of adverse events in the trials. No differences were seen in any other category of adverse events. For studies that compared EPA alone or EPA:DHA ratio greater than 1, no statistically significant differences were seen for any category of adverse events.

Key Question 1e

Only one, very small and poor quality, study compared the efficacy of n-3 fatty acids with that of antidepressants head to head. Both arms showed decreased depression scale scores and a similar proportion of responders. The quality of evidence for this finding is very low based on the paucity of studies and the poor quality of the one identified study.

Conclusions

Dietary supplements of n-3 fatty acids that contain higher concentrations of EPA than DHA may have some benefit in treating individuals with MDD; however, the quality of evidence is weak, with inconsistent results across outcomes and evidence of publication bias.

Too few studies assessed effects of n-3 fatty acids on remission and quality of life to draw conclusions. Too few studies compared n-3 fatty acid monotherapy with adjunctive therapy (n-3 fatty acids plus antidepressants) or with antidepressants alone to draw conclusions about comparative efficacy. Too few studies compared EPA with DHA to draw direct conclusions, but subgroup analyses indicated higher efficacy in EPA studies. The evidence base is insufficient to determine whether the efficacy of n-3 fatty acids differs depending on the type of MDD. No serious adverse effects were observed in any studies. N-3 fatty acids were associated with an increased risk for mild gastrointestinal symptoms compared with placebo.

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
ALA	alpha-linolenic acid
AMED	Allied and Complementary Health Database
BDI	Beck Depression Index
CI	confidence interval
CINAHL	Cochrane Central Register of Controlled Trials
CNS	central nervous system
DHA	docosahexaenoic acid
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
E-EPA	ethyl-eicosapentaenoic acid
EPA	eicosapentaenoic acid
EPDS	Edinburgh Postnatal Depression Scale
GDS	Geriatric Depression Scale
GI	gastrointestinal
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HAMD	Hamilton Rating Scale for Depression
ICD	International Classification of Diseases
ITT	intention to treat
KQ	key question
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
n-3	omega-3
OR	odds ratio
PNS	peripheral nervous system
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
RR	risk ratio
SCID	Structured Clinical Interview for DSM Disorders

SD	standard deviation
SF-36	RAND 36-Item Short-Form Health Survey
SMD	standardized mean difference
USPSTF	U.S. Preventive Services Task Force

Chapter One: Introduction

Major depressive disorder (MDD) is a serious mental health condition that affects quality of life, interferes with productivity, and may exacerbate or precipitate other health conditions and increase the risk for attempted suicide and substance abuse (Ustun et al., 2004). Globally, depressive disorders are the leading cause of disability and a major contributor to the global burden of disease. More than 350 million people worldwide suffer from depression, and this number is on the rise (World Health Organization, 2012). In the United States, the condition affects approximately 15 million individuals, with a lifetime prevalence of 8 to 12 percent in men and 20 to 26 percent in women, yet the condition remains underdiagnosed and undertreated, particularly among active-duty military personnel and veterans (Management of Major Depressive Disorder Working Group, 2009) Although evidence shows that pharmacotherapy and behavioral therapy are effective and safe, individuals often fail to seek treatment, compliance with treatment is often poor, and a certain proportion of individuals experience resistance to treatment (Ustun et al., 2004).

In the late 1990s, epidemiological studies began to identify an association of dietary omega-3 (n-3) fatty acids, particularly intake of fatty fish and fish oils (which deliver a balanced combination of certain long-chain polyunsaturated fatty acids), with lower risk for depression (Hibbeln et al., 1998). Dietary n-3 fatty acids include, primarily, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). The hypothesis that n-3 fatty acids might be associated with mood and depression (the n-3 fatty acids deficiency hypothesis of depression) was based on the observation of an association between plasma levels of n-3 fatty acids and disruptions in cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA) (Horrobin and Bennett, 1999). 5-HIAA is a metabolite of serotonin, the neurotransmitter thought to be most closely associated with depression. Subsequently, clinical trials began to assess the effects of supplementary n-3 fatty acids as a monotherapy or adjunctive therapy for depression. The findings of these studies have been analyzed in numerous systematic reviews, (Parker et al., 2006; Lin and Su, 2007; Freeman, Hibbeln, et al., 2006; Appleton et al., 2014; Bloch and Hannestad, 2012; Rocha Araujo, Vilarim, and Nardi, 2010; Ortega, Rodriguez-Rodriguez, and Lopez-Sobaler, 2012; Appleton, Rogers, and Ness, 2010), and in 2010, the American Psychiatric Association Task Force on the Use of Complementary and Alternative Medicine for the Treatment of MDD reviewed the literature and concluded that more studies are needed to determine conclusively whether n-3 fatty acids are effective either as a monotherapy or an adjunctive therapy in treating depression but that because of their low risk and apparent cardiovascular benefits, they are a useful adjunctive therapy (Freeman, Fava, et al., 2010).

The current U.S. Department of Veterans Affairs and U.S. Department of Defense *Clinical Practice Guideline on the Management of MDD* does not cover the use of n-3 fatty acids (Management of Major Depressive Disorder Working Group, 2009).

Key Questions

The following key questions (KQs) guide this systematic review:

- KQ 1. What are the efficacy and safety of n-3 supplements for depressive symptoms and quality of life in adults with MDD compared with placebo or active comparator?
  - KQ 1a: Are n-3 fatty acids more effective as monotherapy than as an adjunctive therapy?
  - KQ 1b: Does efficacy differ depending on the type—EPA, DHA, or ALA—and amount of n-3 fatty acid used?
  - KQ 1c: Does the efficacy of n-3 fatty acids differ depending on the type of MDD (i.e., mild, moderate, severe, recurrent, postpartum)?
  - KQ 1d: What is the safety (e.g., adverse effects, drug-nutrient interactions) of n-3 use in individuals with MDD compared with standard antidepressant therapy or placebo?
  - KQ 1e: How does the efficacy of n-3 fatty acids compare with that of standard antidepressant therapy?

Chapter Two: Methods

We performed a systematic review to identify randomized controlled trials (RCTs) testing the efficacy and safety of n-3 fatty acids to treat adults with MDD. (The literature flow is discussed in the next chapter and is documented in Figure 3.1.)

Sources

We searched PubMed, PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, and AMED (Allied and Complementary Health Database) for English-language RCTs published from 2004 to the present. The choice of 2004 as the initiation point for the searches is based on the release in 2005 of an Agency for Healthcare Research and Quality Evidence-Based Practice Center systematic review on the effects of n-3 fatty acids on mental health. That report should have captured all interventional studies published prior to 2004 and was used to identify earlier studies. To ensure that we did not miss older studies, we searched the reference lists of all included studies. In addition, we cross-compared the systematic reviews that have been published since the 2005 review on n-3 fatty acids and depression to assess which studies they included to ensure that all studies that meet our inclusion criteria (see below) were identified in our searches. In addition to reference-mining included studies, we also looked at the results of an informal environmental scan we conducted in October 2014 (unpublished RAND research by Melony Sorbero, Sean Grant, and Susanne Hempel) that identified studies published since the most recent systematic review and compared those results with the results of our database searches to ensure that we included all relevant studies.

Search Strategy

The search strings were developed by the chief reference librarian for RAND's Knowledge Services, based on searches conducted for two other systematic reviews on n-3 fatty acids conducted at RAND and recent systematic reviews on the same topic. The search strings for all databases we used are included in Appendix A.

Eligibility Criteria

The inclusion and exclusion criteria were developed using the framework of participants, interventions, comparators, outcomes, timing, settings, and study design, or PICOTSS.

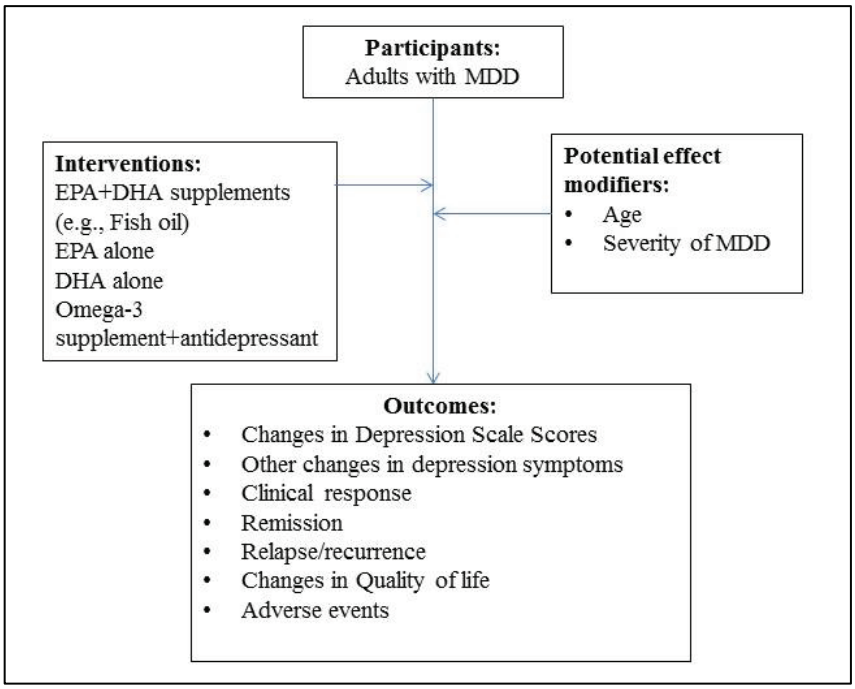
- *Participants*: Studies were limited to adults, male and female, 18 years of age and over, with a diagnosis of MDD. If studies did not refer to a clinical diagnosis based on *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or International

Classification of Diseases (ICD) criteria, we applied a prespecified threshold on validated depression scales (see Appendix D). Studies that enrolled individuals with other comorbid conditions, such as traumatic brain injury, posttraumatic stress disorder, or chronic pain, were included. Studies in postnatal depression were included if the criteria were in accordance with DSM-V criteria for MDD (peripartum onset or four weeks following delivery). Studies of individuals with diagnoses of bipolar disorder or schizophrenia, alone or in combination with MDD, were excluded in accordance with DSM-V criteria. Studies that evaluated the efficacy of n-3 fatty acids for multiple psychiatric conditions were included if the data for patients with MDD were analyzed separately. Studies that did not exclude individuals who might be taking high-dose n-3 fatty acid products for other indications (e.g., high serum cholesterol) were excluded.

- *Interventions/exposures*: Studies that administered a dietary supplement that contained a known amount of DHA, EPA, or ALA, or a mixture of these, either alone or in conjunction with pharmacologic and/or psychotherapy were included, providing that the use of adjunctive therapies was tracked and measured. Studies that administered n-3 fatty acids in the form of a food that naturally contains high levels of n-3 fatty acids (e.g., salmon) or a fortified food were included if the content of the food was known and the intake was tracked (or a biomarker was measured).
- *Comparators (designs)*: For studies of n-3 fatty acids in the form of dietary supplements as monotherapy, only those that included a placebo-treated group, that compared two n-3 fatty acids head to head, or that compared an n-3 with active comparators, including standard antidepressant therapy, were included. For studies that administered n-3 fatty acids as a fortified food, those with a blinded control group that received a comparable food without n-3 fatty acids were included. For studies of n-3 fatty acids as an adjunctive therapy, only studies that provided a placebo treatment to the arm that was not given n-3 fatty acids were included.
- *Outcomes*: Studies that reported Hamilton Rating Scale for Depression (HAMD) scores or other validated depression scale scores at baseline and throughout followup were included. Studies that reported other changes in depressive symptoms were included, such as suicidal ideation or risk for suicide. Studies that reported quality-of-life assessment scores, such as those of the RAND 36-Item Short-Form Health Survey, or SF-36, were included if the studies also assessed changes in depression. Studies that reported rates of depression relapse were included. Studies that reported on biomarkers alone without reporting efficacy for depression outcomes were not included. Studies of provider outcomes, acceptance, prevalence, use, costs, study design features, or intervention features that did not report efficacy for depression-related patient health outcomes were not included. Studies that reported adverse events in adults taking supplemental n-3 fatty acids for MDD were included if adverse events were reported by study arm.
- *Timing*: Only studies with a treatment duration of four weeks or longer were included.
- *Setting*: Study setting was not a criterion for inclusion or exclusion.
- *Study design*: Included studies were limited to RCTs. Parallel and cross-over trials were eligible for inclusion.

Inclusion criteria pertaining to study designs are described in Figure 2.1.

Figure 2.1. Analytic Framework



Inclusion Screening

Two independent reviewers (the project lead, who is an experienced systematic reviewer, and a clinical psychologist with experience in systematic reviews) screened titles and abstracts of retrieved citations (after a session to ensure similar interpretation of the inclusion and exclusion criteria and reasonable inter-rater reliability) and recorded decisions in an electronic database.

Citations deemed potentially relevant by at least one reviewer were obtained as full text. The full-text publications were screened against the specified inclusion criteria by the two independent reviewers; any disagreements were resolved through discussion within the review team. The researchers documented the literature flow in an electronic database (Distiller SR) and recorded the reasons for excluding any full-text publications. (See Table 3.1 for the numbers of studies that met the inclusion criteria for each key question.)

Data Extraction

Accepted studies underwent dual abstraction of study-level data in an electronic database. Data collection forms were designed by the project lead and a research assistant. They were then pilot-tested by the reviewers and further modified, and then the final forms were pilot-tested with a random selection of approximately ten included studies to ensure agreement of interpretation. The following study-level data were abstracted, if reported in the study:

- participant number, sex, mean age and age range; health status (comorbidities, including traumatic brain injury); baseline n-3 fatty acid status; baseline n-3 fatty acid intake (and method of assessment); diagnostic criteria; baseline HAMD (or other measure of depression severity); depression history; baseline quality of life; inclusion and exclusion criteria
- intervention setting (city, state, nation, type of health care setting, number of sites); type (type of n-3, daily dose, form of n-3 fatty acid, how concentration of active ingredient(s) assessed); co-intervention(s), if any; washout period, if any
- comparator identity(ies)
- outcomes assessed (including biomarkers), methods of assessment, validation of methods, method of data expression (e.g., standardized mean difference [SMD], proportion of patients reporting improvement above a minimum clinically important difference), primary endpoint, and corresponding results (effect estimate, precision)
- timing/duration of intervention and follow-up assessment
- other: characteristics necessary to assess risk of bias, including recruitment methods, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest.

Outcome data, including clinical outcomes and intermediate outcomes (concentrations of biomarkers), were abstracted by biostatisticians from the RAND Evidence-based Practice Center. If study outcomes appeared to have been reported in more than one published article, descriptions of participants were compared to determine whether they were from the same study populations. Outcome data were abstracted for the longest follow-up times possible; however, if a study reported outcomes over a number of follow-up times, we abstracted these data to assess response trajectories and effect durations, if possible.

Risk of Bias

Risk of bias of original studies was assessed using the Cochrane Risk of Bias tool (Higgins and Green, 2011, Table 8.5.a), and U.S. Preventive Services Task Force (USPSTF) quality criteria were used to assign overall ratings. The items assessed included selection bias (recruitment method, random sequence generation, and concealment of allocation), performance bias (participant and personnel blinding), detection bias (assessor blinding), attrition bias (completeness of reporting of outcome data), reporting bias (selective outcome reporting), and other sources of bias, such as add-on trials (where both treatment arms received treatment as usual, with the treatment group receiving n-3 fatty acids and the control group receiving no additional treatment), appropriateness of washout period (or exclusion of those taking personal supplements, if relevant), appropriateness of the statistical analytic method, study funding, and investigator conflict of interest (see Table 3.2 for assessment criteria and definitions of ratings). A small number of nutrition-specific items were also assessed, including assessment and reporting of initial n-3 fatty acid status and compliance. We also assessed other biases related to the USPSTF criteria for internal validity—that is, those related to baseline control for potential

confounders; crossover or cross-contamination between groups; equal, valid, and reliable outcome measurement; clear definitions of interventions; and intention-to-treat (ITT) analysis. These criteria were used to rate the quality of evidence of individual studies using the following guidelines:

- *Good*: Comparable groups are initially assembled and maintained throughout the study with at least 80-percent follow-up; reliable, valid measurement is used and applied equally to all groups; interventions are clearly described; all important outcomes are considered; appropriate attention is given to confounders in analysis; and ITT analysis is used.
- *Fair*: One or more of the following issues is found in the study: some though not major differences between groups exist at follow-up; measurement instruments are acceptable but not ideal, though are generally applied equally; some but not all important outcomes are considered; some but not all potential confounders are account for in analyses. ITT analysis must be done.
- *Poor*: One or more of the following "fatal flaws" is found in the study: initially assembled groups are not comparable or maintained throughout the study; unreliable or invalid measurements are used or applied unequally across groups; key confounders are given little to no attention in analyses; ITT analysis is not used.

Data Synthesis

When sufficient data were available and clinical heterogeneity was minimal, we conducted meta-analysis to pool effectiveness results across included studies for the outcomes of interest. The choice of a random-effects model over a fixed-effects one for pooling results of RCTs was based on our assessments of study result similarities and heterogeneity across studies. The statisticians performed meta-analysis using the Hartung-Knapp-Sidik-Jonkman method for random-effects models (Hartung, 1999; Hartung and Knapp, 2001; Sidik and Jonkman, 2006). The Hartung-Knapp-Sidik-Jonkman method was chosen for its superior performance with relatively small numbers of studies of similar size (IntHout, Ioannidis, and Borm, 2014). Sensitivity analyses were conducted using a fixed-effects model for comparisons with significant treatment effects.

If studies reported outcomes for more than one depression scale, we preferentially included HAMD scores, if reported, to minimize heterogeneity. However, because a number of studies used different scales as their sole or primary outcome measure, SMDs were calculated for continuous outcomes (change in depression scale scores). We imputed missing standard deviations (SD) from the average of SDs in included studies. For studies with more than one n-3 arm, we used a combination of arms for the main effectiveness analyses. Weighted means and SD (using the formula sqrt(((n1+1)*sd1^2+(n2+1)*sd2^2)/(n1+n2-2))) were calculated across arms. Most studies reported outcomes at one time point. For studies that reported outcomes at multiple time points, we included the longest time point.

Pooled effect sizes for dichotomous outcomes of clinical response to treatment and remission were expressed as odds ratios (ORs), in keeping with our use of ORs for the assessment of adverse events. However, we conducted sensitivity analyses for these outcomes and reported risk ratios as well.

For each pooled analysis, we estimated heterogeneity by calculating the I-squared (I^2) statistic. Publication bias was assessed using the Egger and the Begg tests, and funnel plots are presented when evidence of publication bias was found. For comparisons that showed significant treatment effects but evidence of publication bias, we conducted sensitivity analyses computing effect estimates using the trim-and-fill method. We conducted meta-regressions and subgroup analyses where possible (e.g., on specific n-3 fatty acids), to answer individual key questions, and to support our qualitative synthesis. Where possible, we conducted subgroup analyses by age, n-3 type, comorbidity (including traumatic brain injury), and adjunctive therapies. For meta-analysis of data with clear outliers, sensitivity analysis was conducted (excluding the outliers), if appropriate (Greenland and Longnecker, 1992; Orsini et al., 2012; Hamling et al., 2008; Higgins et al., 2011). We attempted to assess dose-response using within-study comparisons, to the extent possible; however, few dose-optimization studies were identified. We compared outcomes across studies based on dose but did not attempt to infer dose-response, because of lack of homogeneity of study participants, designs, and intervention conditions.

Because of the number of studies that compared EPA alone or DHA alone with placebo, we pooled studies that administered EPA alone with those that administered mixtures of EPA and DHA where the ratio of EPA to DHA was greater than 1 (EPA:DHA>1). Likewise, we combined studies that administered DHA alone with those that administered mixtures where the ratio of DHA to EPA was greater than 1 (DHA:EPA>1).

For each included study, findings are reported in Appendix B, which provides an evidence table that includes the intervention details, specific comparisons, and outcomes for each comparison.

Quality of Evidence

The quality of evidence was assessed for major outcomes and exposure types using an adaptation of the Grades of Recommendation, Assessment, Development, and Evaluation (or GRADE) methodology (Berkman et al., 2014), in which the body of evidence is assessed based on the following dimensions: number of studies, study limitations (risk of bias), directness (of study outcome measures), consistency across studies, precision, reporting bias, and other criteria where necessary based on the identified literature.

The quality of evidence was graded on a four-item scale:

- *High* indicates that the review authors are very confident that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has few or no deficiencies. As such, the reviewers believe the findings are stable (i.e., further research is very unlikely to change confidence in the effect estimate).

- *Moderate* indicates that the review authors are moderately confident that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has some deficiencies. As such, the reviewers believe that the findings are likely to be stable, but further research may change confidence in the effect estimate and may even change the estimate.
- *Low* indicates that the review authors have limited confidence that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has major or numerous (or both) deficiencies. As such, the reviewers believe that additional evidence is needed before concluding either that the findings are stable or that the effect estimate lies close to the true effect.
- *Very low* indicates that the review authors have very little confidence that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has very major deficiencies. As such, the true effect is likely to be substantially different from the estimated effect; thus, any estimate of effect is very uncertain.

The quality of the body of evidence was downgraded when results were primarily based on studies with substantial limitations; when results were inconsistent across individual studies, in the presence of substantial heterogeneity in pooled analyses, and when the result was based only on a single study without replication in an independent research study; when conclusions were based on indirect evidence (e.g., effects based on subgroup analyses or meta-regressions in the absence of head-to-head comparisons); and when pooled results were imprecise estimates of the treatment effect, with wide confidence intervals spanning effect sizes with different clinical conclusions.

The quality of the evidence regarding adverse event assessments was rated differently from that of the efficacy assessments, in keeping with the model used for other reports in this series. The quality of the adverse event reporting was not rated for individual studies (using, for example, a McHarm assessment). Instead, we assessed whether studies used a predesigned adverse event assessment and whether authors used a pre-existing classification system to query participants or to classify adverse events for reporting, and we evaluated the pooled ORs for precision.

Summary of Findings

Review findings were summarized in a table organized by key outcomes and describing the intervention and the comparator; the study design, number of studies, and number of participants; the direction and the magnitude of effect; and the quality of evidence summary assessment for the finding (see Table 4.1). For each outcome, results of pooled analyses are described first, followed by narrative descriptions of individual studies not included in the pooled analyses.

Findings are first reported for the broad comparison of any n-3 fatty acid intervention compared with placebo. Findings are then reported separately for results based on monotherapy and results for n-3 fatty acid adjunct therapy (KQ 1a). Findings were then organized by types of n-3 fatty acid interventions (i.e., purified DHA, EPA, or combinations; food sources; fish oil)

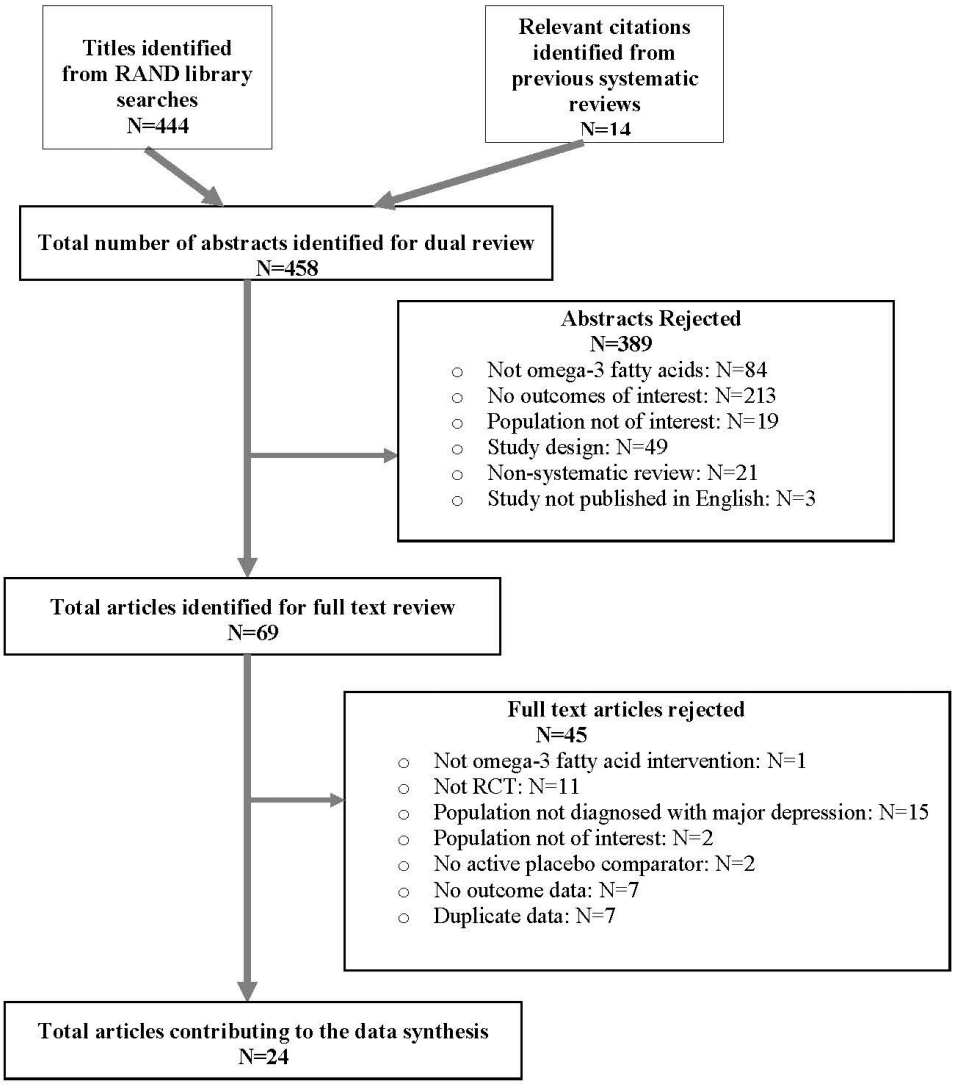
(KQ 1b). Depression severity was distinguished where possible (KQ 1c). Finally, the comparative safety (KQ 1d) and efficacy (KQ 1e) was determined, distinguishing the comparator antidepressant medication and psychotherapy.

Chapter Three: Results

Results of Literature Searches

We identified 458 potentially relevant citations by searching electronic databases and reviewing the studies cited in prior systematic reviews. The disposition of these citations is described in Figure 3.1.

Figure 3.1. Flow Diagram



Of the 458 abstracts we reviewed, we identified 69 for full text screening. All but 24 were excluded because they did not meet eligibility criteria. The remaining 24 articles underwent

abstraction of study-level details and outcome data (see Appendix B). A list of excluded publications is shown in Appendix C. The number and type of studies that address each key question and subquestion are described in Table 3.1.

Table 3.1 Evidence Base for Key Questions

Key Question		Number of RCTs
KQ 1	What are the efficacy and safety of n-3 supplements for depressive symptoms and quality of life in adults with MDD compared with placebo or active comparator?	24 RCTs
KQ 1a	Are n-3 fatty acids more effective as monotherapy than as an adjunctive therapy?	1 RCT directly comparing monotherapy vs. adjunctive therapy
KQ 1b	Does efficacy differ depending on the type—EPA, DHA, or ALA—and amount of n-3 fatty acid used?	2 RCTs EPA vs. DHA 6 RCTs EPA vs. placebo 9 RCTs EPA:DHA>1 3 RCTs DHA vs. placebo 3 RCTs DHA+DHA:EPA>1
KQ 1c	Does the efficacy of n-3 fatty acids differ depending on the type of MDD (i.e., mild, moderate, severe, peripartum)?	3 RCTs of mild, mild-to-moderate MDD 18 severity not described 4 RCTs peripartum depression
KQ 1d	What is the safety (e.g., adverse effects, drug-nutrient interactions) of n-3 use in individuals with MDD compared with standard antidepressant therapy or placebo?	20 RCTs vs. placebo 1 RCT with active comparator
KQ 1e	How does the efficacy of n-3 fatty acids compare with that of standard antidepressant therapy?	1 RCT directly comparing omega-3 fatty acids with antidepressant therapy

Description of Included Studies

Key Question

All 24 included studies reported efficacy outcomes. Of the 24 that reported on efficacy, 21 also reported safety outcomes.

For KQ 1a, regarding whether n-3 fatty acids are more effective as monotherapy than as adjunctive therapy, we identified three RCTs that compared outcomes for participants taking only n-3 fatty acids with those for participants taking both n-3 fatty acids and antidepressants (Jazayeri et al., 2008; da Silva et al., 2008; Tajalizadekhoob et al., 2011). Eight RCTs required that participants take only n-3s and did not allow maintenance antidepressant therapy (four were studies of peripartum women) (Marangell et al., 2003; Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Mischoulon, Nierenberg, et al., 2014; Kaviani et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014); eight studies required adjunctive maintenance therapy (antidepressants or psychotherapy) (Mischoulon, Papakostas, et al., 2009;

Mischoulon, Best-Popescu, et al., 2008; Bot et al., 2010). The remainder of the studies that assessed efficacy allowed—but did not require—the use of antidepressants.

For KQ 1b, which assesses whether efficacy differs by the type and amount of n-3, we identified two head-to-head placebo-controlled trials that compared EPA with DHA (or high-EPA oil with high-DHA oil) (Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013). We identified one head-to-head placebo-controlled trial that compared increasing doses of EPA (Peet and Horrobin, 2002) and one trial with no placebo control that compared increasing doses of DHA (Mischoulon, Best-Popescu, et al., 2008). Six studies compared EPA alone with placebo (Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Mischoulon, Papakostas, et al., 2009; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Bot et al., 2010). Nine studies compared preparations with EPA:DHA ratios greater than or equal to 1 (i.e., higher EPA) with placebo (Su et al., 2003; da Silva et al., 2008; Rondanelli et al., 2011; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Tajalizadekhoob et al., 2011; Lesperance et al., 2011). Three trials compared DHA alone with placebo (Marangell et al., 2003; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013). Three trials compared preparations with DHA:EPA greater than 1 (i.e., higher DHA) with placebo (Silvers et al., 2005; Meyer et al., 2013).

For KQ 1c, regarding whether efficacy is affected by the severity or type of depression, we identified three studies that limited inclusion to patients with mild (Kaviani et al., 2014) or mild-to-moderate (Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011) depression. No studies stratified outcomes by depression severity. Two studies assessed only elderly patients (Rondanelli et al., 2011; Tajalizadekhoob et al., 2011). Four studies assessed efficacy in pregnant and/or postpartum women (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Kaviani et al., 2014). Five studies assessed patients with a medical comorbidity (da Silva et al., 2008; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Bot et al., 2010; Carney et al., 2009).

For KQ 1d, regarding safety, we identified 21 studies that reported on adverse events (Su et al., 2003; Silvers et al., 2005; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Jazayeri et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Mischoulon, Papakostas, et al., 2009; Rondanelli et al., 2011; Gertsik et al., 2012; Freeman and Sinha, 2007; Mischoulon, Best-Popescu, et al., 2008; Mischoulon, Nierenberg, et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Bot et al., 2010; Carney et al., 2009).

For KQ 1e, regarding how the efficacy of n-3 fatty acids compares with that of antidepressants, we identified only one study that compared an n-3 fatty acid plus placebo with an n-3 placebo plus fluoxetine (Jazayeri et al., 2008).

Design

All studies were parallel RCTs that randomized individual participants, rather than clusters of participants. The total number of participants for all studies of non-peripartum adults was 1,552, and the number of peripartum women was 201. Studies ranged in participant number (n) included in the analyses from 20 to 432. Eight studies performed a power calculation to determine enrollment size needed (Silvers et al., 2005; Jazayeri et al., 2008; Gertsik et al., 2012; Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Bot et al., 2010; Carney et al., 2009).

Of the 24 included studies, eight performed only a per-protocol analysis. Nine studies performed ITT analysis or both per-protocol and ITT analysis. Seven studies performed what they referred to as a modified ITT analysis (Marangell et al., 2003; Freeman, Davis, et al., 2008; Mischoulon, Papakostas, et al., 2009; Freeman and Sinha, 2007; Mischoulon, Best-Popescu, et al., 2008; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013).

Setting

Seven studies were conducted in the United States. Six studies were conducted in Iran. Two studies were conducted in Australia and two in Taiwan. One study was conducted in each of the following countries: Brazil, Canada, Israel, Italy, New Zealand, the Netherlands, and the United Kingdom.

Two studies were conducted in long-term care facilities for the elderly (in Iran and Italy); the remainder were community-based studies based in academic medical centers. One study was conducted at two sites in the United States (Mischoulon, Nierenberg, et al., 2014), one was conducted at eight sites in Canada (Lesperance et al., 2011), and the rest were single-site studies.

Participants

The mean age of participants ranged from 34.0 to 84.9. Two studies enrolled only elderly participants (Rondanelli et al., 2011; Tajalizadekhoob et al., 2011).

Four studies enrolled only pregnant or postpartum women (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Kaviani et al., 2014). In the remaining 20 studies, the proportion of men ranged from 15 percent (Nemets, Stahl, and Belmaker, 2002) to 55 percent (Gharekhani et al., 2014); females outnumbered male participants in most studies.

One of the studies specified that the participants had mild depression (Kaviani et al., 2014). Two of the 24 studies specified that the participants had "mild-to-moderate" depression, according to diagnostic criteria (Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011). The remaining studies specified criteria for MDD used as inclusion criteria. Two studies described participants as having treatment-resistant depression (Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002).

The majority of studies enrolled healthy adults with MDD (some also had anxiety disorders, not otherwise specified) but no physical comorbidities. One study enrolled only individuals diagnosed with Parkinson's disease and MDD (da Silva et al., 2008). One study enrolled individuals with coronary heart disease and MDD (Carney et al., 2009). One study enrolled only adults with diabetes mellitus (type 1 or 2) and MDD (Bot et al., 2010). Two studies enrolled only participants with end-stage renal disease on maintenance dialysis (Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014).

Interventions

We identified 20 studies that included comparisons of the efficacy of EPA, DHA, or a combination of EPA and DHA with that of placebo alone for the treatment of depression (Su et al., 2003; Silvers et al., 2005; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Rondanelli et al., 2011; Mischoulon, Nierenberg, et al., 2014; Kaviani et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Bot et al., 2010). However, 12 of these studies allowed or required maintenance antidepressant use (Su et al., 2003; Silvers et al., 2005; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Rondanelli et al., 2011; Mozaffari-Khosravi et al., 2013; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Bot et al., 2010).

Six studies compared EPA alone with placebo. Doses ranged from 1 to 4 grams (g) daily (Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Mischoulon, Papakostas, et al., 2009; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Bot et al., 2010). Eight studies compared mixtures of EPA and DHA with a ratio of EPA to DHA greater than 1 (Su et al., 2003; da Silva et al., 2008; Rondanelli et al., 2011; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Mischoulon, Nierenberg, et al., 2014). Doses of EPA in these studies ranged from 0.72 g to 4.4 g daily, and total n-3 intake ranged from 1.1 g to 6.6 g daily.

Three studies compared DHA alone with placebo (Freeman, Davis, et al., 2008; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013). Doses ranged from 1 g to 2 g daily. Two studies compared mixtures of EPA and DHA with a ratio of DHA to EPA greater than 1 (Silvers et al., 2005; Meyer et al., 2013). Doses of DHA were 2.4 g and 2.5 g daily, and total n-3 intakes were 3.0 g and 3.2 g daily.

Two studies compared DHA with EPA head to head (Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013).

One study compared varying doses and dosing schedules of DHA with no placebo control (Mischoulon, Best-Popescu, et al., 2008). One study compared varying doses of EPA (with a placebo control) (Peet and Horrobin, 2002).

One study compared the efficacy of n-3 fatty acids with that of a selective serotonin reuptake inhibitor (Jazayeri et al., 2008). Two studies compared adjunctive therapy with that of an antidepressant alone (Gertsik et al., 2012; Carney et al., 2009). One study that allowed maintenance therapy performed a subgroup analysis on effectiveness of n-3s by use of adjunctive antidepressant (Tajalizadekhoob et al., 2011).

Study duration ranged from four weeks to 26 weeks. Most studies were eight or 12 weeks in duration.

Comparators

Active intervention comparators were described above. For inactive placebo controls that were described, comparators were nearly always paraffin oil, olive oil, or another food-grade oil.

Outcome Measures

Included studies were those that measured an indicator of depression, quality of life, suicidality, and/or adverse events.

Of the studies that measured depression in non-peripartum adults, 13 used some form of the HAMD (e.g., HAMD-9, 17, or 21) alone or with another measure. Five studies used the Montgomery-Åsberg Depression Rating Scale (MADRS), alone or with another measure. Seven used the Beck Depression Inventory (BDI), two used the Geriatric Depression Scale (GDS), and one used the self-reported Inventory of Depressive Symptomatology. Among the four studies of peripartum women, three used the Edinburgh Postnatal Depression Scale (EPDS), two used the HAMD, and two used the BDI.

The percentage of participants who achieved a clinical response to treatment was reported in 11 studies. Definition of clinical response varied but was most often a 50-percent or greater mean improvement in baseline depression score (e.g., decrease in mean HAMD score). Seven studies reported on rates of remission, usually defined as a change in depression score to within the normal range.

Two studies assessed quality of life (Rondanelli et al., 2011; Dashti-Khavidaki et al., 2014). Both used the SF-36.

Adverse events were abstracted from 21 studies and categorized according to the Common Terminology Criteria for Adverse Events classification system.

Risk of Bias

The quality of the studies was generally fair to poor, as assessed using the USPSTF ratings, which are based in part on the Cochrane Risk of Bias criteria (see Table 3.2). Specifically, nine studies (reported in ten publications) received a "poor" rating (Su et al., 2003; Freeman, Davis, et al., 2008; Jazayeri et al., 2008; da Silva et al., 2008; Freeman and Sinha, 2007; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Bot et al., 2010); eight studies received a "fair" rating (Peet and Horrobin, 2002; Nemets, Stahl, and

Belmaker, 2002; Marangell et al., 2003; Su et al., 2008; Gertsik et al., 2012; Mischoulon, Best-Popescu, et al., 2008; Lesperance et al., 2011; Carney et al., 2009); and seven studies received a rating of "good" (Silvers et al., 2005; Rees, Austin, and Parker, 2008; Mischoulon, Papakostas, et al., 2009; Rondanelli et al., 2011; Mischoulon, Nierenberg, et al., 2014; Kaviani et al., 2014; Mozaffari-Khosravi et al., 2013).

Assessing the individual Cochrane Risk of Bias criteria, the criterion with the highest number of unclear or high risk of bias ratings was "selective reporting of outcome data," with 16 "unclear" ratings (Su et al., 2003; Silvers et al., 2005; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Jazayeri et al., 2008; Rees, Austin, and Parker, 2008; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Rondanelli et al., 2011; Gertsik et al., 2012; Freeman and Sinha, 2007; Mischoulon, Best-Popescu, et al., 2008; Tajalizadekhoob et al., 2011; Lesperance et al., 2011).

"Blinding of outcome assessment" had 15 studies with "unclear" ratings (Su et al., 2003; Peet and Horrobin, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Su et al., 2008; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Gertsik et al., 2012; Mischoulon, Best-Popescu, et al., 2008; Kaviani et al., 2014; Gharekhani et al., 2014; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Bot et al., 2010; Carney et al., 2009) and 10 "low" ratings (Silvers et al., 2005; Nemets, Stahl, and Belmaker, 2002; Jazayeri et al., 2008; Rees, Austin, and Parker, 2008; Rondanelli et al., 2011; Freeman and Sinha, 2007; Mischoulon, Nierenberg, et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Lesperance et al., 2011).

"Recruitment method" had "unclear" ratings for 14 studies (Su et al., 2003; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Jazayeri et al., 2008; Su et al., 2008; da Silva et al., 2008; Gertsik et al., 2012; Freeman and Sinha, 2007; Mischoulon, Best-Popescu, et al., 2008; Mischoulon, Nierenberg, et al., 2014; Gharekhani et al., 2014; Lesperance et al., 2011; Bot et al., 2010) and "low" ratings for 11 studies (Silvers et al., 2005; Peet and Horrobin, 2002; Rees, Austin, and Parker, 2008; Mischoulon, Papakostas, et al., 2009; Rondanelli et al., 2011; Kaviani et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Carney et al., 2009).

"Allocation concealment method" had "unclear" ratings for 14 studies (Su et al., 2003; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Jazayeri et al., 2008; Su et al., 2008; Gertsik et al., 2012; Freeman and Sinha, 2007; Mischoulon, Best-Popescu, et al., 2008; Kaviani et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Bot et al., 2010; Carney et al., 2009) and "low" ratings for the remaining 11 studies (Silvers et al., 2005; Peet and Horrobin, 2002; Rees, Austin, and Parker, 2008; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Rondanelli et al., 2011; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011).

Table 3.2. Study Quality/Risk of Bias for Individual Included Studies

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessors (detection bias)	Completeness of Reporting Outcome Data (attrition bias)	Selective Outcome Reporting (reporting bias)	Other Biases			USPSTF Quality Rating[a]
							Both Arms Receive Treatment as Usual, Only Treatment Group Receives n-3 Fatty Acid	Appropriate Washout Period or Exclusion of Individuals Taking Personal Supplements	Baseline Assessment, Appropriate Statistical Analysis, COI)	
Bot et al., 2010	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Poor
Carney et al., 2009	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Fair
Dashti-Khavidaki et al., 2014	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Poor
da Silva et al., 2008	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Poor
Freeman, Davis, et al., 2008	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Poor
Gertsik et al., 2012	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair
Gharekhani et al., 2014	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Poor
Jazayeri et al., 2008	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Poor
Kaviani et al., 2014	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
Lesperance et al., 2010	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Fair
Marangell et al., 2003	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Fair
Meyer et al., 2013	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Poor
Mischoulon, Best-Popescu, et al., 2008	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair
Mischoulon, Papakostas, et al., 2009	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Good
Mischoulon, Nierenberg, et al., 2014	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
Mozaffari-Khosravi et al., 2013	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Good
Nemets, Stahl, and Belmaker, 2002	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Fair

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessors (detection bias)	Completeness of Reporting Outcome Data (attrition bias)	Selective Outcome Reporting (reporting bias)	Other Biases			USPSTF Quality Rating[a]
							Both Arms Receive Treatment as Usual, Only Treatment Group Receives n-3 Fatty Acid	Appropriate Washout Period or Exclusion of Individuals Taking Personal Supplements	Baseline Assessment, Appropriate Statistical Analysis, COI)	
Peet and Horrobin, 2002	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Fair
Rees, Austin, and Parker, 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Good
Rondanelli et al., 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Good
Silvers et al., 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Good
Su et al., 2003	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Poor
Su et al., 2008	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Fair
Tajalizadekhoob et al., 2011	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Poor

NOTE: COI = conflict of interest; USPSTF = U.S. Preventive Services Task Force.

[a] The USPSTF criteria (U.S. Preventive Services Task Force, 2008) for study quality involve assessment of various factors related to the internal validity of the study. "Good" is the highest ranking, which involves comparable groups with low attrition, with outcomes being reliably and validly measured and analyzed. "Fair" is the next highest rating and involves studies with one or a few potential concerns (e.g., some though not major differences between groups exist at follow-up), though intention-to-treat analysis was performed. "Poor" is the lowest ranking and involves studies with one or more "fatal flaws" (e.g., no intention-to-treat analysis).

Results of the Literature Review

The results of the review of studies that met the inclusion criteria are presented here, in order of the key questions or subquestions they address. For each question, we first describe the results of our meta-analyses. We then narratively describe findings of studies that could not be included in a meta-analysis. All study details are described in the evidence table in Appendix B.

KQ 1: What Are the Efficacy and Safety of n-3 Supplements for Depressive Symptoms and Quality of Life in Adults with MDD Compared with Placebo or Active Comparator?

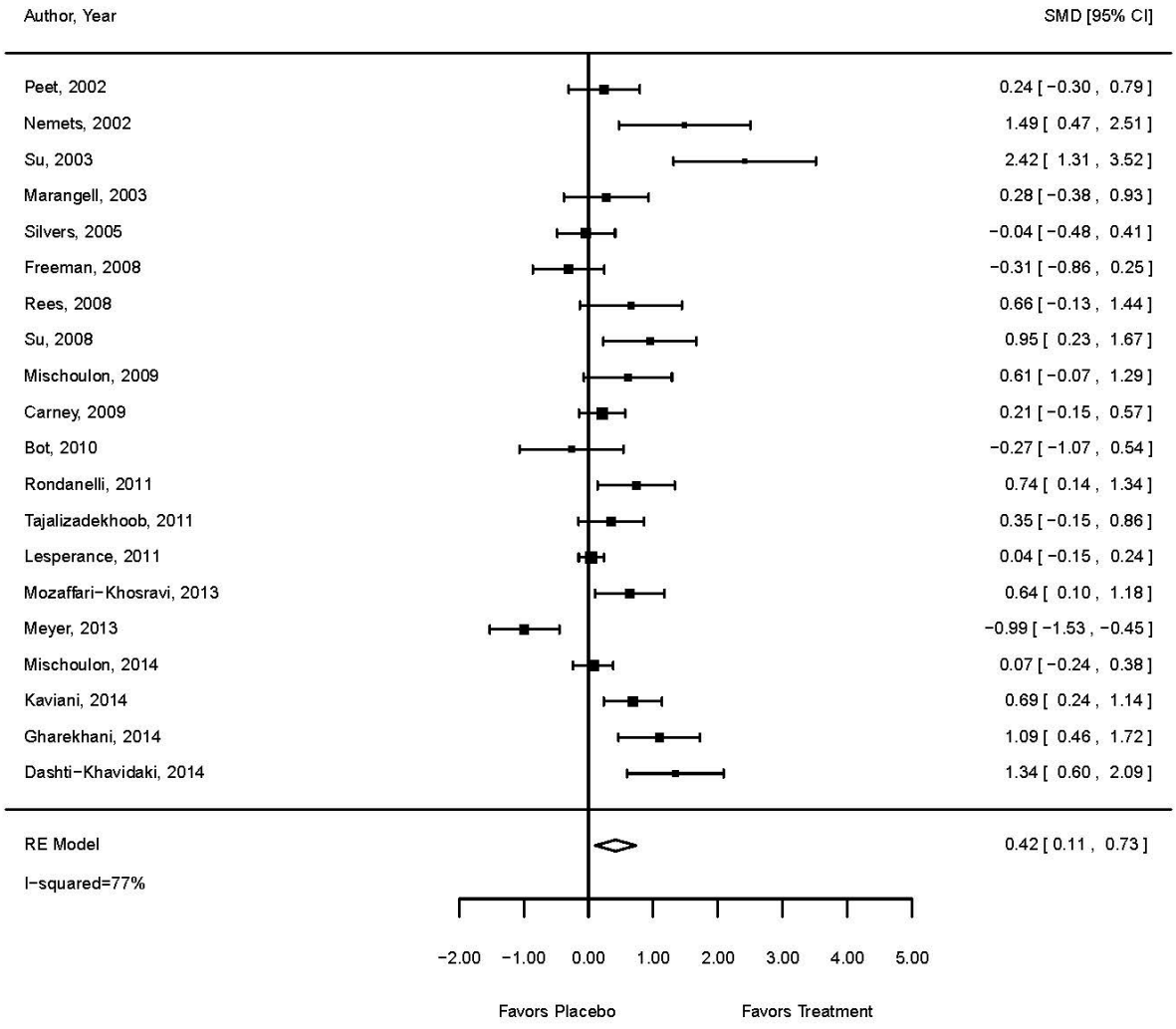
Depression Treatment Response Standardized Mean Differences

We identified 20 studies of the efficacy of EPA, DHA, or a combination of EPA and DHA compared with that of placebo for treating depression as measured using the HAMD, BDI, MADRS, EPDS, or GDS (Su et al., 2003; Silvers et al., 2005; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Marangell et al., 2003; Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Mischoulon, Papakostas, et al., 2009; da Silva et al., 2008; Rondanelli et al., 2011; Mischoulon, Nierenberg, et al., 2014; Kaviani et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Meyer et al., 2013; Tajalizadekhoob et al., 2011; Lesperance et al., 2011; Bot et al., 2010). These studies are summarized in the evidence table in Appendix B. The mean ages of participants ranged from 26.3 (Kaviani et al., 2014) to 84.9 (Rondanelli et al., 2011). The proportion of women was greater than 50 percent in the 16 studies of non-peripartum adults. Total daily doses of n-3 fatty acids ranged from 1 g to 6.6 g (comparisons of findings by dose and for EPA alone, DHA alone, and higher and lower ratios of DHA:EPA are described in the response to KQ 1b below).

Treatment duration ranged from four weeks (Nemets, Stahl, and Belmaker, 2002) to 26 weeks (Tajalizadekhoob et al., 2011). One study had a duration of four weeks, three had a duration of six weeks, seven had a duration of eight weeks, five had a duration of 12 weeks, two had a duration of 16 weeks, and one had a duration of 26 weeks.

Of the 20 studies, 11 showed a significant positive effect of the n-3 fatty acid on depression symptoms compared with placebo (a decrease in mean scores from baseline to final follow-up) on at least one depression scale (Su et al., 2003; Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Su et al., 2008; da Silva et al., 2008; Rondanelli et al., 2011; Kaviani et al., 2014; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011). Compared with placebo, n-3 fatty acids showed a significant effect of n-3 fatty acid treatment on depressive symptoms, but high heterogeneity (SMD 0.42; 95% confidence interval [CI] 0.11, 0.73; I^2 77%) (Figure 3.2).

Figure 3.2. Omega-3 Fatty Acids Versus Placebo, Depression Standardized Mean Differences



Sensitivity analysis using a fixed-effects model showed a smaller but still statistically significant effect size compared with the random-effects model (SMD 0.24; CI 0.14, 0.35). The random-effects pooled assessment showed evidence of publication bias (Egger test p=0.008, Begg test p=0.007). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the efficacy of n-3 fatty acids was no longer statistically significant based on a random-effects model (SMD 0.23; CI –0.03, 0.48) but showed a small and statistically significant effect using a fixed-effects model (SMD 0.18; CI 0.018, 0.217).

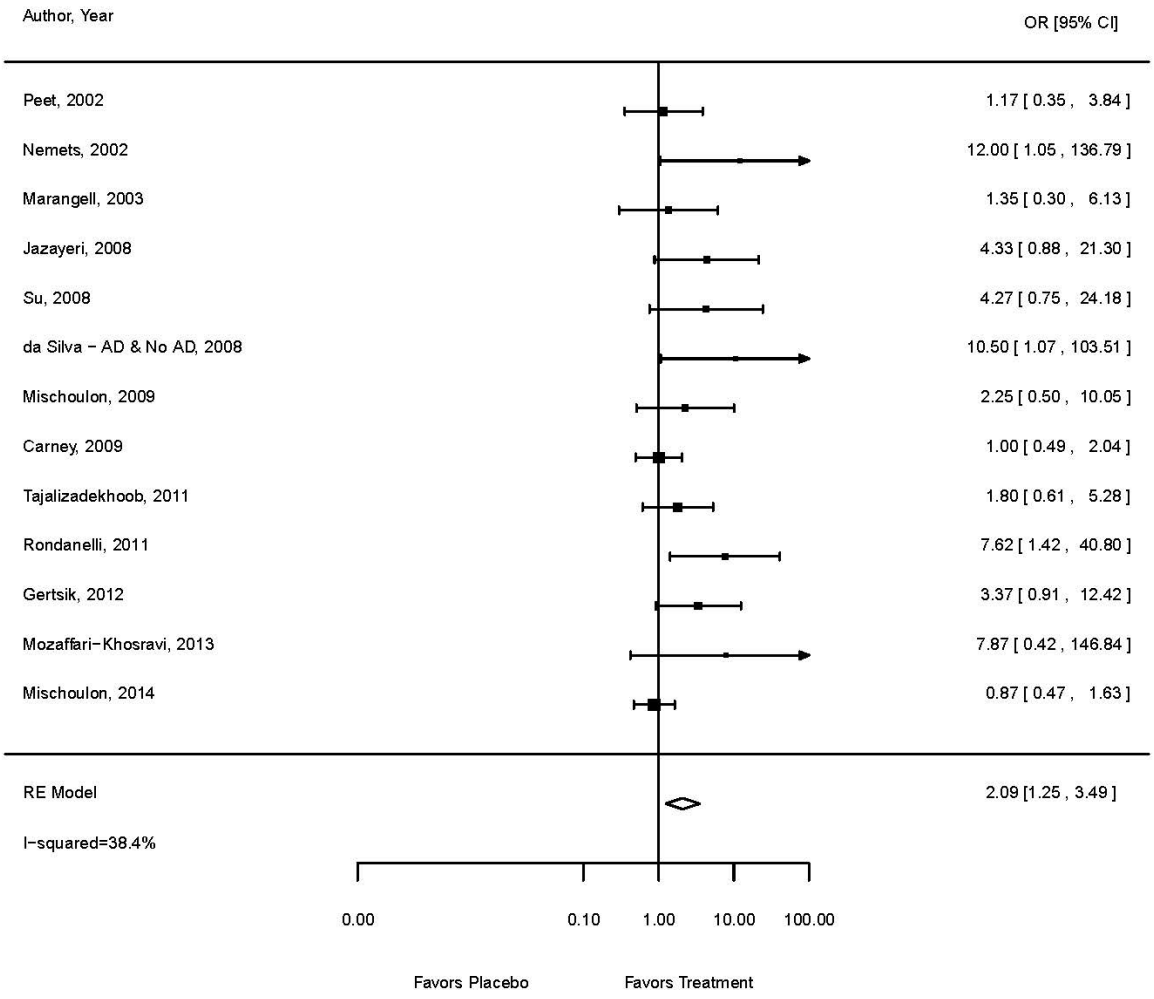
Depression Treatment Responders

Twelve studies reported the percentage of participants who experienced clinical response to treatment or clinical improvement with n-3 fatty acids compared with placebo. Clinical response to treatment was usually defined as a decrease of 50 percent or more in baseline depression scale score (or a comparable increase if a lower score was associated with depression).

Of the 13 studies that reported clinical improvement (of mixed quality), four administered EPA alone (Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Mischoulon, Papakostas, et al., 2009; Mozaffari-Khosravi et al., 2013), three administered DHA alone (Marangell et al., 2003; Mischoulon, Best-Popescu, et al., 2008; Mozaffari-Khosravi et al., 2013), and the remainder administered a mixture of EPA and DHA, including fish oil (Su et al., 2008; da Silva et al., 2008; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011; Carney et al., 2009).

Overall, active treatment was associated with a significant increase in the proportion of participants responding to treatment (OR 2.09; CI 1.25, 3.49; 12 RCTs; I^2 38%) (Figure 3.3).

Figure 3.3. Omega-3 Fatty Acids Versus Placebo, Depression Treatment Responders



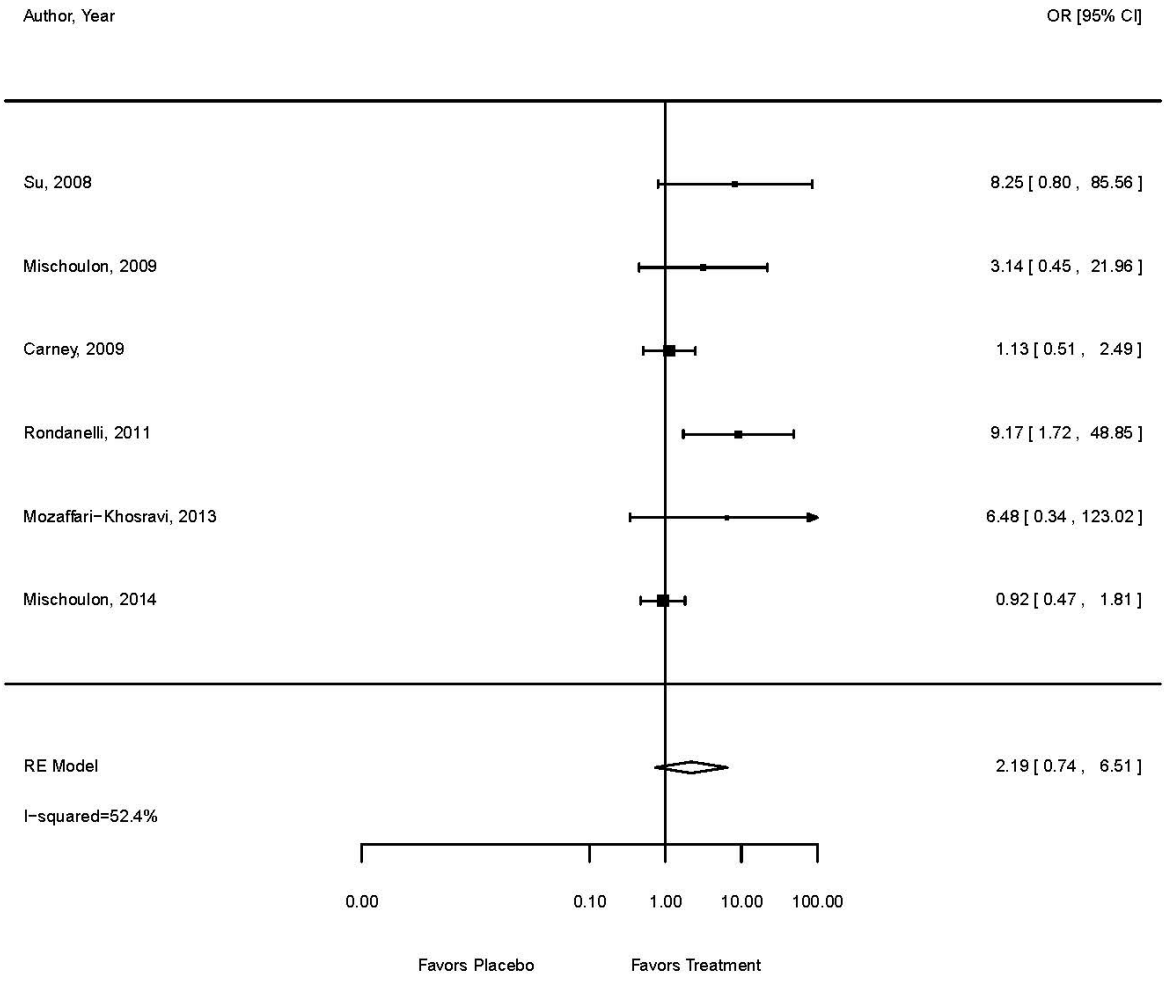
Sensitivity analysis using a fixed-effects model showed similar findings to the random-effects model (OR 1.61; CI 1.61, 2.25). The random-effects pooled assessment showed evidence of publication bias (Egger test $p<0.001$, Begg test $p=0.004$). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the efficacy

of n-3 fatty acids was not statistically different from placebo using a random-effects model (OR 1.22; CI 0.89, 1.65) or a fixed-effects model (OR 3.31; CI 0.88, 1.67).

Depression Remission

The percentage of participants who achieved remission was reported in six studies—five studies of non-peripartum adults (Mischoulon, Papakostas, et al., 2009; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Carney et al., 2009; Gerstik et al., 2012) and one study of peripartum women (Su et al., 2008). Three studies administered EPA alone (Mischoulon, Papakostas, et al., 2009; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013), two studies administered DHA alone (Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013), and three studies administered a mixture of EPA and DHA with an EPA:DHA ratio greater than 1 (Su et al., 2008; Carney et al., 2009; Gerstik et al., 2012). The numbers of participants who achieved remission was small, and the pooled effect size showed a non-significant difference between n-3-treated and placebo participants (OR 2.19; CI 0.74, 6.51; 6 RCTs; I^2 52%) (Figure 3.4).

Figure 3.4. Omega-3 Fatty Acids Versus Placebo, Depression Remission



Sensitivity analysis using a fixed-effects model showed similar findings to the random-effects model (OR 1.44; CI 0.91, 2.27). Sensitivity analysis that expressed the pooled outcome as a risk ratio (RR) showed a similar effect size to the OR (RR 1.53; 0.76, 3.05). The random-effects pooled assessment indicated evidence of publication bias in the Egger but not the Begg test (Egger test p=0.014, Begg test p=0.272). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the effect for the outcome remission was smaller than in the main analysis and not statistically significant (random-effects model: OR 1.18; CI 0.49, 2.85; fixed-effects model: OR 1.08; CI 0.70, 1.66).

Quality of Life

Two trials reported on the effects of n-3 fatty acids on a measure of quality of life (Rondanelli et al., 2011; Dashti-Khavidaki et al., 2014).

A study conducted in a long-term care facility in Italy randomized 46 elderly female patients with MDD to 2.5 g DHA plus EPA daily (as fish oil) or placebo for eight weeks. Participants

were allowed maintenance benzodiazepines for sleep but no other psychotropic medications. Patients treated with n-3 fatty acids (who, as reported above, experienced improvement in depressive symptoms) also showed a significant improvement in the SF-36 composite score for mental functioning compared with the placebo group at follow-up (SMD –0.68; CI –1.27, –0.08) and improvement in physical functioning (SMD –0.8; CI –1.4, –0.2) (Rondanelli et al., 2011).

A study described above enrolled 40 adults in Iran with end-stage renal disease and MDD and randomized them to 1.8 g per day EPA plus DHA (Dashti-Khavidaki et al., 2014). Administering the SF-36, the researchers observed a significant improvement in mental functioning (SMD –1.11; CI –1.83, –0.39) but not in physical functioning (SMD –0.63; CI –1.32, 0.06) at 16 weeks follow-up.

In summary, SMDs for mental quality of life showed significant improvement in both studies; however, SMDs for physical functioning showed positive results for one study (Rondanelli et al., 2010) but not the other (Dashti-Khavidaki, et al., 2014). The small number of studies, combined with the inconsistency in results, does not allow conclusions to be drawn about the effects of n-3 fatty acids for quality of life.

KQ 1a: Are n-3 Fatty Acids More Effective as Monotherapy Than as an Adjunctive Therapy?

Omega-3 Fatty Acids as Monotherapy Versus Adjunctive Therapy

Eleven studies gave n-3 fatty acids systematically together with another depression treatment, including antidepressant medication and psychotherapy. Twelve studies gave n-3 fatty acids as monotherapy, but some of the studies permitted maintenance pharmacological treatment or psychotherapy as long as no change was initiated during the trial phase.

Head-to-Head Trials of Monotherapy Versus Adjunctive Therapy

Only one study was designed to systematically compare the efficacy of n-3 fatty acids alone with that of pharmacotherapy plus n-3 fatty acids (Jazayeri et al., 2008). This small study enrolled 48 Iranian adults with MDD (33 women), of mean age 34.8. One-third of the participants received 1 g EPA from rapeseed oil and 20 mg fluoxetine daily, another third received 1 g EPA and a placebo pill, and the remaining third received fluoxetine and an oil capsule (as a placebo for EPA) (Jazayeri et al., 2008). The duration of the intervention was eight weeks. Baseline and final depression status were assessed using the HAMD. Depression scores began to decrease in response to EPA, fluoxetine, and EPA plus fluoxetine by two weeks and continued to decrease through week eight. EPA and fluoxetine alone were equally effective in lowering depression scores. The combination of EPA plus fluoxetine showed an increased effect beginning at week four ($p=0.016$) and continuing through week eight ($p=0.005$). The study reported a higher proportion of treatment responders for the combination therapy EPA and antidepressants compared with EPA monotherapy, but the difference was not statistically significant (OR 0.29; CI 0.06, 1.47).

Subgroup Analysis of Monotherapy Studies

The monotherapy studies that provided sufficient data to estimate the effect on depression scale score differences (that is, studies in which no use of antidepressants was allowed) showed a statistically significant effect favoring n-3 fatty acids over placebo (SMD 0.62; CI 0.37, 0.87; 11 RCTs, I^2 49%), but there was some indication of publication bias (Egger test p=0.010, Begg test p=0.218).

The outcome number of treatment responders was not statistically significant (OR 1.45; CI 0.74, 2.83; 6 RCTs; I^2 12%) in this subgroup.

Studies reporting on the outcome patients in remission also showed no differences between patients receiving n-3 and antidepressant treatment compared with patients receiving antidepressant treatment and a placebo (OR 2.26; CI 0.42, 12.13; 4 RCTs; I^2 44%).

Subgroup Analysis of Adjunctive Therapy Studies

In studies that systematically gave n-3 fatty acids together with standard antidepressant treatments and compared results with a control group that also received standard antidepressant treatment, no statistically significant differences were observed between study arms (SMD 0.16; CI –0.52, 0.83; 9 RCTs; I^2 82%).

There was also no statistically significant effect on the outcome number of responders in this subgroup (OR 2.05; CI 0.67, 6.24; 5 RCTs; I^2 45%).

One study reported on the outcome remission but found no difference (OR 1.13; CI 0.51, 2.49) in this subgroup.

Meta-Regression Monotherapy Versus Adjunctive Therapy

A meta-regression comparing the effects in the monotherapy and adjunctive therapy subgroups was suggestive of a systematic difference that favored monotherapy but was not statistically significant (p=0.0898).

KQ 1b: Does Efficacy Differ Depending on the Type—EPA, DHA, or ALA—and Amount of n-3 Fatty Acid Used?

We identified only two trials that compared the efficacy of EPA supplementation alone with that of DHA, head to head. We also identified only one placebo-controlled study that compared the efficacy of increasing doses of EPA, and we found no placebo-controlled studies that compared the efficacy of increasing doses of DHA. Therefore, in this section, we also describe the outcomes of studies that compared the efficacy of one n-3 fatty acid alone with placebo, as well as studies in which the ratio of DHA to EPA was higher (high DHA) or lower (low DHA) than 1. We found no studies that met our inclusion criteria that assessed the efficacy of supplemental ALA.

Head-to-Head Trials of DHA Versus EPA

Two trials compared the efficacy of supplemental DHA with that of EPA head to head (Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013).

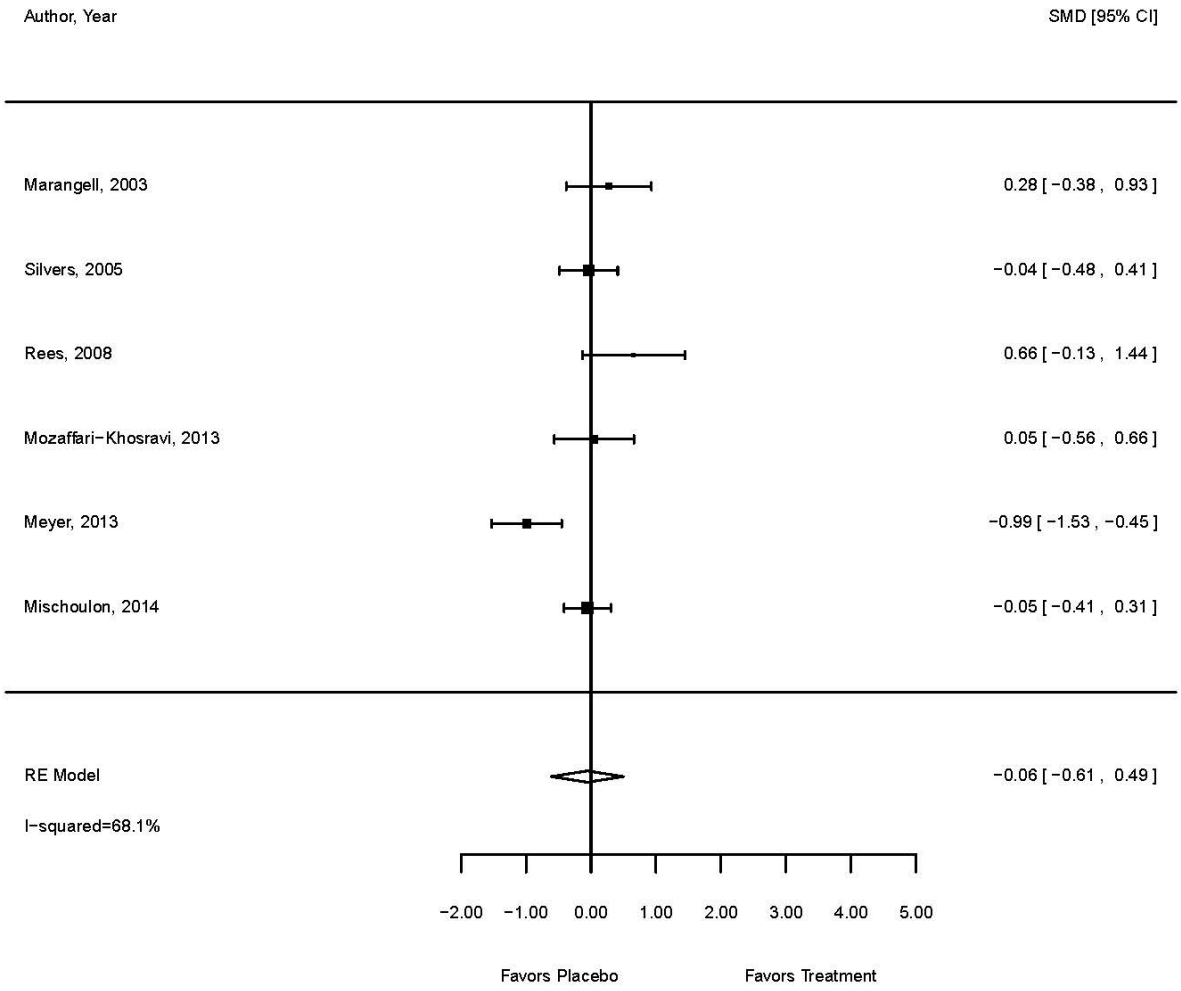
One study randomized 62 Iranian adults (mean age 35.1 years) with mild-to-moderate depression (38 women) to 1 g per day of DHA, EPA, or placebo (Mozaffari-Khosravi et al., 2013). Participants were permitted maintenance therapy. At 12 weeks, EPA significantly improved HAMD-17 (the original, shorter form of the current HAMD, which includes 24 items) depression symptoms, compared with DHA (SMD 1.24; CI 0.57, 1.91). Six of the 21 patients who received EPA achieved clinical response (i.e., decrease of 50 percent or more in baseline scores), compared with none in the DHA group, a non-significant difference (OR 17.19; CI 0.90, 328.87). Five of the participants who achieved a clinical response to EPA achieved remission, compared with none of the participants taking DHA, also a non-significant difference (OR 13.67; CI 0.70, 265.52).

A multi-site U.S. study randomized 154 adults with MDD (mean age 44.7 years; 91 females) to receive 1 g per day of DHA-enriched oil (DHA:EPA ratio of 5:1), 1 g per day of EPA-enriched oil (EPA:DHA ratio of 4:1), or placebo (soybean oil) (Mischoulon, Nierenberg, et al., 2014). Participants were not permitted maintenance pharmacotherapy. At eight weeks, participants taking EPA showed decreases in HAMD-17 scores comparable to participants taking DHA (SMD 0.23; CI –0.14, 0.59). Clinical response rates and remission rates also did not differ between EPA and DHA recipients (OR 0.94; CI 0.46, 1.95 for response rates, and OR 1.31; CI 0.60, 2.88 for remission rates).

Placebo-Controlled Trials of DHA or High DHA:EPA Ratio

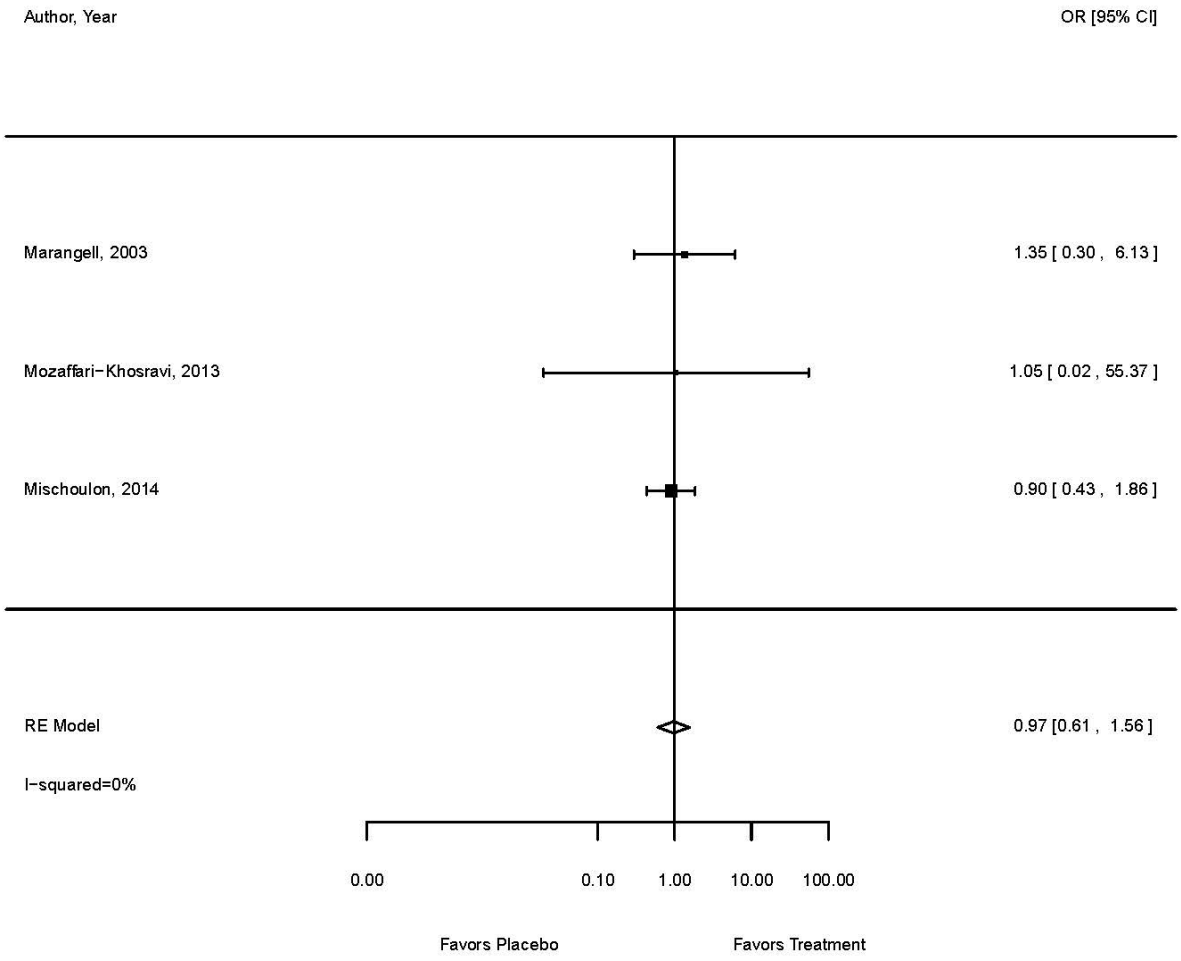
Three trials compared the efficacy of DHA alone with that of placebo (Marangell et al., 2003; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013), and three additional studies compared supplements with a higher DHA:EPA ratio with placebo (Silvers et al., 2005; Rees, Austin, and Parker, 2008; Meyer et al., 2013). None of these trials showed a significant beneficial effect of DHA (or high DHA:EPA ratio) over that of placebo. The pooled effect size for DHA versus placebo and higher DHA:EPA ratio versus placebo also showed no effect of DHA (SMD −0.06; CI −0.61, 0.49; 6 RCTs; I^2 68%) (Figure 3.5). There was no evidence of publication bias in this subgroup assessment (Egger test p=0.79, Begg test p=0.817).

Figure 3.5. DHA Alone or a High DHA:EPA Ratio Versus Placebo, Depression Standardized Mean Differences



Three trials compared the efficacy of DHA or a high DHA:EPA ratio with that of placebo for response to treatment (Marangell et al., 2003; Mozaffari-Khosravi et al., 2013; Mischoulon, Nierenberg et al., 2014) (Figure 3.6). No significant effect was found (OR 0.97; CI 0.61, 1.56; 3 RCTs; I^2 0%).

Figure 3.6 Response to Treatment with DHA Alone or a High DHA:EPA Ratio



Publication bias tests were not statistically significant in this subgroup (Egger test p=0.299, Begg test p=0.056).

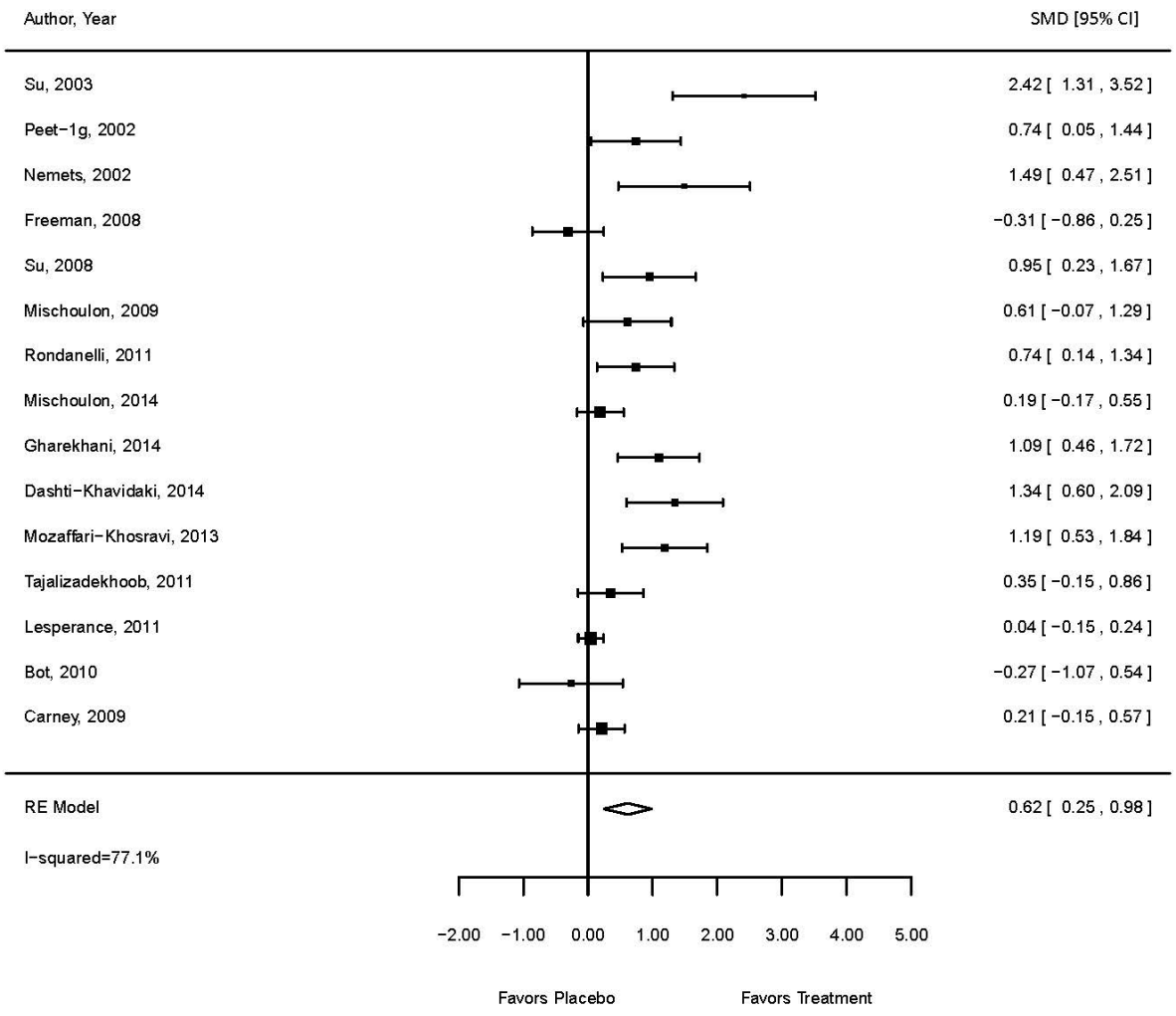
Two trials compared the effect of DHA or a high DHA:EPA ratio on depression remission. Neither observed a significant effect over that of placebo (OR 0.81; 0.42, 1.56) (Mozaffari-Khosravi et al., 2013; Mischoulon, Nierenberg et al., 2014).

Placebo-Controlled Trials of EPA or High EPA:DHA Ratio

Six trials compared the efficacy of EPA alone with that of placebo (Peet and Horrobin, 2002; Nemets, Stahl, and Belmaker, 2002; Mischoulon, Papakostas, et al., 2009; Mischoulon, Nierenberg, et al., 2014; Mozaffari-Khosravi et al., 2013; Bot et al., 2010). Mean ages ranged from 34.8 to 53.4. Nine additional studies compared supplements with a higher EPA:DHA ratio with placebo (Su et al., 2003; Freeman, Davis, et al., 2008; Su et al., 2008; da Silva et al., 2008; Rondanelli et al., 2011; Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014; Tajalizadekhoob et al., 2011; Lesperance et al., 2011).

Comparing EPA-only and high EPA:DHA studies with placebo showed a significant difference favoring n-3 fatty acid treatment (SMD 0.62; CI 0.25, 0.98; 15 RCTs; I^2 77%) (Figure 3.7).

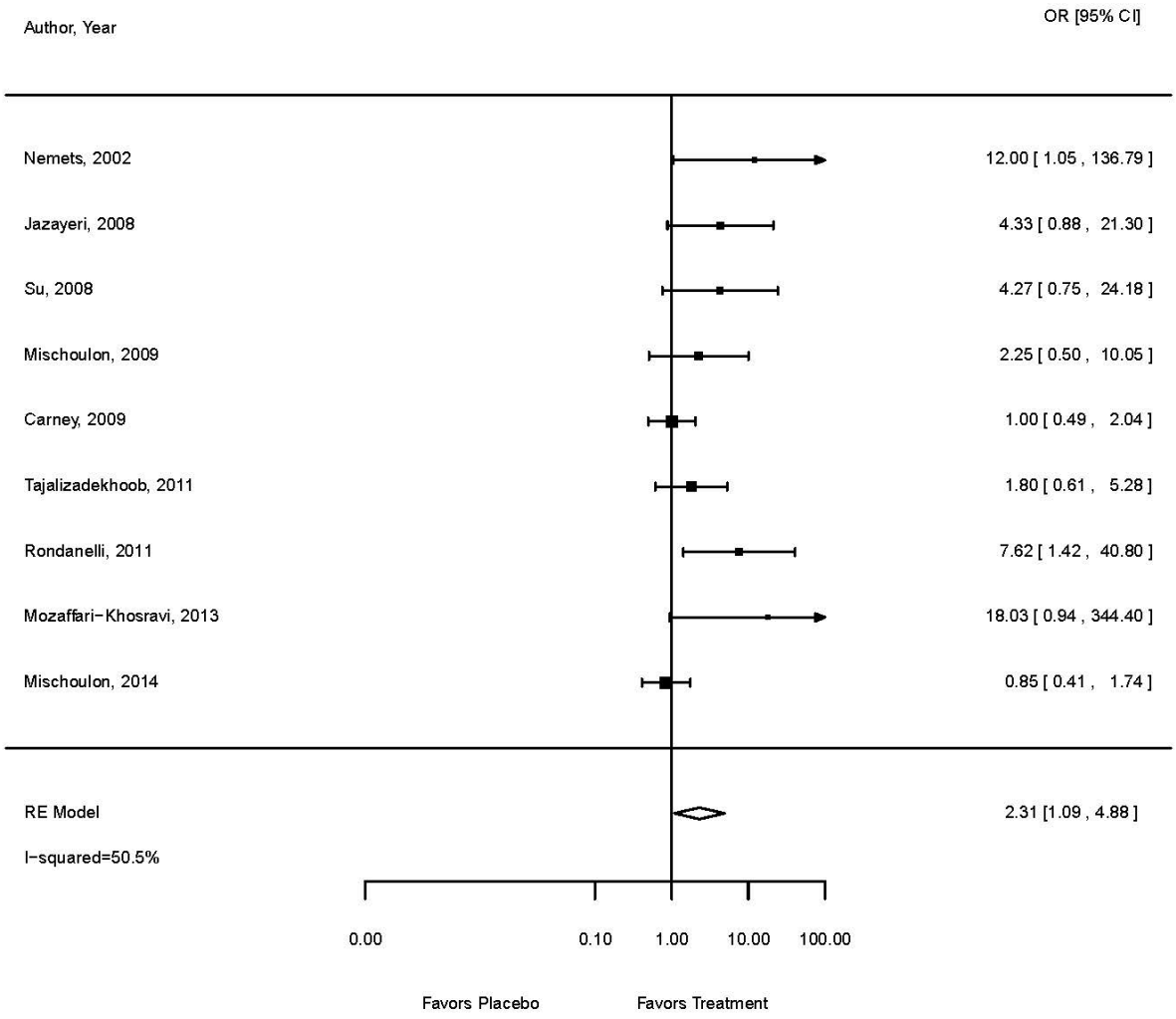
Figure 3.7. EPA Alone or a High EPA:DHA Ratio Versus Placebo, Depression Standardized Mean Differences



Sensitivity analysis using a fixed-effects model showed findings similar to the random-effects model but smaller in magnitude (SMD 0.31; CI 0.19, 0.44). The random-effects pooled assessment suggested evidence of publication bias in this subgroup (Egger test p=0.005, Begg test p=0.036). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the effect was similar to that of the fixed-effects estimate in magnitude, still favoring n-3 fatty acids (SMD 0.33; CI 0.02, 0.64).

Nine trials compared the efficacy of EPA or a high EPA:DHA ratio with that of placebo for response to treatment (Figure 3.8). A statistically significant difference was found between study arms, favoring active treatment (OR 2.31; CI 1.09, 4.88; 9 RCTs; I^2 51%).

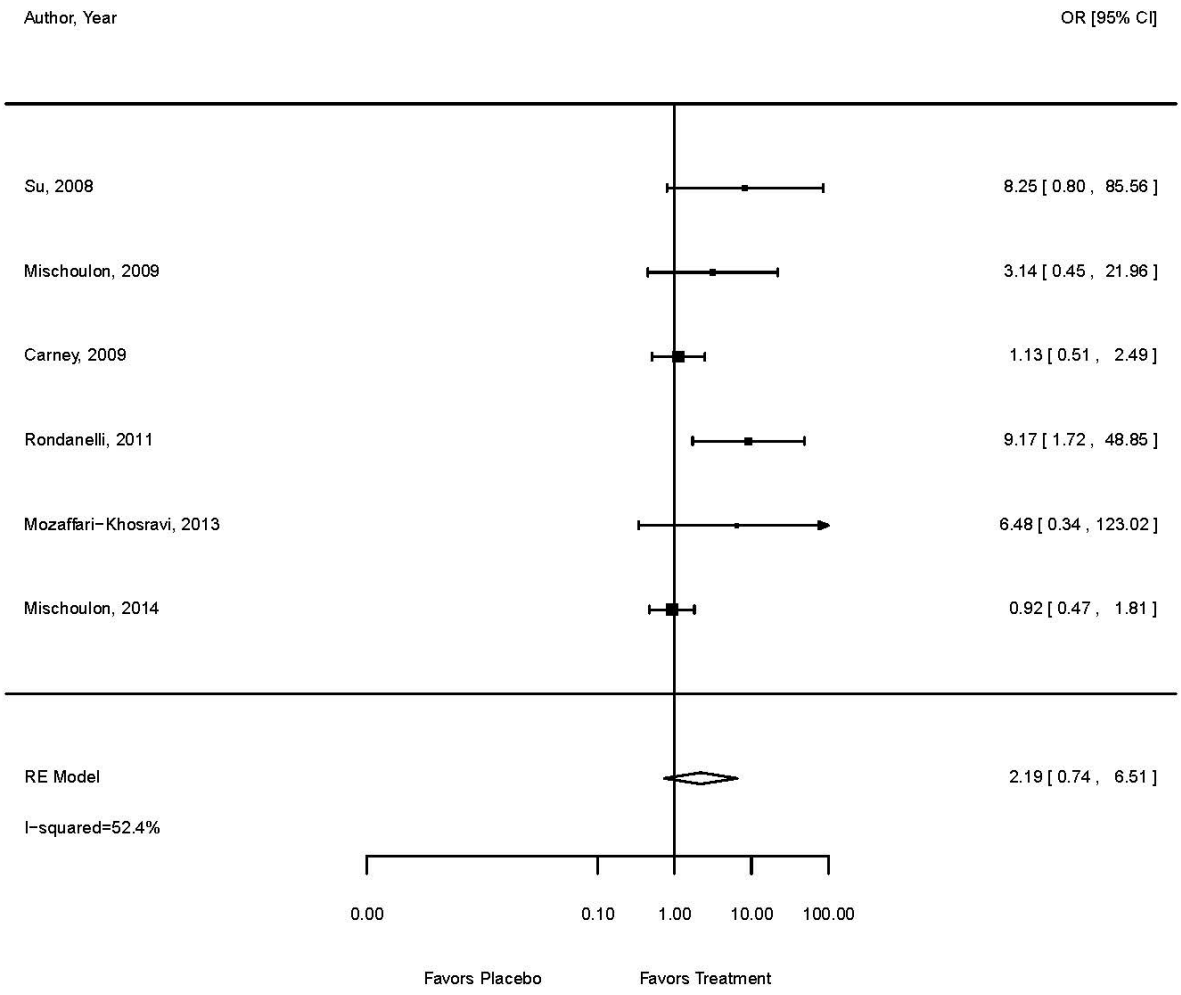
Figure 3.8 Response to Treatment with EPA Alone or a High EPA:DHA Ratio



A sensitivity analysis that reported the pooled outcome as a RR showed no difference from the OR (RR 1.49; CI 0.95, 2.32). The random-effects pooled assessment of OR suggested evidence of publication bias in this subgroup (Egger test p=0.013, Begg test p<0.001). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the effect was similar in magnitude to that of the fixed-effects estimate (OR 1.38; CI 0.71, 2.68; I^2 45%).

Six trials compared the effect of EPA or a high EPA:EPA ratio on depression remission (Figure 3.9). No statistically significant effect was observed over that of placebo (OR 2.19; CI 0.74, 6.51; 6 RCTs; I^2 52%).

Figure 3.9 Remission with EPA Alone or a High EPA:DHA Ratio



The random-effects pooled assessment suggested mixed evidence of publication bias in this subgroup (Egger test p=0.136, Begg test p=0.008). The funnel plot is shown in Appendix E. Using the trim-and-fill method to adjust for potential publication bias, the effect was similar in magnitude to that of the fixed-effects estimate (OR 1.27; CI 0.51, 3.18).

Meta-Regression Comparing Higher EPA to Higher DHA Ratios

To compare the efficacy of EPA with that of DHA, we conducted a random-effects meta-regression that included an indicator for interventions that used EPA only or higher EPA:DHA ratios. Three studies had DHA only, three studies had higher DHA:EPA ratios, and the remainder were EPA or higher EPA studies. The meta-regression indicated that EPA studies showed systematically larger effect estimates than DHA (p=0.01).

Head-to-Head Trials of Different Doses of EPA

Only one study (Peet and Horrobin, 2002) compared the effects of three doses of EPA—1 g, 2 g, and 4 g daily—among 77 adults (59 women) with treatment-resistant MDD. After 12 weeks of treatment, only the 1 g-per-day dose was effective in decreasing depression symptoms (using the HAMD, MADRS, and BDI). Four of the remaining five studies of EPA alone all administered 1 g daily, and the remaining study administered 2 mg, so it was not possible to assess dose-response across these studies.

Head-to-Head Trials of Different Doses of DHA

Only one study (Mischoulon, Best-Popescu, et al., 2008) compared the effects of different escalating doses (i.e., different dosing schedules) of DHA with that of a daily 1 g dose of DHA on depressive symptoms in adults. This study randomized 35 participants into three groups: The control group received 1 g DHA daily for 12 weeks; the second group received 1 g daily for one week and 2 g daily for weeks two through 12; and the third group took 1 g daily the first week, 2 g daily the second week, and 4 g daily during weeks three through 12. Only the 1 g daily group experienced significant relief from depression symptoms: 50 percent of completers showed clinically significant improvement.

KQ 1c: Does the Efficacy of n-3 Fatty Acids Differ Depending on the Type of MDD (i.e., Mild, Moderate, Severe, Recurrent, Postpartum)?

Depression Severity

Three studies that met the inclusion criteria described participants as having mild-to-moderate (Mozaffari-Khosravi et al., 2013; Tajalizadekhoob et al., 2011) or mild (Kaviani et al., 2014) depression (the remainder described participants as having MDD or peripartum depression).

A 2011 study randomized 66 elderly Iranian long-term care residents with mild-to-moderate depression to 1.2 g fish oil daily (0.6 g EPA/0.6 g DHA) or coconut oil placebo capsules. After six months, the fish oil group had significantly lower GDS scores than the placebo group (SMD 1.8; CI 0.61, 5.28) (Tajalizadekhoob et al., 2011).

A study described above that randomized 62 Iranian adults with mild-to-moderate depression (38 women) to 1 g per day of DHA, EPA, or placebo for 12 weeks (Mozaffari-Khosravi et al., 2013) found that EPA significantly improved HAMD-17 depression symptoms, compared with placebo (SMD 1.19; CI 0.53, 1.84). DHA had no significant effect (SMD 0.05; CI –0.56, 0.66). Six of the 21 patients who received EPA achieved clinical response (decrease of 50 percent or more in baseline scores).

Finally, a study of pregnant women with mild depression in Iran that administered 1 g per day of an unspecified n-3 fatty acid supplement or placebo for eight weeks reported that both the n-3-treated group and the placebo group experienced decreased depressive symptoms at follow-

up, but the n-3-treated group had a significantly greater improvement (SMD 0.69; CI 0.24, 1.14) (Kaviani et al., 2014).

Four studies described having conducted a subgroup analysis to assess whether baseline depression severity affected outcomes (Peet and Horrobin, 2002; Freeman, Davis, et al., 2008; Jazayeri et al., 2008; Gharekhani et al., 2014). A study that randomized 70 adults with MDD on maintenance pharmacotherapy to one of three doses of EPA or placebo for 12 weeks reported no effect of baseline scores on HAMD or MADRS outcomes but did not show data (Peet and Horrobin, 2002). A study that compared the effect of eight weeks of EPA with that of fluoxetine or fluoxetine plus EPA conducted an analysis of covariance that showed that the effect on HAMD scores at eight weeks was significantly affected by baseline HAMD scores (Jazayeri et al., 2008). A study that randomized 54 patients with end-stage renal disease to a low dose of EPA and DHA or placebo for 16 weeks reported no apparent effect of baseline depression (as measured by BDI) on response to n-3 fatty acid treatment, based on regression analysis (Gharekhani et al., 2014). Finally, a study that randomized peripartum women with MDD to eight weeks of EPA plus DHA or placebo reported that in their multivariate analysis, the number of previous medication trials but not baseline EPDS and HAMD scores predicted response to n-3 fatty acid treatment (Freeman, Davis, et al., 2008).

Comorbid Anxiety

The potential role of comorbid anxiety in the response to n-3 fatty acid treatment was assessed in two studies. A study that randomized 432 adults with MDD to 1.05 g EPA:0.15 g DHA or placebo daily for eight weeks reported no significant overall effect of n-3 fatty acid treatment (Lesperance et al., 2011). However, mixed-effect regression model analysis showed a significant interaction effect of comorbid anxiety disorders ($p=0.035$); participants with no comorbid anxiety disorder who received n-3 fatty acids showed significant improvement in symptoms (adjusted mean difference 1.93; CI 0.50, 3.36) on the MADRS.

A study that randomized 177 adults with MDD to 1 g DHA-enriched oil, EPA-enriched oil, or placebo daily for eight weeks reported no significant effects for EPA or DHA treatment overall (Mischoulon, Nierenberg, et al., 2014). Of the 177 participants, 45 had comorbid anxiety disorders; this subgroup had smaller improvements in depression scores than those without comorbid anxiety disorders with both EPA (SMD –0.43 and –0.21, respectively) and DHA (SMD –0.474 and 0.180, respectively).

Peripartum Versus Non-Peripartum Participants

Four studies, ranging in size from 26 to 80 women, assessed the effects of n-3 fatty acid supplementation compared with placebo on women diagnosed with MDD during pregnancy or the postpartum (peripartum) period (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008; Kaviani et al., 2014). Two of the four studies enrolled women with MDD onset during pregnancy or the postpartum period (Freeman, Davis, et al., 2008; Rees, Austin, and

Parker, 2008), and the other two enrolled women diagnosed only during pregnancy (Su et al., 2008; Kaviani et al., 2014). Two of the studies found a significantly greater response to n-3 fatty acids than to placebo (Su et al., 2008; Kaviani et al., 2014). The other two studies found no difference between n-3 fatty acid supplementation and placebo but found a trend toward improvement in both (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008). One of the two, a small Australian study, employed a high-dose supplement that comprised mostly DHA (Freeman, Davis, et al., 2008). The other study, larger and conducted in the United States, employed 2.7 g per day of a supplement that was approximately 60 percent EPA (Rees, Austin, and Parker, 2008).

Three of the trials administered some combination of DHA and EPA as fish oil (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008); the fourth study did not specify the type of n-3 fatty acid administered (Kaviani et al., 2014). Daily doses ranged from 1 g (Kaviani et al., 2014) to 6 g (Rees, Austin, and Parker, 2008). Study durations were six (Rees, Austin, and Parker, 2008; Kaviani et al., 2014) or eight weeks (Freeman, Davis, et al., 2008; Su et al., 2008). None of the four trials allowed patients any adjunctive or maintenance pharmacotherapy therapy, although one trial provided psychotherapy for both the intervention and placebo group (Freeman, Davis, et al., 2008).

Outcome measures for three of the studies included the EPDS (Freeman, Davis, et al., 2008; Rees, Austin, and Parker, 2008; Su et al., 2008). The fourth trial administered only the BDI (Kaviani et al., 2014).

A pooled analysis of the four studies showed no significant effect of n-3 fatty acids compared with placebo (SMD 0.47; CI −0.44, 1.34; I^2 69%).

A sensitivity analysis restricted to non-peripartum adults only also showed a statistically significant difference compared with placebo (SMD 0.62; CI 0.11, 1.12; I^2 81%), moderately favoring n-3 fatty acid treatment, but substantial heterogeneity remained.

Omega-3 Fatty Acid Supplementation of Adults with MDD and Comorbidities

The efficacy of n-3 fatty acids in individuals with MDD and comorbidities was assessed in four studies. One study enrolled patients with Parkinson's disease (da Silva et al., 2008), one enrolled patients with diabetes (Type 1 or 2) (Bot et al., 2010), and two enrolled patients with end-stage renal disease who were on maintenance dialysis (Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014). A pilot study of 29 patients with Parkinson's disease (58 percent female), half of whom were given fish oil for 12 weeks, found a significant decrease in MADRS scores but not in BDI scores among the group that received fish oil compared with the placebo group (da Silva et al., 2008). A small study in the Netherlands randomized 25 patients with diabetes to receive either 3-ethyl-EPA or placebo; no difference was seen between groups in depression scores after 12 weeks (Bot et al., 2010). Finally, two studies randomized end-stage renal disease patients to receive 1.8 g EPA/DHA daily for 16 weeks; BDI scores at the end of 16

weeks were significantly lower in the groups that received n-3 fatty acids compared with the placebo groups (Gharekhani et al., 2014; Dashti-Khavidaki et al., 2014).

Meta-Regressions by Type of MDD

A meta-regression that compared the outcomes for the three studies in participants with mild or mild-to-moderate depression with those for the other studies found no difference between them (p=0.79). Meta-regressions for other patient characteristics did also not suggest systematic differences between studies for peripartum participants (p=0.86), medical comorbidities (p=0.365), or comorbid anxiety disorders (p=0.241).

KQ 1d: What Is the Safety (e.g., Adverse Effects, Drug-Nutrient Interactions) of n-3 Use in Individuals with MDD Compared with Standard Antidepressant Therapy or Placebo?

Of the 24 studies we identified, 21 reported adverse events by intervention group. All but two were placebo-controlled trials; the remaining studies were head-to-head trials (one comparing EPA with DHA and one comparing EPA with antidepressant). None of the studies reported serious adverse events. The adverse events reported in the placebo-controlled trials fell into 15 of the 26 Common Terminology Criteria for Adverse Events categories. The risk for adverse events in the intervention group exceeded that in the placebo group in only one category, gastrointestinal (GI) disorders (for overall comparisons with placebo: OR 2.58; CI 1.73, 3.91; for comparisons of studies of EPA only plus EPA:DHA>1 versus placebo: OR 4.71; CI 2.44, 9.72). This category includes burping, belching, nausea, reflux, mild vomiting, gastritis, and diarrhea. The ORs for adverse event categories reported in two or more studies are shown in Table 4.1. They include eight studies that reported no difference in adverse events in the psychiatric disorder category, and seven studies that reported no difference in adverse events in the neurological disorder category.

The study that compared adverse events between EPA-treated and antidepressant-treated participants found a higher number of GI and psychiatric events in the antidepressant group than in the EPA group (Jazayeri et al., 2008).

The adverse events were also assessed in the trials that compared EPA alone and EPA:DHA>1 with placebo. Adverse events in the EPA+EPA:DHA>1 group did not significantly exceed those in the placebo group for any category of adverse events.

The one head-to-head trial that reported adverse events reported events in six categories. In no category did the risk for adverse events in one treatment group exceed that in the other group (Mischoulon, Best-Popescu, et al., 2008).

KQ 1e: How Does the Efficacy of n-3 Fatty Acids Compare with That of Standard Antidepressant Therapy?

Of the studies that met inclusion criteria, only one study was designed to comparatively assess the efficacy of n-3 monotherapy and standard antidepressants (Jazayeri et al., 2008). Fourteen studies allowed or required maintenance antidepressants or were not designed to compare n-3 fatty acid monotherapy with antidepressant monotherapy. The remaining studies proscribed the use of maintenance antidepressants.

The 2008 study by Jazayeri and colleagues reported that eight weeks' treatment with EPA alone and fluoxetine alone was similar in decreasing depressive symptoms, while the best results were found for the combination of EPA and fluoxetine. Clinical effectiveness (response rate 50 percent or higher) was 50 percent in the fluoxetine arm and 56 percent in the EPA arm (OR 1.29; CI 0.32, 5.17).

Chapter Four: Discussion and Conclusions

In this chapter, we first summarize the findings in response to each of the key questions, along with the quality of the evidence (see Table 4.1). We briefly discuss the findings in the context of prior systematic review findings. We then describe the limitations of the body of literature and provide suggestions for further research based on those limitations.

Summary of Findings

KQ 1: What Are the Efficacy and Safety of n-3 Supplements for Depressive Symptoms and Quality of Life in Adults with MDD Compared with Placebo or Active Comparator?

We identified 24 studies that met the inclusion criteria and assessed the efficacy of n-3 fatty acids for MDD, of which 20 were placebo comparisons (SMD 0.42; CI 0.11, 0.73; I^2 77%), indicating a small but significant effect of n-3 fatty acid treatment on depressive symptoms compared with placebo. Publication bias was likely, and trim-and-fill analyses did not find a statistically significant effect. Benefits were primarily based on monotherapy studies, but systematic comparisons with patients already receiving standard antidepressant treatments have not been conducted. Study quality was mixed. The quality of evidence for this conclusion is low because of publication bias and lack of consistency.

Thirteen studies assessed the effects of n-3 fatty acids on clinical response, identifying a significant positive response for n-3 fatty acids (OR 2.09; CI 1.25, 3.49; I^2 38%). Evidence for publication bias was strong. The quality of evidence for this conclusion is moderate because of publication bias.

Six studies assessed effects of n-3 fatty acids on remission; the number of participants who achieved remission was small, and n-3 fatty acids had a non-significant effect (OR 2.19; CI 0.74, 6.51; I^2 52%). The quality of evidence for a conclusion of no statistically significant effect of n-3 fatty acids on remission is low because of heterogeneity and publication bias.

Two studies assessed effects of n-3 fatty acids on quality of life, using the SF-36. Both studies reported positive effects of n-3 fatty acids on mental functioning, but effects on physical function were inconsistent. The quality of evidence regarding efficacy of n-3 fatty acids for quality of life is very low.

KQ 1a: Are n-3 Fatty Acids More Effective as Monotherapy Than as an Adjunctive Therapy?

Only one small, poor quality study was designed to test n-3 fatty acids as monotherapy against n-3 fatty acids systematically given as adjunctive therapy to antidepressants. The study showed a significantly greater efficacy for adjunctive therapy compared with n-3 fatty acids or antidepressants alone for depression scale scores, but the study was poor quality.

Benefits of n-3 fatty acids were seen in monotherapy studies comparing n-3 fatty acids with placebo, while in studies in which both treatment arms received antidepressants, n-3 fatty acid effects were not statistically significant. A meta-regression was suggestive of a systematic difference but was not statistically significant.

The quality of evidence is very low based on the identification of only one, very poor quality study that directly addressed the review question.

KQ 1b: Does Efficacy Differ Depending on the Type—EPA, DHA, or ALA—and Amount of n-3 Fatty Acid Used?

Two good quality RCTs compared EPA and DHA head to head. One showed slightly higher efficacy for EPA than DHA for depression scale scores and a non-significant effect on percentage of treatment responders, whereas the other showed no difference in either outcome. The quality of evidence for superiority of one n-3 fatty acid over the other based on direct comparisons is very low.

A meta-regression showed a significant difference in efficacy between the studies of EPA or a higher EPA:DHA ratio and the studies of DHA or a higher DHA:EPA ratio.

Fifteen RCTs of mixed quality comparing EPA alone or EPA:DHA of 1 or higher showed a significant increase in efficacy compared with placebo (SMD 0.62; CI 0.25, 0.98; I^2 77%); heterogeneity was present and analyses suggested publication bias. The quality of evidence for the effect estimate is low based on heterogeneity and publication bias. Nine studies assessed the effects of EPA alone or EPA:DHA>1 on clinical response, identifying a significant positive response for EPA (OR 2.09; CI 1.09, 4.88; I^2 51%). Evidence for publication bias was strong. The quality of evidence for this conclusion is low because of publication bias and heterogeneity.

Six RCTs of mixed quality comparing DHA alone or DHA:EPA>1 showed no significant increase in efficacy compared with placebo based on depression scores (SMD –0.0.06; CI –0.61, 0.49; I^2 68%). Studies were heterogeneous. There was no evidence of publication bias in this subgroup (Egger test p=0.790, Begg test p=0.817). The quality of evidence for this finding is moderate.

One study each compared high- to low-dose EPA (fair quality) and high- to low-dose DHA (good quality), both favoring the lowest dose. The quality of evidence for these findings is low.

KQ 1c: Does the Efficacy of n-3 Fatty Acids Differ Depending on the Type of MDD (i.e., Mild, Moderate, Severe, Recurrent, Postpartum)?

The majority of studies did not specify depression severity or use samples with mixed depression severity. Of those that specified the severity, one study assessed the effects of n-3 fatty acids in participants with mild depression, and two studies assessed the effects of n-3 fatty acids in participants with "mild-to-moderate" depression. No study explicitly assessed the effects of n-3 fatty acids on participants with moderate and severe depression. Four studies assessed effects in peripartum depression and four in samples with various medical comorbidities.

Meta-regression for participant characteristics indicated no systematic effect of depression type, but the evidence base is insufficient to determine whether the efficacy of n-3 fatty acids differs depending on the type of MDD.

KQ 1d: What Is the Safety (e.g., Adverse Effects, Drug-Nutrient Interactions) of n-3 Use in Individuals with MDD Compared with Standard Antidepressant Therapy or Placebo?

Of 24 studies that met inclusion criteria, 21 reported adverse event assessment: 19 placebo-controlled trials and two head-to-head trials. No studies reported serious adverse events. Only one category of adverse events, GI events, was significantly increased in n-3-treated participants compared with placebo-treated groups (OR 2.58; CI 1.73, 3.91). The quality of evidence for this finding is moderate. No differences were seen in any other category of adverse events.

KQ 1e: How Does the Efficacy of n-3 Fatty Acids Compare with That of Standard Antidepressant Therapy?

Only one very small and poor quality study compared the efficacy of n-3 fatty acids with that of antidepressants head to head. The study reported no statistically significant differences in results between the n-3 fatty acids and antidepressant groups. The quality of evidence for this finding is very low.

Table 4.1. Summary of Findings and Quality of Evidence

Outcome	Study Design (number of RCTs and participants)[a]	Findings (direction and magnitude of effect)	Study Limitations (study quality; risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of Evidence for Outcome
KQ 1: Comparison: n-3 fatty acid versus placebo							
Depression scale score	20 RCTs, N=1,603	SMD 0.42 (CI 0.11, 0.73), favors n-3 FA	7 good, 6 fair, 7 poor quality; publication bias*	Heterogeneity*	Direct	Precise	Low
Depression, proportion of treatment responders	13 RCTs, N=765	OR 2.09 (CI 1.25, 3.49), favors n-3 FA	5 good, 6 fair, 2 poor quality; publication bias*	Consistent	Direct	Precise	Moderate
Depression remission	6 RCTs, N=503	OR 2.19 (CI 0.74, 6.51), n.s.	4 good, 2 fair quality; publication bias*	Heterogeneity*	Direct	Precise	Low
Quality of life – mental	2 RCTs, n=86	SMD –1.11 (CI −1.83, −0.39), favors n-3 FA SMD –0.68 (CI −1.27, −0.08), favors n-3 FA	1 poor, 1 good quality*	Consistent	Direct	Imprecise*	Very Low
Quality of life – physical	2 RCTs, n=86	SMD –0.63 (CI −1.32, 0.06), n.s. SMD –0.8 (CI −1.4, −0.2), favors n-3 FA	1 poor, 1 good quality*	Inconsistent*	Direct	Imprecise*	Very low
KQ 1a: Comparison: n-3 fatty acid as monotherapy versus as adjunctive therapy to standard treatment							
Depression scale score	1 RCT head-to-head, n=48	Significant difference favors adjunctive therapy (p=0.005)	Poor quality*	No replication**	Direct	NR	Very low
Depression, proportion of treatment responders	1 RCT head-to-head, n=48	OR 0.29 (CI 0.06, 1.47), favors adjunctive therapy over EPA alone	Poor quality*	No replication**	Direct	Precise	Very low
KQ 1a: Comparison: Monotherapy versus adjunctive n-3 fatty acid therapy, indirect							
Depression scale score	20 RCTs, N=1,603	Meta-regression comparing monotherapy and adjunctive therapy studies did not suggest systematic differences (p=0.090)	Mixed quality*	Treatment effect only statistically significant in monotherapy studies*	Indirect**	NR	Very low

Outcome	Study Design (number of RCTs and participants)[a]	Findings (direction and magnitude of effect)	Study Limitations (study quality; risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of Evidence for Outcome
KQ 1b: Comparison: EPA versus DHA head to head							
Depression scale score	2 RCTs, n=258	SMD 0.23 (CI −0.14, 0.59), n.s. SMD 1.24 (CI 0.57, 1.91), n.s.	Good quality	Inconsistent**	Direct	Imprecise	Very Low
Depression, proportion of treatment responders	2 RCTs, n=258	OR 0.94 (CI 0.46, 1.95), n.s. OR 17.19 (CI 0.90, 328.87), n.s.	Good quality	Inconsistent**	Direct	Imprecise	Very Low
Depression remission	2 RCTs, n=258	OR 1.31 (CI 0.62, 2.88), n.s. OR 13.67 (CI 0.70, 2.65.52), n.s.	Good quality	Inconsistent**	Direct	Imprecise	Very Low
KQ 1b: Comparison: EPA versus DHA, indirect							
Depression scale score	20 RCTs, N=1,603	Meta-regression suggested a systematic difference between EPA and DHA study effects (p=0.008)	7 good, 6 fair, 7 poor quality	NR	Indirect**	NR	Low
KQ 1b: Comparison: EPA and a high EPA:DHA ratio versus placebo							
Depression scale score	15 RCTs, N=1,378	SMD 0.62 (CI 0.25, 0.98), favors EPA	3 good, 5 fair, 7 poor quality (effect still significant but lower estimate using trim-and-fill)*	Heterogeneity*	Direct	Precise	Low
Depression, proportion of treatment responders	9 RCTs, N=560	OR 2.31 (CI 1.09, 4.88), favors EPA	4 good, 3 fair, 2 poor quality; publication bias*	Heterogeneity*	Direct	Imprecision	Low
Depression remission	6 RCTs, N=433	OR 2.19 (CI 0.79, 6.51), n.s.	4 good, 2 fair quality; publication bias*	Heterogeneity*	Direct	Imprecision	Low
KQ 1b: Comparison: DHA and a high DHA:EPA ratio versus placebo							
Depression scale score	6 RCTs, N=393	SMD –0.06 (CI –0.61, 0.49), n.s.	4 good, 1 fair, 1 poor quality	Heterogeneity*	Direct	Precise	Moderate
Depression, proportion of treatment responders	3 RCTs, N=207	OR 0.97 (CI 0.61, 1.56), n.s.	2 good, 1 fair quality	Consistent	Direct	Precise	High
Depression remission	2 RCTs, N=172	OR 0.81 (CI 0.42, 1.56), n.s.	Good quality	Consistent	Direct	NR**	Low
KQ 1b: Comparison: High- versus low-dose EPA							
Depression scale score	1 RCT, n=70	P=0.02 in favor of lowest dose (1 g/d)	Fair quality*	No replication**	Direct	NR	Very low

Outcome	Study Design (number of RCTs and participants)[a]	Findings (direction and magnitude of effect)	Study Limitations (study quality; risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of Evidence for Outcome
KQ 1b: Comparison: High- versus low-dose DHA							
Depression scale score	1 RCT, n=35	P=0.04 in favor of lowest dose (1 g/d)	Good quality	No replication**	Direct	NR	Very Low
KQ 1c: Effect of depression severity							
Depression scale score	20 RCTs, N=1,603	Meta-regression did not suggest differences between patient subgroups (p=0.79)	Mixed quality*	Most studies did not specify severity*	Indirect*	NR	Very Low
KQ 1c: Effect of depression type (peripartum)							
Depression scale score	20 RCTs, N=1,603	Meta-regression did not suggest differences between patient subgroups (p=0.86)	Mixed quality*	NR	Indirect*	NR	Very Low
KQ 1d: Safety comparison: n-3 fatty acid versus placebo							
Cardiac disorders	2 RCTs, N=188	OR 0.80 (CI 0.18, 3.29), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Eye disorders	2 RCTs, N=136	OR 0.00 (CI 0.00, 13.50), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Imprecise*	Very Low
Gastrointestinal disorders	17 RCTs, N=1,318	OR 2.58 (CI 1.73, 3.91), n-3 FA>placebo	Reporting quality varies*	Consistency somewhat unclear but assessed in most studies	Direct	Precise	Moderate
General disorders/ administration site conditions	6 RCTs, N=786	OR 1.45 (CI 0.87, 2.46), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Infectious conditions and infestations	2 RCTs, N=147	OR 0.61 (CI 0.15, 2.67), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Metabolism and nutrition disorders	2 RCTs, N=136	OR 0.33 (CI 0.02, 4.84), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Musculoskeletal and connective tissue disorders	4 RCTs, N=629	OR 0.85 (CI 0.47, 1.54), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Nervous system disorders	8 RCTs, N=962	OR 1.07 (CI 0.72, 1.58), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Psychiatric disorders	7 RCTs, N=353	OR 1.03 (CI 0.38, 2.90), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low
Respiratory, thoracic, and mediastinal disorders	2 RCTs, N=136	OR 1.03 (CI 0.15, 11.83), n.s.	Reporting quality varies*	Consistency unclear*	Direct	Imprecise	Low
Skin and subcutaneous tissue disorders	3 RCTs, N=559	OR 1.17 (CI 0.56, 2.51)	Reporting quality varies*	Consistency unclear*	Direct	Precise	Low

Outcome	Study Design (number of RCTs and participants)[a]	Findings (direction and magnitude of effect)	Study Limitations (study quality; risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of Evidence for Outcome
KQ 1e: Comparison: n-3 fatty acid versus antidepressants							
Depression scale score	1 RCT, n=48	p=0.426, n.s.	Poor quality*	No replication*	Direct	Imprecise*	Very low
Depression, proportion of treatment responders	1 RCT, n=48	OR 1.29 (CI 0.32, 5.17), n.s.	Poor quality*	No replication*	Direct	Imprecise*	Very low

NOTES: n-3 FA = omega-3 fatty acid; n.s. = no significant difference; NR = not relevant.
[a] N = number in pooled analysis; n = number in single study or two non-pooled studies.
* Quality of evidence downgraded by one.
** Quality of evidence downgraded by two.

Discussion of the Findings in the Context of What Was Known

Numerous systematic reviews have attempted to synthesize the data on the efficacy of n-3 fatty acids for treating depression, with varying results. The most recent example involves the 2012 systematic review and meta-analysis by Bloch and Hannestad (2012), which reported no significant benefit of n-3 fatty acids for treating depressive symptoms; this was followed by a critique and re-assessment of the same studies by Martins, Bentsen, and Puri (2012), who reported a positive effect. Martins, Bentsen, and Puri, among others, have posited a number of reasons for these discrepancies. Differing inclusion and exclusion criteria (e.g., including or excluding individuals with comorbid psychiatric disorders) and use of different outcome measures are among the most prominent.

The current report finds a small but significant benefit for supplementation with n-3 fatty acid preparations of pure EPA or ratios of EPA to DHA greater than 1. We estimate that this improvement represents a decrease of approximately 1.8 points on the HAMD-17 scale. However, the estimate is based on only four studies, as most studies used different versions of the HAMD or different depression scales. In addition, studies were highly heterogeneous in other respects, findings were inconsistent, more than one-third of studies were of poor quality, and evidence suggested probable publication bias. The limitations of the literature are discussed in detail below.

Limitations of the Literature

The duration of most studies we identified was relatively short: The longest intervention was 26 weeks, and most were eight or 12 weeks. Patients who are prescribed antidepressants and who experience benefit are generally advised to continue to take them for at least a year. Thus, even if EPA shows promise for treating depression under study conditions, it is unclear whether it would continue to work for the period of time needed in the community health care setting.

Most studies that examined combinations of EPA and DHA used different ratios of EPA to DHA, making it difficult to pool studies with confidence or to try to assess whether the two n-3 fatty acids may be working in concert, opposing each other, or not interacting at all. Similarly, sources of n-3 fatty acids were not always identified (e.g., tuna oil, menhaden oil), most studies seemed to use different sources, manufacturers were rarely named, and contents were never verified. Some studies assessed biomarkers of n-3 fatty acid status or dietary intake, but few studies were powered to assess whether baseline status or dietary intake was associated with baseline depression scores or response to treatment. Baseline status and/or dietary intake may in fact determine responsivity to supplementation.

A major reason for the lack of apparent effect of n-3 fatty acids may be the significant placebo effect observed in most studies. Su and colleagues (Su et al., 2003; Su et al., 2008) employed a one-week placebo run-in to exclude potential participants who responded positively

to placebo. The response to placebo among those who remained in the studies appears to be less than that of placebo groups in other studies. A substantial proportion of studies that reported conducting ITT analysis did not include all enrolled participants in the analysis. Many included only participants who were seen for at least one follow-up visit; several studies reported this method as a modified ITT analysis. Because studies tended to be small, even small absolute numbers of dropouts would affect outcomes (and dropouts would be more likely to be non-responsive to the treatment or to be experiencing adverse effects than retained participants). We did not attempt to conduct an analysis that included only true ITT studies.

We identified no studies that enrolled participants with comorbid posttraumatic stress disorder, a group that would be disproportionately seen and treated in military treatment facilities and the U.S. Department of Veterans Affairs health care system. Only two studies we identified assessed the effect of n-3 fatty acids in participants with both MDD and an anxiety disorder. We identified few studies of individuals with comorbid medical conditions, the elderly, and pregnant/postpartum women. Studies in these and other populations that may not be able to take antidepressants are important because of the benefit of a treatment that does not have the potential to interact with other medications or have other contraindications.

Although studies of the efficacy of n-3 fatty acids for treatment of depressive symptoms consistently assess baseline depression scores and apply fairly consistent depression scale criteria to inclusion of patients in studies, few studies seem powered to assess the effect of baseline depression severity on response to treatment. Only a small number of studies attempted to assess efficacy in those taking antidepressants separately from those not taking antidepressants, and even fewer studies employed a block randomization design to truly compare the efficacy of monotherapy with n-3 fatty acids alone or antidepressants alone, adjunctive therapy, and placebo. Similarly, it might be difficult if not impossible to take into account the degree to which individual patients' symptoms were adequately responsive to their regimen of antidepressants (it might be argued that patients satisfied with their current antidepressant treatment might be less likely to enroll in a trial of a novel treatment). Likewise, patients willing to enroll in a trial that required discontinuation of (or not initiating) antidepressant treatment might be systematically different from patients enrolling in a study where continuation or initiation of an antidepressant is required.

Although most studies reported on adverse events, they seldom described rigorous or systematic efforts to assess them. In general, n-3 fatty acids have been relatively free of safety concerns at lower doses, but more research may be warranted on the safety of n-3 fatty acids among individuals with comorbid health conditions and on n-3 fatty acids' interaction with other medications, such as antihypertensives and anticoagulants.

Finally, nearly every pooled analysis showed evidence of probable publication bias. Applying the trim-and-fill method, the overall effect of all n-3 fatty acids compared with placebo on depression scale scores and the proportion of participants showing a clinical response no longer statistically significantly favor n-3 fatty acids. However, the comparison of EPA and

higher EPA:DHA ratios with placebo still favored EPA based on depression scale scores, but the estimated size of the treatment effect was considerably smaller. Hence, we cannot rule out the possibility that analyses that favored n-3 fatty acids (or EPA) for reducing symptoms of MDD are failing to reflect the true effect of n-3 fatty acids.

Limitations of the Current Review

The current review did not contact manufacturers or use other means to obtain unpublished studies of the use of n-3 fatty acids for treating MDD.

The review also did not assess the quality of adverse event reporting in individual studies using a quality assessment tool such as the McHarm scale, designed specifically for that purpose. Instead, we assessed the overall quality of evidence for the conclusion for each adverse event category for which events were reported in more than one study. This assessment was based on our assessment of whether authors used a pre-designed adverse event assessment form and asked participants about adverse events, whether they assessed and/or reported adverse events using a published classification system, and the precision of the pooled estimate.

We also did not abstract data on baseline n-3 biomarkers or dietary polyunsaturated fatty acid (PUFA) intakes in an attempt to assess relationships with outcomes—that is, the possible role of baseline status and response to supplementation (because few studies reported these data). We also did not summarize the findings of studies that conducted subgroup analyses to assess the possible association.

In addition, this review did not do sensitivity analysis to assess the effects of excluding individuals with high intakes of fish or use of high-dose supplements, because most studies did not report the data needed. It is possible that the effect of n-3 fatty acid supplementation is limited to individuals whose baseline biomarker status (or dietary intake) is low.

Suggestions for Future Research

Based on our assessment of the limitations of the existing literature and the relatively low risks involved, we believe two large trials are warranted. One trial should employ a 2x2 factorial design to assess the effects of mono- and adjunctive therapy in patients who have already responded to antidepressant therapy. A second trial should assess the effects of EPA monotherapy in individuals who may not be able to take antidepressants, including community-dwelling elderly, pregnant/postpartum women, and those with end-stage renal disease.

Furthermore, research on differential effects of n-3 fatty acids for individuals of different depression severity are needed, particularly their use in severe depression.

Assessment is also needed to identify those most likely to respond, presumably via a simple rapid biomarker test.

Appendix A: Search Strategy

PubMed

Time Period Covered:
1/1/2004–11/4/2014

Search Strategy:
"Fatty Acids, Omega-3"[Mesh] OR "Fatty Acids, Essential"[Mesh] OR "Fish Oils"[Mesh] OR "omega 3"[tiab] OR omega-3[tiab] OR omega3[tiab] OR polyunsaturated OR pufa OR dha OR epa[tiab] OR "long chain" OR long-chain OR longchain OR "long chain" OR Docosapentanoic OR docosapentaenoic OR docosahexanoic OR docosahexaenoic OR dpa OR eicosapent* OR icosapent* OR (fatty acid* AND essential) OR fish oil* OR linolenic OR alpha-linolenic OR "alpha linolenic" OR alphali OR linolenate OR cervonic OR timnodonic OR stearidonic OR ((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids)) OR ((menhaden[tiab] OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils)) OR walnut* OR butternut* OR soybean* OR "pumpkin seed" OR pumpkinseed* OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat" OR salmon[TIAB] OR mackerel OR herring[TIAB] OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR mediterranean diet* OR (fish AND (consum* OR intake OR diet OR dietary)) OR ((red blood cell* OR phospholipid OR plasma OR triacylglycerol OR cholesteryl OR ester[tiab] OR adipos* OR fatty acid* OR erythrocyte OR ghost OR platelet OR granulocyte OR neutrophil OR mononuclear OR LDL OR HDL) AND (EPA[tiab] OR SDA OR stearidonic OR omega*))
AND
"Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR depress*[tiab] OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*
AND
random* OR randomized controlled trial[mh] OR "Randomized Controlled Trials as Topic"[Mesh] OR randomized controlled trial[pt] or rct*

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PsycINFO

Time Period Covered:
1/1/2004–1/12/2015

Search Strategy:
[omega 3 OR omega-3 OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR "long chain" OR long-chain OR longchain

OR “long chain” OR fish oil* OR linolenic OR alpha-linolenic OR “alpha linolenic” OR alphalinolenic
OR
(fatty acid* AND essential) OR linolenate OR cervonic OR timnodonic OR stearidonic OR ((menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils))
OR
((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids)) OR walnut* OR butternut* OR soybean* OR “pumpkin seed” OR pumpkinseed* OR “cod liver oil” OR “codliver oil” OR “marine oil” OR “marine oils” OR “marine fat”
OR
salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR (fish AND (consum* OR intake OR diet OR dietary))
OR
mediterranean diet*]
AND
depression OR depressed OR Depressive OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*
AND
random* OR rct*

Number of Results: 88

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CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Time Period Covered:
1/1/2004–1/12/2015

Search Strategy:
[omega 3 OR omega-3 OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR “long chain” OR long-chain OR longchain OR “long chain” OR fish oil* OR linolenic OR alpha-linolenic OR “alpha linolenic” OR alphalinolenic
OR
(fatty acid* AND essential) OR linolenate OR cervonic OR timnodonic OR stearidonic OR ((menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils))
OR
((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids)) OR walnut* OR butternut* OR soybean* OR “pumpkin seed” OR pumpkinseed* OR “cod liver oil” OR “codliver oil” OR “marine oil” OR “marine oils” OR “marine fat”

OR
salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR (fish AND (consum* OR intake OR diet OR dietary))
OR
mediterranean diet*]
AND
depression OR depressed OR depressive OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*
AND
random* OR rct*

Number of Results: 76

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Embase

Time Period Covered:
1/1/2004–1/12/2015

Search Strategy:
[((‘omega’/exp OR omega) AND 3) OR ‘omega 3’/exp OR ‘omega 3’ OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR longchain OR ‘long chain’ OR ((‘fish’/exp OR fish) AND oil*) OR linolenic OR ‘alpha linolenic’ OR alphalinolenic
OR
fatty AND acid* AND essential
OR
‘linolenate’/exp OR linolenate OR cervonic OR timnodonic OR stearidonic
OR
menhaden OR ‘flaxseed’/exp OR flaxseed OR ((‘flax’/exp OR flax) AND (‘seed’/exp OR seed)) OR ‘linseed’/exp OR linseed OR ((‘rape’/exp OR rape) AND (‘seed’/exp OR seed)) OR ‘rapeseed’/exp OR rapeseed OR ‘canola’/exp OR canola OR soy OR ‘soybean’/exp OR soybean OR ‘walnut’/exp OR walnut OR ((‘mustard’/exp OR mustard) AND (‘seed’/exp OR seed)) OR ((‘perilla’/exp OR perilla OR shiso) AND (‘oil’/exp OR oil OR ‘oils’/exp OR oils))
OR
((n AND 3) OR n3 OR ‘n 3’) AND (‘oil’/exp OR oil OR ‘oils’/exp OR oils)) OR pufa OR ((fatty AND (‘acid’/exp OR acid)) OR ((fatty AND (‘acids’/exp OR acids))
OR
‘salmon’/exp OR salmon OR mackerel OR ‘herring’/exp OR herring OR ‘tuna’/exp OR tuna OR ‘halibut’/exp OR halibut OR ‘seaweed’/exp OR seaweed OR anchov* OR sardine* OR ropufa OR ‘maxepa’/exp OR maxepa OR ‘omacor’/exp OR omacor OR ‘efamed’/exp OR efamed OR resq OR epagis OR almarin OR coromega OR ‘lovaza’/exp OR lovaza OR ‘vascepa’/exp OR vascepa OR ‘icosapent ethyl’/exp OR ‘icosapent ethyl’
OR

butternut* OR ‘pumpkin seed’ OR pumpkinseed* OR ‘cod liver oil’/exp OR ‘cod liver oil’ OR ‘codliver oil’/exp OR ‘codliver oil’ OR ‘marine oil’ OR ‘marine oils’ OR ‘marine fat’
OR
(‘fish’/exp OR fish) AND (consum* OR intake OR ‘diet’/exp OR diet OR dietary)
OR
mediterranean AND diet*]
AND
‘depression’/exp OR depression OR depressive OR depressed OR unipolar OR ‘mood’/exp OR (mood AND disorder*) OR ((‘mood’/exp OR mood) AND disturbance*) OR (affective AND disorder*)
AND
random* OR rct*
AND
[humans]/lim

Number of Results: 85

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AMED (Allied and Complementary Medicine Database)

Time Period Covered:
1/1/2004–1/13/2015

Search Strategy:
[ab(omega 3 OR omega-3 OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR “long chain” OR long-chain OR longchain OR “long chain” OR fish oil* OR linolenic OR alpha-linolenic OR “alpha linolenic” OR alphalinolenic) OR ti(omega 3 OR omega-3 OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR “long chain” OR long-chain OR longchain OR “long chain” OR fish oil* OR linolenic OR alpha-linolenic OR “alpha linolenic” OR alphalinolenic) OR su(omega 3 OR omega-3 OR omega3 OR docosapent* OR docosahex* OR eicosapent* OR icosapent* OR polyunsaturated OR pufa OR dha OR “long chain” OR long-chain OR longchain OR “long chain” OR fish oil* OR linolenic OR alpha-linolenic OR “alpha linolenic” OR alphalinolenic)
OR
ab(fatty acid* AND essential) OR ti(fatty acid* AND essential) OR su(fatty acid* AND essential)
OR
ab(linolenate OR cervonic OR timnodonic OR stearidonic) OR ti(linolenate OR cervonic OR timnodonic OR stearidonic) OR su(linolenate OR cervonic OR timnodonic OR stearidonic)
OR
ab((menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils)) OR ti((menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils))

OR su((menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso) and (oil OR oils))
OR
ab((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids)) OR ti((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids)) OR su((n 3 OR n3 OR n-3) AND (oil OR oils OR pufa OR fatty acid OR fatty acids))
OR
ab(walnut* OR butternut* OR soybean* OR "pumpkin seed" OR pumpkinseed* OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat") OR ti(walnut* OR butternut* OR soybean* OR "pumpkin seed" OR pumpkinseed* OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat") OR su(walnut* OR butternut* OR soybean* OR "pumpkin seed" OR pumpkinseed* OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat")
OR
ab(salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl) OR ti(salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl) OR su(salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl)
OR
ab(fish AND (consum* OR intake OR diet OR dietary)) OR ti(fish AND (consum* OR intake OR diet OR dietary)) OR su(fish AND (consum* OR intake OR diet OR dietary))
OR
ab(Mediterranean AND diet*) OR ti(Mediterranean AND diet*) OR su(Mediterranean AND diet*)]
AND
ab(depression OR depressed OR depressive OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*) OR ti(depression OR depressed OR depressive OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*) OR su(depression OR depressed OR depressive OR unipolar OR mood disorder* OR mood disturbance* OR affective disorder*)

Number of Results: 23

Appendix B: Evidence Table of Included Studies

Study Details	Participants	Intervention	Outcomes/Results
Bot et al., 2010 Country: Netherlands Study Design: RCT Purpose: "Randomized controlled trial to test the efficacy of n-3 ethyl-eicosapentaenoic acid (E-EPA) as adjuvant to antidepressant medication in the treatment of depression in adults with diabetes mellitus" Quality Rating: Poor	Number of Participants: 12 Diagnosis: MDD-DSM, Other diagnosis, MDD using the Composite International Diagnostic Interview Comorbidities: Diabetes mellitus Age (Years): E-EPA: 53.1 (SD 13.8); Placebo: 55.0 (SD 8.6) Gender (% Male): E-EPA: 38%, Placebo: 58% Inclusion Criteria: "aged 18–75 years, diagnosed with diabetes (type 1 or type 2), and currently being on antidepressant medication for at least two months. Furthermore, participants had to meet the criteria for current Major Depressive Disorder (MDD), determined with the Composite International Diagnostic Interview . . . . Diabetes was verified with the medical status when the patient attended the [medical center]. For those who were not patients of the [medical center], persons who used insulin or oral hypoglycemic agents were regarded as diabetes patients." Exclusion Criteria: "serious co-morbid disease, using fish oil supplementation, consuming more than three servings of fish per week, alcohol or drug abuse, suicidal ideation, and/or allergy to fish, fish products, or rapeseed oil."	Extract: E-EPA Dosage: E-EPA: 1 g daily for 12 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: The primary outcome was severity of depressive symptoms, assessed by the MADRS Power calculation: Yes	Depression Measures: • MADRS, SMD –0.27 (CI −1.07, 0.54)

Study Details	Participants	Intervention	Outcomes/Results
Carney et al., 2009 Country: United States Study Design: RCT Purpose: "To determine whether omega-3 improves the response to sertraline in patients with major depression and coronary heart disease (CHD)" Quality Rating: Fair, blinding methods not described, used ITT sample	Number of Participants: 59 Diagnosis: MDD-DSM, Rating scale Comorbidities: Coronary heart disease Age (Years): Placebo: 58.6 (SD 8.5); Omega-3: 58.1 (SD 9.4) Gender (% Male): Placebo: 68.3%; Omega-3: 64.5% Inclusion Criteria: "patients who provided written informed consent and who had CHD as documented by at least 50% stenosis in at least 1 major coronary artery, a history of revascularization, or hospitalization for an acute coronary syndrome completed the Patient Health Questionnaire 9 for depression." Exclusion Criteria: (1) cognitive impairment, comorbid psychiatric disorders, psychosis, high risk of suicide, or current substance abuse; (2) an acute coronary syndrome within the previous 2 months, a left ventricular ejection fraction of less than 30%, advanced malignancy, or physical inability to participate; (3) use of antidepressants, anticonvulsants, lithium, or omega-3 supplements; (4) sensitivity to sertraline or omega-3; and (5) physician or patient refusal.	Extract: Omega-3 acid ethyl esters (930 mg of EPA and 750 mg of DHA) Dosage: 2 g daily for 10 weeks Co-interventions: sertraline 50 mg Comparator: Placebo Primary Endpoint: Scores on the BDI-II and the HAMD. Power calculation: Yes	Depression Measures: • HAMD, SMD 0.21 (CI −0.16, 0.58) • HAMD Responder, OR 0.96 (CI 0.46, 2) Adverse Events: • Omega-3: Prolonged bleeding 0 out of 62; Non-cardiac hospitalizations 3 out of 62; Cardiac hospitalizations 4 out of 62 • Placebo: Prolonged bleeding 1 out of 60; Non-cardiac hospitalizations 3 out of 60; Cardiac hospitalizations 4 out of 60

Study Details	Participants	Intervention	Outcomes/Results
Dashti-Khavidaki et al., 2014 Country: Iran Study Design: Multisite RCT, 2 sites Purpose: "This study examined effects of omega-3 fatty acids on depression and [health-related quality of life] in chronic [hemodialysis] patients." Quality Rating: Poor, no ITT analysis	Number of Participants: 16 Diagnosis: Rating scale Comorbidities: All undergoing hemodialysis (end-stage renal disease) Age (Years): Placebo: 56.5 (SD 14.5); Omega-3: 56.1 (SD 13.9) Gender (% Male): Placebo: 50%; Omega-3: 50% Inclusion Criteria: Adults, receiving regular hemodialysis treatment (4-hour, twice weekly treatment). Exclusion Criteria: BDI <16, inability to fill in questionnaires, unwillingness to participate, malignancy, pregnancy, the presence of other psychiatric disorders, hypothyroidism, concurrent participation in other trials, a history of surgical or medical illness in recent 3 months, poor adherence to medication or hemodialysis treatment, malabsorption syndrome, coagulopathies, increased risk of bleeding, chronic anticoagulation therapy, consumption of fish oil or supplements containing omega-3 fatty acids in recent 3 months, hypersensitivity to fish or fish-derived products, concurrent use of antipsychotic or antidepressant.	Extract: Omega-3 (180 mg EPA and 120 mg DHA) Dosage: 2 capsules (180 mg EPA and 120 mg DHA) three times daily for 16 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: Depression (BDI) and health-related quality of life Power calculation: No	Depression Measures: • BDI, SMD 1.34 (CI 0.6, 2.09) Quality of Life measure: • SF-36 • Physical function: SMD −0.63 (CI −1.32, 0.06) • Mental function: SMD –1.11 (CI −1.83, −0.39) Adverse Events: • Omega-3: Side effects causing patient withdrawal 0 out of 18; GI complaints 8 out of 18 • Placebo: Side effects causing patient withdrawal 0 out of 16; GI complaints 0 out of 16

Study Details	Participants	Intervention	Outcomes/Results
da Silva et al., 2008 Country: Brazil Study Design: RCT Purpose: To study the effect of alimentary supplementation with fish oil, rich in omega-3 PUFAs, over depression symptoms in parkinsonian patients with major depression Quality Rating: Poor, no ITT analysis, unclear methods	Number of Participants: 14 Diagnosis: MDD-DSM Comorbidities: Parkinson's disease Age (Years): 64.4 (range= 49–78 years) Gender (% Male): 42% Inclusion Criteria: Eligible patients met DSM-IV criteria for major depressive episode. In addition, patients had to have a score lower than 2.5 in the Hoehn and Yahr scale for Parkinson's disease and no signs of dementia, evaluated by Mini-Mental State Examination. They were also evaluated on motor, mental, and emotional state through the Unified Parkinson's Disease Rating Scale. If the patient met DSM-IV criteria and was not taking antidepressant medication, he/she was referred to psychiatric counseling. Only patients who had already taken antidepressant for at least 1 year or those who refused to take the medication entered in the research. Exclusion Criteria: Patients who initiated the antidepressant use after depression diagnosis, patients with symptoms of cognitive and memory declines, and drug and alcohol dependent users. Moreover, the patients who had presented any alteration of Parkinson's disease in Hoehn and Yahr scale above 0.5 point after 3 months of supplementation had also been excluded from the research, so that the worsening of the illness would not interfere with the evaluation of the depressive state in this research.	Extract: Omega-3 capsules (180 mg EPA, 120 mg DHA and tocopherol) Dosage: 4 omega-3 capsules (180 mg EPA, 120 mg DHA and tocopherol) daily for 12 weeks Co-interventions: antidepressants, psychotherapy Comparator: Placebo Primary Endpoint: MADRS Power calculation: No	Depression Measures: • MADRS Responder, OR 10.5 (CI 1.07, 103.51)

Study Details	Participants	Intervention	Outcomes/Results
Freeman, Davis, et al., 2008 Country: United States Study Design: RCT Purpose: To investigate the feasibility, safety, and efficacy of omega-3 fatty acids for perinatal depression in addition to supportive psychotherapy Quality Rating: Poor, no ITT analysis, unclear methods	Number of Participants: 28 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 31.0 (SD 5.8) Omega-3, 29.7 (SD 6.2) placebo Gender (% Male): 0 Inclusion Criteria: Women 18–45 years of age who were either pregnant (12–32 weeks gestation) or postpartum (within six months of childbirth) and met criteria for MDD, verified with the Structured Clinical Interview for DSM Disorders (SCID)-IV (postpartum women must have experienced onset of MDD by 4 weeks postpartum); scored ≥9 on the EPDS, outpatient status; and could provide written informed consent. Exclusion Criteria: Previous intolerance to omega-3 fatty acids, current use of antidepressants or anticoagulants, psychosis, diagnosis of bipolar disorder, active substance abuse, or active suicidal ideation.	Extract: Omega-3 (EPA 1.1 g and DHA 0.8 g) Dosage: 1.9 g per day (divided into 4 capsules) for 8 weeks Co-interventions: Manualized supportive psychotherapy Comparator: Placebo Primary Endpoint: EPDS, HAMD Power calculation: No	Depression Measures: • HAMD, SMD –0.31 (CI −0.86, 0.25) Adverse Events: • Omega-3: Central nervous system (CNS) and peripheral nervous system (PNS) - Dizziness 0 out of 31; GI - Diarrhea 0 out of 31; GI - Nausea 1 out of 31; GI - Burping 2 out of 31; GI - Difficulty swallowing 0 out of 31; GI - Foul breath/bad taste 4 out of 31; Heartburn/reflux 3 out of 31; Other - tired 0 out of 31 • Placebo: CNS and PNS - Dizziness 1 out of 28; GI - Diarrhea 1 out of 28; GI - Nausea 0 out of 28; GI - Burping 1 out of 28; GI - Difficulty swallowing 1 out of 28; GI - Foul breath/bad taste 1 out of 28; Heartburn/reflux 2 out of 28; Other - tired 1 out of 28 • Postpartum: CNS and PNS - Dizziness 1 out of 36; GI - Diarrhea 1 out of 36; GI - Nausea 1 out of 36; GI - Burping 1 out of 36; GI - Difficulty swallowing 0 out of 36; GI - Foul breath/bad taste 3 out of 36; Heartburn/reflux 3 out of 36; Other - tired 1 out of 36 • Pregnant: CNS and PNS - Dizziness 0 out of 23; GI - Diarrhea 0 out of 23; GI - Nausea 0 out of 23; GI - Burping 2 out of 23; GI - Difficulty swallowing 1 out of 23; GI - Foul breath/bad taste 2 out of 23; Heartburn/reflux 2 out of 23; Other - tired 0 out of 23

Study Details	Participants	Intervention	Outcomes/Results
Gertsik et al., 2012 Country: United States Study Design: RCT Purpose: To explore the efficacy of combination therapy with citalopram plus omega-3 fatty acids versus citalopram plus placebo (olive oil) in the initial treatment of individuals with MDD Quality Rating: Fair, blinding, allocation concealment unclear	Number of Participants: 18 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 40.5 (SD 10.2) Gender (% Male): NR Inclusion Criteria: Subjects were between 18 to 65 years of age who met DSM-IV criteria for current major depression by SCID and had a 21-item HAMD score greater than 17. Women of childbearing potential were required to use effective contraception. Exclusion Criteria: (1) diagnosis of psychotic disorders, including psychotic depression and bipolar disorders; (2) current drug or alcohol abuse or dependence, or history of drug or alcohol abuse or dependence within the previous six months; (3) unstable medical or neurological conditions that were likely to interfere with the treatment of depression; (4) history of allergy to citalopram or omega-3 fatty acids, finfish, or shellfish; (5) history of failure of response to adequate trial of citalopram; (6) history of seizure disorder; (7) pregnancy; (8) need for concomitant therapy with psychotropic medications, including antidepressants other than citalopram or neuroleptics; (9) active suicidal ideation or other safety concerns; (10) exposure to treatment with fluoxetine or monoamine oxidase inhibitors in the previous two months; (11) being on anticoagulant therapy; and (12) a dietary intake greater than 3.0 g total omega-3 per day at baseline as assessed by a three-day food diary evaluated by a certified nutritionist.	Extract: EPA, DHA, and other omega-3 fatty acids Dosage: 2 capsules (each 450 mg EPA, 100 mg DHA, and 50 mg other omega-3 fatty acids) twice daily for 8 weeks Co-interventions: Citalopram Comparator: Placebo Primary Endpoint: HAMD Power calculation: Yes	Depression Measures: • HAMD Responder, OR 3.37 (CI 0.91, 12.42) Adverse Events: • Omega-3: Significant adverse events 0 out of 18 • Placebo: Significant adverse events 0 out of 22

Study Details	Participants	Intervention	Outcomes/Results
Gharekhani et al., 2014 Country: Iran Study Design: RCT Purpose: "To investigate the effects of omega-3 fatty acids on depression and chronic inflammation in hemodialysis patients" Quality Rating: Poor, no ITT analysis, but >80% follow-up	Number of Participants: 20 Diagnosis: Rating scale Comorbidities: End-stage renal disease and on maintenance hemodialysis Age (Years): Placebo: 57.2 (SD 15.9); Omega-3: 56.8 (SD 13.09) Gender (% Male): Placebo: 60%; Omega-3: 52% Inclusion Criteria: "Adult patients who were undergoing regular [hemodialysis] treatment for more than 3 months were recruited from the [hemodialysis] units of two teaching hospitals (Imam-Khomeini Hospital Complex and Sinai Hospital) affiliated with Tehran University of Medical Sciences, Iran." Exclusion Criteria: "Having BDI score of less than 16; pregnancy; current inflammatory or infectious diseases; malignancy; a life expectancy of less than 4 months (based on physician prognosis); asthma or chronic obstructive pulmonary disease; other known psychiatric disorders; hypothyroidism; hemoglobinopathies; concurrent involvement in other research studies; a history of medical or surgical illness in recent 3 months; previous medication or [hemodialysis] noncompliance; malabsorption syndrome; coagulopathies or increased risk of bleeding; need to take anticoagulant medications including warfarin; intake of omega-3 fatty acids supplement in recent 3 months; hypersensitivity to fish or fish-derived products; concurrent use of corticosteroid, immunosuppressive, immunomodulator, anti-depressant, anti-epileptic (except gabapentin), anti-psychotic, or nonsteroidal anti-inflammatory medications."	Extract: Oemga-3 (each capsule contains 180 mg EPA and 120 mg DHA) Dosage: 1,800 mg daily for 16 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: Depression (BDI) and indicators of chronic inflammation Power calculation: Insufficient power (posthoc analysis)	Depression Measures: • BDI, SMD 1.09 (CI 0.46, 1.72) Adverse Events: • Omega-3: Serious adverse event leading to patient withdrawal 0 out of 25; GI complaints 8 out of 25 • Placebo: Serious adverse event leading to patient withdrawal 0 out of 20; GI complaints 0 out of 20

Study Details	Participants	Intervention	Outcomes/Results
Jazayeri et al., 2008 Country: Iran Study Design: RCT Purpose: To compare therapeutic effects of EPA, fluoxetine, and a combination of them in major depression Quality Rating: Poor, no ITT analysis	Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 34.9 (SD 8.7) EPA, 35.1 (SD 9.4) fluoxetine, 34.5 (SD 11.3) fluoxetine + EPA Gender (% Male): 31% Inclusion Criteria: The patients were 20–59 years of age and met DSM-IV criteria for MDD without psychotic features based on the semistructured clinical interview. Their scores on the 17-item HAMD were ≥15 and they were free of medication for at least 6 weeks. Exclusion Criteria: Comorbid psychiatric diagnosis other than dysthymia and anxiety; significant medical illness established by medical history, physical examination, or laboratory tests; suicidal thoughts; substance abuse; history of hypomanic/manic/mixed episode; pregnancy and lactation; consumption of v-3 fatty acid supplements in the previous year; and dietary intake of more than one serving of fish per week.	Extract: E-EPA Dosage: 550 mg twice daily for 8 weeks Co-interventions: NA Comparator: Antidepressant fluoxetine 20 mg, Placebo Primary Endpoint: HAMD Power calculation: Yes	Adverse Events: • EPA: Acne 0 out of 16; Anxiety 1 out of 16; Constipation 0 out of 16; Diarrhea 1 out of 16; Drowsiness 1 out of 16; Dyspepsia 0 out of 16; Decreased appetite 0 out of 16; Fatigue 0 out of 16; Fish aftertaste 2 out of 16; Insomnia 0 out of 16; Nausea 0 out of 16; Nightmare 0 out of 16; Reflux 0 out of 16; Sexual disturbances 0 out of 16; Skin rash 0 out of 16; Tremor 0 out of 16 • Fluoxetine: Acne 0 out of 16; Anxiety 9 out of 16; Constipation 1 out of 16; Diarrhea 0 out of 16; Drowsiness 2 out of 16; Dyspepsia 0 out of 16; Decreased appetite 6 out of 16; Fatigue 0 out of 16; Fish aftertaste 0 out of 16; Insomnia 1 out of 16; Nausea 3 out of 16; Nightmare 1 out of 16; Reflux 2 out of 16; Sexual disturbances 2 out of 16; Skin rash 0 out of 16; Tremor 1 out of 16 • Fluoxetine + EPA: Acne 2 out of 16; Anxiety 3 out of 16; Constipation 0 out of 16; Diarrhea 0 out of 16; Drowsiness 0 out of 16; Dyspepsia 3 out of 16; Decreased appetite 0 out of 16; Fatigue 2 out of 16; Fish aftertaste 2 out of 16; Insomnia 2 out of 16; Nausea 0 out of 16; Nightmare 1 out of 16; Reflux 1 out of 16; Sexual disturbances 2 out of 16; Skin rash 1 out of 16; Tremor 1 out of 16

Study Details	Participants	Intervention	Outcomes/Results
Kaviani et al., 2014 Country: Iran Study Design: RCT Purpose: "To determine the effect of omega-3 fatty acid on mild depression during pregnancy in primiparous women" Quality Rating: Good,	Number of Participants: 40 Diagnosis: Rating scale Comorbidities: Pregnancy Age (Years): Omega-3: 26.33 (SD 4.2); Placebo: 25.15 (SD 4.2) Gender (% Male): 0% Inclusion Criteria: "Being primiparous with intrauterine pregnancy over 20 weeks, obtaining a score of 14 to 19 in BDI, being above 18 years old, not consuming fish twice a week (those who regularly used fish were removed from the study and were replaced by the next individual), not suffering from schizophrenia, bipolar disorders, blood disorders, such as VonWillebrand, hypertension, and hyperlipidemia, and renal and thyroid diseases, not taking anticoagulants and antidepressants, not smoking or using narcotics, and not participating in activities such as yoga, relaxation, and psychological consultations." Exclusion Criteria: "Having allergic reaction or digestive disease to the medicines."	Extract: Not described Dosage: 1 g daily for 6 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: NA Power calculation: No	Depression Measures: • BDI, SMD 0.69 (CI 0.24, 1.14)

Study Details	Participants	Intervention	Outcomes/Results
Lesperance et al., 2010 Country: Canada Study Design: Multisite RCT, 8 sites Purpose: "To document the short-term efficacy of omega-3 supplementation in reducing depressive symptoms in patients experiencing a major depressive episode (MDE)" Quality Rating: Fair, ITT analysis, some unclear methods	Number of Participants: 188 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): Placebo: 45.4 (SD 13.27); EPA: 46.6 (SD 11.54) Gender (% Male): Placebo: 28.5%; EPA: 34.4 Inclusion Criteria: "Patients had to be ≥18 years old; to meet diagnostic criteria for an MDE based on the Mini-International Neuropsychiatric Interview, version 5.0.024; to have a baseline score ≥27 on the self-report Inventory of Depressive Symptomatology (IDS-SR30)25; to have had clinically significant depressive symptoms for ≥4 weeks; if taking antidepressants, to have been at maximum tolerated dosage for > 4 weeks; if not on antidepressants, to have been intolerant to ≥2 previous antidepressants or to refuse to take antidepressants despite medical advice; and to have signed an informed consent." Exclusion Criteria: "Known allergy to fish or sun-flower oil; history of fish oil intolerance; having taken >14 g of omega-3 supplements during the past 4 weeks; diagnosis of alcohol or drug abuse or dependency during the past 12 months or bipolar disorder based on the [Mini-International Neuropsychiatric Interview]; significant suicidal risk based on clinical judgment; history of myocardial infarction, pancreatic insufficiency, or coagulation diseases or regularly taking any drugs or herbs with antiplatelet or anticoagulant properties. Nonmenopausal women with positive pregnancy tests or not using an accepted method of contraception were excluded."	Extract: EPA and DHA Dosage: 1,050 mg of EPA and 150 mg of DHA in 3 capsules daily for 8 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: Self-report Inventory of Depressive Symptomatology Power calculation: Yes	Depression Measures: • MADRS, SMD 0.04 (CI −0.16, 0.25) Adverse Events: • EPA: Diarrhea 50 out of 210; Fishy aftertaste 66 out of 210; Heartburn 45 out of 210; Headache 26 out of 210; Sore muscles/joints 24 out of 210; Bloating 19 out of 210; Sore throat 22 out of 210; Nausea 19 out of 210; Constipation 16 out of 210; Skin problems 18 out of 210; Dizziness 17 out of 210 • Placebo: Diarrhea 58 out of 206; Fishy aftertaste 11 out of 206; Heartburn 46 out of 206; Headache 37 out of 206; Sore muscles/joints 30 out of 206; Bloating 26 out of 206; Sore throat 20 out of 206; Nausea 20 out of 206; Constipation 20 out of 206; Skin problems 15 out of 206; Dizziness 11 out of 206

Study Details	Participants	Intervention	Outcomes/Results
Marangell et al., 2003 Country: United States Study Design: RCT Purpose: Evaluate DHA for treating major depression Quality Rating: Fair, unclear blinding, randomization, and allocation concealment; ITT analysis used	Number of Participants: 18 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 46.8 (SD 11.6) DHA, 47.9 (SD 11.2) placebo Gender (% Male): 20% Inclusion Criteria: A score of 12 or higher on MADRS, a score of 17 or higher on HAMD, no psychotropic medication for at least 2 weeks, dietary intake of no more than one serving of fish per week. Exclusion Criteria: Significant comorbid psychiatric or medical illness and treatment resistance, defined as a lifetime failure of two or more adequate antidepressant trials.	Extract: DHA Dosage: 2 g daily for 6 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: MADRS Power calculation: No	Depression Measures: • HAMD, SMD 0.26 (CI −0.39, 0.94) • HAMD Responder, OR 1.25 (CI 0.27, 5.73) Adverse Events: • DHA: Fish aftertaste 14 out of 18; Belching 3 out of 18; Lightheadedness or dizziness 3 out of 18; Loose stools 2 out of 18; Headache 2 out of 18; Insomnia 1 out of 18; Fatigue 3 out of 18; Withdrawals due to adverse events 0 out of 18 • Placebo: Fish aftertaste 0 out of 17; Belching 0 out of 17; Lightheadedness or dizziness 0 out of 17; Loose stools 1 out of 17; Headache 0 out of 17; Insomnia 1 out of 17; Fatigue 0 out of 17; Withdrawals due to adverse events 0 out of 17

Study Details	Participants	Intervention	Outcomes/Results
Meyer et al., 2013 Country: Australia Study Design: RCT Purpose: To determine if changes in omega-3 PUFA status following tuna oil supplementation correlated with changes in scores of depression Quality Rating: Poor, no ITT analysis, < 80% completed	Number of Participants: 32 Diagnosis: Rating scale Comorbidities: NA Age (Years): Range 18–75 years Gender (% Male): NR Inclusion Criteria: Primary diagnosis of major depression with HAMD score (16 to ensure depression severity). Exclusion Criteria: NA	Extract: HiDHA pure South Pacific tuna oil (250 mg DHA, 70 mg EPA, and 10 mg Vitamin E per 1 g capsule) Dosage: Eight 1 g capsules daily for 16 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: Depression scores Power calculation: No	Depression Measures: • HAMD, SMD –0.99 (CI −1.53, −0.45)

Study Details	Participants	Intervention	Outcomes/Results
Mischoulon, Best-Popescu, et al., 2008 Country: United States Study Design: RCT Purpose: "In view of the need to further investigate the anti-depressant efficacy of DHA, we sought to examine its dose–response pattern in subjects with MDD. We designed a pilot dose-finding study using three regimens of DHA (1 g/day, 2 g/day, and 4 g/day). We also examined the impact of DHA supplementation on plasma levels of DHA, EPA, and the n-6/ n-3 ratio, and whether these parameters were associated with severity of depression and response to DHA treatment." Quality Rating: Fair, methods not very clear (randomization, allocation, blinding); ITT analysis used	Number of Participants: 35 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 42 (SD 14) Gender (% Male): 54% Inclusion Criteria: "Subjects were required to meet criteria for MDD, as per the Structured Clinical Interview for DSM-IV (SCID-patient edition) . . . . The following conditions were also required: ability to provide written informed consent; ages between 18–80 years; a 17-item [HAMD-17] score of 18 or greater; and a Clinical Global Impression-Severity (CGI-S) . . . score of 3 or greater." Exclusion Criteria: "Pregnancy or no use of a medically accepted means of contraception in women of child bearing potential; breastfeeding; a current, serious suicidal or homicidal risk; serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; history of unstable seizure disorder; use of anticoagulants, such as heparin or warfarin; DSM-IV diagnoses, including organic mental disorders, substance use disorders, including alcohol (active within the last 6 months), schizophrenia, delusional disorder, psychotic disorders not elsewhere classified; bipolar disorder; history of multiple adverse drug reactions or allergy to the study drugs; psychotic features; current use of antidepressants, lithium, or anticonvulsants for mood stabilization; clinical or laboratory evidence of hypothyroidism; having taken at least 800 mg/day of DHA; history of electroconvulsive therapy (ECT) within the 6 months preceding study entry; use of supplements enriched with n-3 fatty acids, e.g. flax seed oil."	Extract: DHA: Each DHA capsule contained approximately 500 mg DHA extract from microalgae, and small amounts of ascorbyl palmitate (250 ppm) and tocopherols (250 ppm) as antioxidants to increase product shelf life Dosage: Group A: 1 g daily for 12 weeks Group B: 1 g daily for 2 weeks, 2 g daily for 11 weeks Group C: 1 g daily for 1 week, 2 g daily for 1 week, 4 g daily for 10 weeks *Note that all participants received a total of 8 capsules per day. Co-interventions: "Subjects were allowed concurrent psychotherapy if they were already receiving it prior to study entry, but were not allowed to initiate psychotherapy or new psychotropics during the study." Comparator: Other comparator varied doses of DHA Primary Endpoint: Response to treatment, defined as a 50% or greater decrease in HAMD-17 score from the screen visit to study completion Power calculation: Insufficient power (posthoc analysis)	Adverse Events: • DHA 1 g: Mild side effects 2 out of 11 • DHA 2 g: Mild side effects 3 out of 9 • DHA 4 g: Mild side effects 3 out of 8

Study Details	Participants	Intervention	Outcomes/Results
Mischoulon, Papakostas, et al., 2009 Country: United States Study Design: RCT Purpose: Examine the efficacy and tolerability of E-EPA monotherapy for MDD in a double-blind, randomized controlled pilot study Quality Rating: Good	Number of Participants: 11 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 42 (SD 14) Gender (% Male): 35% Inclusion Criteria: Subjects were required to meet criteria for MDD, as per the SCID-patient edition. Also, ability to provide written IRB-approved informed consent, ages between 18–80 years, a baseline HAMD-17 score of 18 or greater; and a baseline Clinical Global Impression-Severity (CGI-S) score of 3 or greater. Exclusion Criteria: “Pregnancy or no use of a medically accepted means of contraception in women of child bearing potential; breastfeeding; a current, serious suicidal or homicidal risk; serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; history of unstable seizure disorder; use of anticoagulants, such as heparin or warfarin; DSM-IV diagnoses, including organic mental disorders, substance use disorders, including alcohol (active within the last six months), schizophrenia, delusional disorder, psychotic disorders not elsewhere classified; bipolar disorder; history of multiple adverse drug reactions or allergy to the study drugs; psychotic features; current use of antidepressants, lithium, or anticonvulsants for mood stabilization; clinical or laboratory evidence of hypothyroidism; current use of other psychotropic drugs; having failed to respond during the course of their current major depressive episode to at least one adequate antidepressant trial, defined as six weeks or more of treatment with citalopram 40 mg/day (or its antidepressant equivalent); having taken at least 1 g/day of an omega-3 product, or any current use of supplements enriched with n-3 fatty acids, e.g. flax seed oil; history of electroconvulsive therapy (ECT) within the 6 months preceding study entry. Subjects were allowed concurrent psychotherapy if they were already receiving it prior to study entry, but were not allowed to initiate psychotherapy during the study.”	Extract: EPA Dosage: 500 mg twice daily for 8 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: HAMD-17 Power calculation: Insufficient power (posthoc analysis)	Depression Measures: • HAMD-17, SMD 0.6 (CI −0.22, 1.42) • HAMD 17 Responder, OR 2.7 (CI 0.51, 14.37) Adverse Events: • EPA: Mild GI side effects 2 out of 11 • Placebo: Mild GI side effects 5 out of 13

Study Details	Participants	Intervention	Outcomes/Results
Mischoulon, Nierenberg, et al., 2014 Country: United States Study Design: Multisite RCT, 2 sites Purpose: "To compare 2 omega-3 (n-3) preparations enriched with [EPA] versus [DHA] as monotherapy for [MDD] in a 2-site, placebo-controlled, randomized, double-blind clinical trial." Quality Rating: Good	Number of Participants: 51 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 45.8 (12.5) Gender (% Male): 40.7% Inclusion Criteria: "Inclusion criteria were a diagnosis of MDD per the Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (SCID I/P), a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥3, and a baseline [HAMD-17]score ≥15. The study was approved by institutional review boards at both sites. Prior to participation, all subjects signed a written informed consent form reviewed and discussed with a study physician." Exclusion Criteria: "Pregnancy or women of childbearing potential who were not using a medically accepted means of contraception; suicidality or homicidality; serious or unstable medical illness; current or past history of organic mental disorders, substance use disorders, any psychotic disorders, and bipolar disorder; history of multiple adverse drug reactions or allergy to the study compounds; concurrent use of psychotropic medications, systematic corticosteroid or steroid antagonists, anticoagulants, or immunosuppressant agents; electroconvulsive therapy during the current episode; any trial of ≥6 weeks with citalopram 40 mg/d or equivalent antidepressant during the current episode (to select a less refractory sample that would be more likely to respond to treatment); history of use of 1 g/d of n-3 supplements; history of a bleeding disorder; psychotherapy; smoking >10 cigarettes per day; vitamin E supplementation >400 IU; menstruating individuals unable to have baseline and posttreatment blood drawn during the follicular phase; and individuals unable to refrain from nonsteroidal anti-inflammatory use for >72 hours prior to blood work. Subjects with a Clinical Global Impressions-Improvement scale (CGI-I) score of 1 or 2 (i.e., "much improved" or "very much improved") during the baseline visit (1 week after the screen visit) were excluded from the study."	Extract: EPA-enriched: ProEPAxtra: 530 mg EPA, 137 mg DHA per soft gel, 7% stearidonic acid [SDA, n-3], 1% heneicosapentaenoic acid [HPA, n-3], 1% docosapentaenoic acid [DPA, n-3], 1% eicosatetraenoic acid [ETA, n-3], 0.2% ALA [n-3], 3% arachidonic acid [AA, n-6], 0.2% linoleic acid [LA, n-6], and 10–11% unspecified fatty acids); DHA-enriched: ProDHA: 225 mg DHA, 45 mg EPA per soft gel [DHA:EPA = 5:1], plus 10% DPA, 2% HPA, 1% SDA, 1% ETA, 0.4% ALA, 1% AA, 0.5% LA, and 20% unspecified fatty acids); or placebo (980 mg soybean oil per capsule; total 53.6% LA, 7.1% ALA, 0.1% myristic acid, 11% palmitic acid, 4% stearic acid, 0.2% palmitoleic acid, and 24% oleic acid) Dosage: EPA-enriched: 1,000 mg daily for 8 weeks; DHA-enriched: 1,000 mg daily for 8 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: HAMD-17 score Power calculation: Insufficient power (posthoc analysis)	Depression Measures: • HAMD-17, SMD –0.05 (CI −0.44, 0.33) • HAMD-17, SMD 0.19 (CI −0.2, 0.58) • HAMD-17 Responder, OR 0.97 (CI 0.45, 2.1) • HAMD-17 Responder, OR 0.93 (CI 0.43, 2) Adverse Events: • DHA: Discontinuation 0 out of 58 • EPA: Discontinuation 1 out of 60 • Placebo: Constipation out of 59; Tremors out of 59; Discontinuation 1 out of 59

Study Details	Participants	Intervention	Outcomes/Results
Mozaffari-Khosravi et al., 2013 Country: Iran Study Design: RCT Purpose: Conduct a single-center, randomized, double-blind, placebo-controlled, multi-arm, parallel-group trial, comparing the efficacy of EPA versus DHA as adjuvants to maintenance medication treatments for mild-to-moderate depression Quality Rating: Good	Number of Participants: 21 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 35.1 (SD 1.2) Gender (% Male): 38.7% Inclusion Criteria: A diagnose of mild-to-moderate depression, verified with the structured clinical interview according to DSM-IV; ages between 18 and 75 years; a BDI score between 10 and 28; a 17-item HAMD score between 8 and 18; and ability to understand the study and provide written informed consent. Exclusion Criteria: Any change in type or dose of antidepressant medications during the study period or within the 4 weeks before enrollment; taking fish oil or n-3 PUFA supplements in the preceding 6 months; consuming more than 3 servings of fish per week; any diagnosis of mental disorders according to DSM-IV other than mild-to-moderate depression; significant risk of suicide or homicide; current use of anticoagulants, mood stabilizers, or anticonvulsants; history of cupping (a traditional Chinese medicine therapy) in the preceding 3 months; history of multiple adverse drug reactions or allergy to marine foods or the study drugs; history of electroconvulsive therapy; severe or uncontrolled medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, hematologic, or gastrointestinal disorders; alcohol or substance dependence as defined by DSM-IV criteria; smoking; pregnancy, breastfeeding, and in case of fertile women, not using acceptable methods of contraception; development of serious adverse events during the study period; and lack of adherence to the study protocol.	Extract: EPA, DHA Dosage: EPA: 500 mg per dose, 2 doses per day for 12 weeks; DHA: 500 mg per dose, 2 doses per day for 12 weeks Co-interventions: Maintenance antidepressant therapy Comparator: Placebo Primary Endpoint: HAMD Power calculation: Yes	Depression Measures: • HAMD, SMD 0.05 (CI −0.56, 0.66) • HAMD, SMD 1.19 (CI 0.53, 1.84) • HAMD Responder, OR 1.05 (CI 0.02, 55.37) • HAMD Responder, OR 18.03 (CI 0.94, 344.4) Adverse Events: • DHA: Total adverse events 6 out of 20; GI disturbance 5 out of 20; Headache 1 out of 20; Dizziness 2 out of 20 • EPA: Total adverse events 6 out of 21; GI disturbance 4 out of 21; Headache 3 out of 21; Dizziness 1 out of 21 • Placebo: Total adverse events 5 out of 21; GI disturbance 3 out of 21; Headache 2 out of 21; Dizziness 1 out of 21

Study Details	Participants	Intervention	Outcomes/Results
Nemets, Stahl, and Belmaker, 2002 Country: Israel Study Design: RCT Purpose: Study a specific omega-3 fatty acid, E-EPA, as an adjunct to treatment for depressive episodes occurring in patients with recurrent unipolar depressive disorder who were receiving maintenance antidepressant therapy Quality Rating: Fair, achieved adequate double-blinding; conducted an ITT analysis; matched samples adequately; however, recruitment and allocation concealment were not described, and possible use of supplements at baseline was not considered	Number of Participants: 10 Diagnosis: MDD-DSM Comorbidities: NA Age (Years): 54.2 (SD 13.9) Omega 3, 52.1 (SD 10.2) placebo Gender (% Male): 15 Inclusion Criteria: Current MDD according to DSM-IV, 18–75 years old. Exclusion Criteria: Unstable medical disease, alcohol or drug abuse, psychotic features, history of hypomania or mania, comorbid psychiatric disorder other than panic disorder, dysthymic disorder, or obsessive-compulsive disorder (OCD).	Extract: E-EPA Dosage: 1 g twice per day for 4 weeks Co-interventions: Maintenance antidepressant therapy Comparator: Placebo Primary Endpoint: HAMD Power calculation: No	Depression Measures: • HAMD, SMD 1.49 (CI 0.47, 2.51) • HAMD Responder, OR 12 (CI 1.05, 136.79)

Study Details	Participants	Intervention	Outcomes/Results
Peet and Horrobin, 2002 Country: United Kingdom Study Design: Multisite RCT, 2 sites Purpose: To test the antidepressive effect of E-EPA in depressed patients Quality Rating: Fair, no indication of testing for existing omega-3 intake at baseline, but ITT sample analyzed	Number of Participants: 46 Diagnosis: Rating scale Comorbidities: NA Age (Years): 48 EPA 1 g, 43 EPA 2 g, 44 EPA 4 g, 44 placebo Gender (% Male): 16% Inclusion Criteria: Either sex, 18–70 years old, depressed as indicated by a score of 15 or more on 17-item HAMD despite ongoing treatment with a standard antidepressant at an adequate dose. Exclusion Criteria: NA	Extract: E-EPA Dosage: 500 mg capsules, 1 capsule twice each day for 12 weeks; or 500 mg capsules, 2 capsules twice each day for 12 weeks; or 500 mg capsules, 4 capsules twice each day for 12 weeks Co-interventions: Ongoing antidepressant treatment Comparator: Placebo Primary Endpoint: HAMD Power calculation: No	Depression Measures: • HAMD, SMD 0.2 (CI −0.4, 0.8) • HAMD, SMD 0.6 (CI −0.15, 1.34) • HAMD, SMD –0.05 (CI −0.76, 0.67) • HAMD, SMD 0.05 (CI −0.68, 0.78) • HAMD Responder, OR 1.06 (CI 0.3, 3.67) Adverse Events: • All E-EPA Groups Combined: Withdrawal due to adverse events 1 • E-EPA 1 g/day: Total adverse events 18 out of 17; Musculoskeletal system 0 out of 17; CNS and PNS 1 out of 17; Visual system 0 out of 17; Psychiatric event 4 out of 17; GI 7 out of 17; Metabolic 2 out of 17; Endocrine 0 out of 17; Respiratory system 1 out of 17; White blood cells 0 out of 17; Reproductive system 0 out of 17; Whole body 1 out of 17; Resistance (infections) 2 out of 17 • E-EPA 2 g/day: Total adverse events 24 out of 18; Musculoskeletal system 2 out of 18; CNS and PNS 0 out of 18; Visual system 0 out of 18; Psychiatric event 2 out of 18; GI 8 out of 18; Metabolic 0 out of 18; Endocrine 0 out of 18; Respiratory system 2 out of 18; White blood cells 0 out of 18; Reproductive system 1 out of 18; Whole body 6 out of 18; Resistance (infections) 3 out of 18 • E-EPA 4 g/day: Total adverse events 15 out of 17; Musculoskeletal system 1 out of 17; CNS and PNS 1 out of 17; Visual system 0 out of 17; Psychiatric event 0 out of 17; GI 5 out of 17; Metabolic 0 out of 17; Endocrine 1 out of 17; Respiratory system 1 out of 17; White blood cells 0 out of 17; Reproductive system 0 out of 17; Whole body 3 out of 17; Resistance (infections) 3 out of 17 • Placebo: Total adverse events 23 out of 18; Musculoskeletal system 0 out of 18; CNS and PNS 3 out of 18; Visual system 1 out of 18; Psychiatric event 2 out of 18; GI 4 out of 18; Metabolic 2 out of 18; Endocrine 0 out of 18; Respiratory system 2 out of 18; White blood

Study Details	Participants	Intervention	Outcomes/Results
			cells 1 out of 18; Reproductive system 2 out of 18; Whole body 4 out of 18; Resistance (infections) 2 out of 18; Withdrawal due to adverse events 1 out of 18

Study Details	Participants	Intervention	Outcomes/Results
Rees, Austin, and Parker, 2008 Country: Australia Study Design: RCT Purpose: To assess whether omega-3 fatty acid treatment is superior to placebo in the treatment of perinatal depression Quality Rating: Good	Number of Participants: 11 Diagnosis: MDD-DSM Comorbidities: NA Age (Years): 31.2 (SD 4.4) fish oil, 34.5 (SD 3.8) placebo Gender (% Male): 0 Inclusion Criteria: Subjects were required to be 21 years of age; in regard to perinatal status, patients were required to be between the third trimester of pregnancy and 6 months postnatal; and patients were required to meet criteria for a current episode of major depression or dysthymia, according to DSM-IV criteria, and confirmed by both Composite International Diagnostic Interview criteria and clinical assessment by a psychiatrist. Exclusion Criteria: Bipolar disorder, psychosis, drug and alcohol abuse, obsessive compulsive disorder, eating disorder or personality disorder, an unstable medical condition, diabetes, receipt of anticoagulants or having a fish allergy. We also excluded those already receiving an antidepressant or any psychological therapy, as well as those taking fish oil supplements or eating more than three oily fish portions per week.	Extract: Fish oil (27.3% DHA, 6.9% EPA) Dosage: 6 g per day in divided doses for 6 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: EPDS, HAMD, MADRS Power calculation: Insufficient power (posthoc analysis)	Depression Measures: • HAMD, SMD 0.64 (CI −0.26, 1.55) Adverse Events: • Fish oil: Mild reflux 2 out of 13; Mildly increased stool frequency 2 out of 13; Nausea 1 out of 13 • Placebo: Mild reflux 2 out of 13; Mildly increased stool frequency 1 out of 13; Nausea 1 out of 13

Study Details	Participants	Intervention	Outcomes/Results
Rondanelli et al., 2011 Country: Italy Study Design: RCT Purpose: To determine if a supplement containing n-3 long-chain PUFAs improves depressive symptoms, changes phospholipids acids profile, and ameliorates health-related quality of life in depressed elderly patients Quality Rating: Good	Number of Participants: 18 Diagnosis: MDD-DSM Comorbidities: NA Age (Years): 84.9 (SD 6.9) n-3, 83.0 (SD 7.3) Gender (% Male): 0 Inclusion Criteria: Eligible participants were females aged between 65 and 95 years, with body mass index higher than 19 and lower than 30 kg/m^2. Cases were recruited from a nursing home in Pavia, where they had been institutionalized for at least 3 months prior to enrollment. All subjects admitted to treatment met the DSM-IV-TR (34) full criteria for major depression or dysthymia. Exclusion Criteria: (a) presence of a current comorbid psychiatric diagnosis other than major depression or dysthymia; (b) presence of active suicide ideation; (c) presence of psychotic symptoms; (d) current use of psychotropic drugs other than benzodiazepines (antidepressants, mood stabilizers, antipsychotics). Moreover, subjects with a clinically uncontrolled organic disease or with clinically relevant laboratory abnormalities were excluded from the study.	Extract: n-3 long-chain PUFA (1.67 g of EPA and 0.83 g of DHA) Dosage: 2.5 g once per day for 8 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: GDS Power calculation: No	Quality of life: • Depression: GDS SMD 0.74 (CI 0.14, 1.34) • SF-36 MCS: SMD −0.8 (CI −1.4, −0.2) • SF-36 PCS: SMD −0.68 (CI −1.27, −0.08) Adverse Events: • Omega-3: Serious adverse events 0 out of 18 • Placebo: Serious adverse events 0 out of 21

Study Details	Participants	Intervention	Outcomes/Results
Silvers et al., 2005 Country: New Zealand Study Design: RCT Purpose: To determine the effect of adding fish oil (containing both DHA and EPA) to existing therapy in community-based patients being treated for a current depressive episode Quality Rating: Good	Number of Participants: 24 Diagnosis: Rating scale Comorbidities: NA Age (Years): 39.8 (SD 11.9) fish oil, 37.7 (SD 13.6) placebo Gender (% Male): 47% Inclusion Criteria: Participants being treated for a current depressive episode and no co-existing psychiatric disorder (except anxiety disorders) were recruited to the study if they were between 18 and 65 years old, and if female, were premenopausal with a normal menstrual cycle. Participants were also required to have been on their current medication at a constant dose for at least 2 months, to have no objections to providing blood samples, and to be available for the length of the study. Exclusion Criteria: Blood clotting disorders, use of anticoagulant therapy, unstable medical conditions or conditions likely to affect gastrointestinal absorption, allergies to seafood, objections to taking fish-based or olive oil–based products, and those already taking fish oil.	Extract: DHA-enriched tuna fish oil Dosage: 1 g per capsule, 4 capsules twice daily for 12 weeks Co-interventions: Maintenance antidepressant therapy Comparator: Placebo Primary Endpoint: HAMD-SF and BDI-2 Power calculation: Yes	Depression Measures: • HAMD-SF, SMD –0.04 (CI −0.62, 0.55) Adverse Events: • Fish oil: Total adverse events 20 out of 40; Musculoskeletal system 1 out of 40; CNS 4 out of 40; Psychiatric event 0 out of 40; GI disturbance 8 out of 40; Reflux 3 out of 40; Resistance (infections) 0 out of 40; Skin 1 out of 40; General malaise/felt unwell 1 out of 40; Other 2 out of 40 • Placebo: Total adverse events 16 out of 37; Musculoskeletal system 0 out of 37; CNS 1 out of 37; Psychiatric event 2 out of 37; GI disturbance 7 out of 37; Reflux 1 out of 37; Resistance (infections) 2 out of 37; Skin 1 out of 37; General malaise/felt unwell 1 out of 37; Other 1 out of 37

Study Details	Participants	Intervention	Outcomes/Results
Su et al., 2003 Country: Taiwan Study Design: RCT Purpose: To provide more evidence to uncover the relation between pathogenesis in major depression and omega-3 PUFAs and then establish an efficient treatment for it, we conducted an 8-week, preliminary double-blind, placebo-controlled trial Quality Rating: Poor, no ITT analysis, <80% completed, unclear randomization, assessor blinding	Number of Participants: 12 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 35.2 (SD 11.6) omega-3, 42.3 (SD 10.7) placebo Gender (% Male): 18% Inclusion Criteria: Diagnosed with DSM-IV as major depressive disorder; >18 on 21-item HRSD; physically healthy under comprehensive evaluations of medical history, physical examination, and laboratory tests; competent to understand the study and were given written informed consents. Exclusion Criteria: Other comorbid Axis I or Axis II psychiatric disorders, change in medications, or psychotherapy 4 weeks before the enrollment.	Extract: Omega-3 fatty acid concentrate containing 440 mg of EPA and 220 mg of DHA Dosage: 5 capsules, with 440 mg EPA and 220 mg DHA, twice daily for 8 weeks Co-interventions: Maintenance antidepressants Comparator: Placebo Primary Endpoint: HAMD Power calculation: No	Depression Measures: • HAMD, SMD 2.42 (CI 1.31, 3.52) Adverse Events: • Omega-3: Mild excitement 1 out of 12; Mild diarrhea 1 out of 12; Insomnia 0 out of 12 • Placebo: Mild excitement 0 out of 10; Mild diarrhea 0 out of 10; Insomnia 1 out of 10

Study Details	Participants	Intervention	Outcomes/Results
Su et al., 2008 Country: Taiwan Study Design: RCT Purpose: Examine the efficacy of omega-3 PUFA monotherapy for treating depression during pregnancy Quality Rating: Fair, ITT analysis, unclear methods	Number of Participants: 13 Diagnosis: MDD-DSM, Rating scale Comorbidities: NA Age (Years): 30.9 (SD 3.9) omega-3, 31.3 (SD 5.7) placebo Gender (% Male): 0 Inclusion Criteria: Pregnant women, aged 18–40 years, with DSM-IV MDD, onset between 16th and 32nd week of gestation, seen at the Department of Obstetrics during the 24-month study period (June 2004 to June 2006). Participants were required to be free from any psychotropic agents for at least 1 month, to have a score of at least 18 on the 21-item HAMD at screening phase, and to have good physical health as determined by medical history, physical examination, blood laboratory results, electrocardiogram, chest radiography, and urinalysis. Exclusion Criteria: DSM-IV diagnosis of bipolar disorder, psychotic disorder, or substance abuse/dependence or any Axis II diagnosis of borderline or antisocial personality disorder.	Extract: EPA + DHA Dosage: 2.2 g EPA + 1.2 g DHA per capsule, 5 capsules per day for 8 weeks Co-interventions: NA Comparator: Placebo Primary Endpoint: HAMD Power calculation: No	Depression Measures: • HAMD, SMD 0.93 (CI 0.09, 1.78) • HAMD Responder, OR 4.27 (CI 0.75, 24.18) Adverse Events: • Omega-3: Withdrawal due to adverse events 0 out of 13; Insomnia 3 out of 13; Nausea 6 out of 13; Diarrhea 1 out of 13 • Placebo: Withdrawal due to adverse events 0 out of 11; Insomnia 2 out of 11; Nausea 4 out of 11; Diarrhea 2 out of 11

Study Details	Participants	Intervention	Outcomes/Results
Tajalizadekhoob et al., 2011 Country: Iran Study Design: RCT Purpose: To find the effect of low-dose n-3 PUFAs on the treatment of mild to moderate depression in elderly residents of Kahrizak Charity Foundation Quality Rating: Poor, no ITT analysis	Number of Participants: 32 Diagnosis: Rating scale Comorbidities: None Age (Years): Omega-3: 79.64 (SD 7.39), Placebo: 79.73 (SD 7.01) Gender (% Male): 30% Inclusion Criteria: (1) Age >65, (2) No history of any end-stage diseases, Parkinson disease, or any unstable medical conditions, (3) No history of sea food allergies, (4) No consumption of fish oil or supplements enriched with x-3 fatty acids 3 months prior to participation, (5) No history of psychiatric disorders with the exception of depression or anxiety, and (6) No diagnosis of mental retardation. Exclusion Criteria: Individuals with a reported history of dementia based on their Kahrizak Charity Foundation profiles were excluded from the study.	Extract: Each capsule contained cod liver oil, glycerol, water, and fish oil and was comprised of 180 mg EPA and 120 mg DHA. The cod liver oil and fish oil were obtained from cold water fish. Dosage: 1 g daily for 6 months Co-interventions: NA Comparator: Placebo Primary Endpoint: NA Power calculation: Yes	Depression Measures: • GDS-15, SMD 0.35 (CI −0.15, 0.86) • GDS-15 Responder, OR 1.8 (CI 0.61, 5.28) Adverse Events: • Fish oil: CNS Systems 1 out of 33; Visual system 0 out of 33; Psychiatric events 0 out of 33; Cardiovascular system 1 out of 33; Respiratory system 1 out of 33; Urogenital system 1 out of 33; Skin 0 out of 33; GI disturbance 4 out of 33; Metabolic and endocrines 0 out of 33; General (malaise/felt unwell) 1 out of 33; Musculoskeletal system 0 out of 33 • Placebo: CNS Systems 2 out of 33; Visual system 0 out of 33; Psychiatric events 0 out of 33; Cardiovascular system 2 out of 33; Respiratory system 0 out of 33; Urogenital system 0 out of 33; Skin 0 out of 33; GI disturbance 5 out of 33; Metabolic and endocrines 0 out of 33; General (malaise/felt unwell) 3 out of 33; Musculoskeletal system 0 out of 33

NA = not available.

Appendix C: Excluded Full-Text Articles

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Reason Excluded: Not an RCT

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Appendix D: Depression Scale Standard Cut-Points

Scale	Cut-Off Point
Beck Depression Inventory-I	Cut-off for Clinical Diagnosed with Depression: 0–9 = minimal/no depression 10–18 = mild/moderate depression 19–29 = moderate/severe depression 30–63 = severe depression
Beck Depression Inventory-II	0–13 = minimal 14–19 = mild (13-14*= mild) 20–28 = moderate 29–63 = severe
Center for Epidemiologic Studies Depression (CES-D)	CES-D 20: 16 = “significant” or “mild” depressive symptomatology CES-D 10: 11 = recommended as cut-off (equivalent to experiencing 6 symptoms for most of the previous week or a majority of symptoms on 1 or 2 days)
Clinical Diagnosis/Meets DSM Criteria/Major Depression Inventory (MDI)	26 = moderate-severe depression 0–19 = no depression 20–24 = mild depression 25–29 = moderate depression 30–50 = severe depression
Depression Anxiety Stress Scale (DASS)-21 Depression Scale	0–4 = normal 5–6 = mild 7–10 = moderate 11-13 = severe 14+ = extremely severe 12 = recommended cut-point
Depression-Arkansas Scale (D-ARK)	26–37= mild 38–57 = moderate
General Health Questionnaire (GHQ)	4 = usual cut-point
Geriatric Depression Scale (GDS)	GDS-5: $\geq$ 2 = cut-point GDS-15: 5–9 = mild 10–15 = moderate to severe Cut-off scores for GDS-15 Among Special Populations: Cognitive impairment = 8 Dementia = 11 Parkinson’s Disease = 10–11 (but some variation here) Stroke = 11–12 (minor depressed) Post Stroke = 6–7 Elderly home care = 5 GDS Long Form (30 items) 11–20 = mild 21–30 = moderate to severe

Scale	Cut-Off Point
Hamilton Rating Scale for Depression (HAMD)	0–6 = no depression 7–17 = mild depression 18–24 = moderate depression 24+ = severe depression
Hospital Anxiety and Depression Scale	0–7 = no depression 8–10 = “possible case” 11–21 = “probable case” Optimal cut-off point = ≥ 8 for the identification of suspicious cases and ≥ 11 for safe cases on both subscales
Medical Outcomes Study Depression Screen (MOS-D)	0.06 = usual cut-point
Minnesota Multiphasic Personality Inventory (MMPI) Depression Scale	T score of 70 used for MMPI T score of 65 used for MMPI-2
Montgomery-Åsberg Depression Rating Scale (MADRS)	7–19 = mild 20–34 = moderate 35–60 = severe
Montgomery-Åsberg Depression Rating Scale (MADRS)-S	13–19 = mild 20+ = moderate to severe
Patient Health Questionnaire (PHQ)-9	5 = mild 10 = moderate 15 = severe *10 cited as the optimal cut-off point
Primary Care Evaluation of Mental Disorders (PRIME-MD)	1 = usual cut-point
Symptom Checklist (SCL)-20	≥ 1.75 as a cutoff for major depression
SCL-CD6	≥ 17 is indicative of MDD
Symptom Driven Diagnostic System-Primary Care (SDDS-PC)	2 = usual cut-point
Zung Self Assessment Depression Scale (SDS)	50 = mild 60 = moderate 70 = severe
Alasker scale	N/A
Brief Symptom Inventory (BSI)	N/A
Institute for Personality and Ability Testing Depression Scale (IPAT)	N/A
Patient-Reported Outcomes Measurement Information System (PROMIS) Depression	N/A
SCL-90	N/A

N/A = not applicable.

Appendix E: Funnel Plots for Comparisons with Publication Bias

Figure E.1. Funnel Plot for Overall Comparison of Omega-3 Fatty Acids with Placebo, Depression Scale Scores

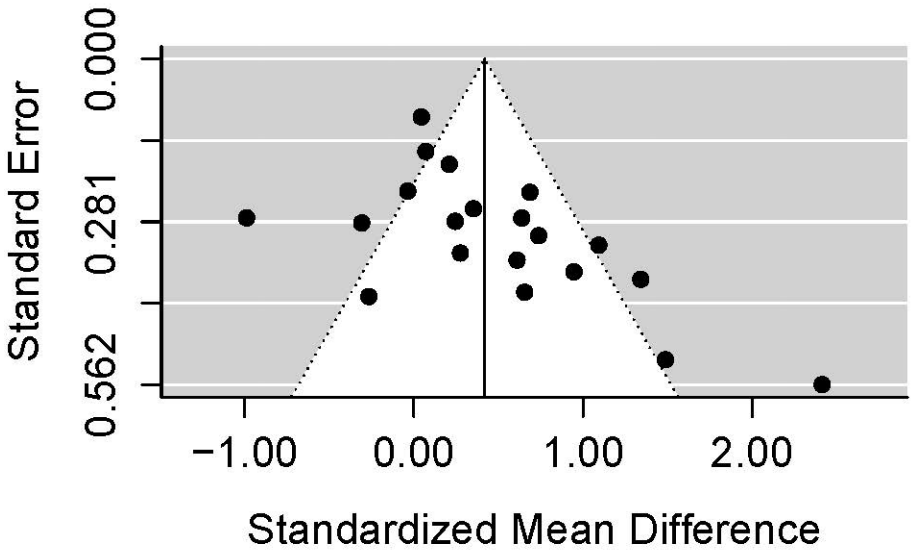


Figure E.2. Funnel Plot for Overall Comparison of Omega-3 Fatty Acids with Placebo, Percentage of Responders

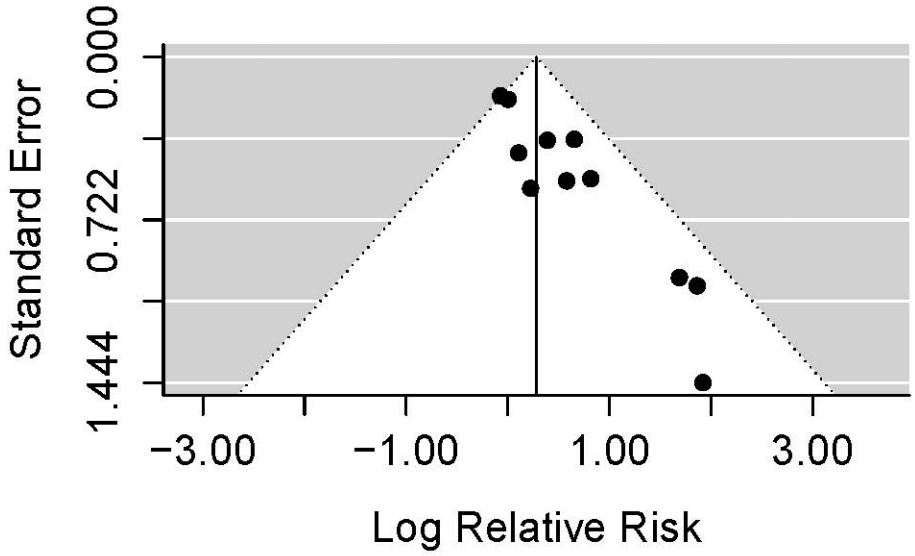


Figure E.3. Funnel Plot for Overall Comparison of Omega-3 Fatty Acids with Placebo, Percentage of Remission

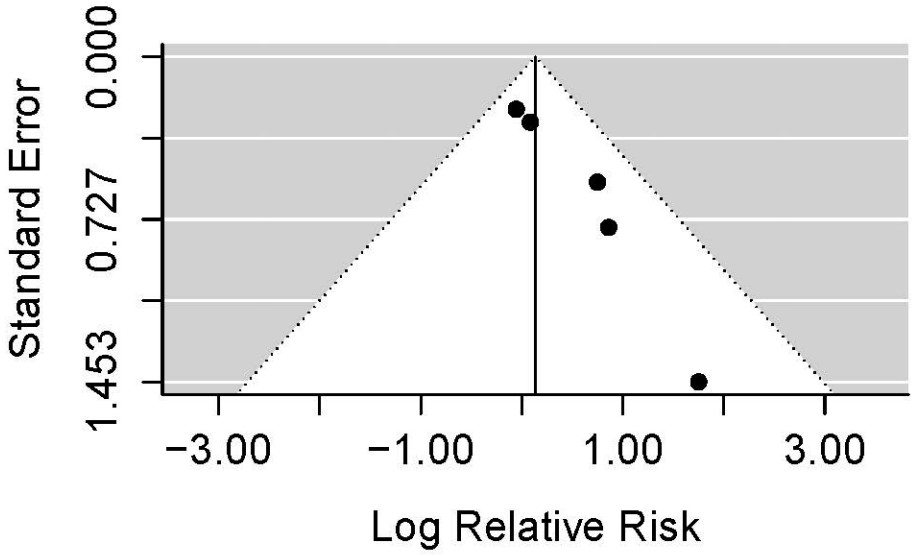


Figure E.4. Funnel Plot for Comparison of EPA and a High EPA:DHA Ratio with Placebo, Depression Scale Scores

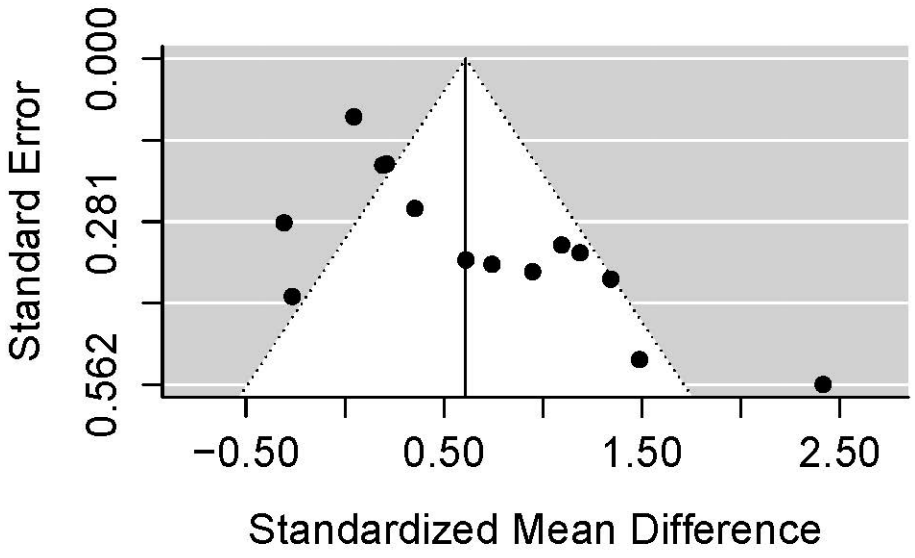


Figure E. 5. Funnel Plot for Comparison of EPA and a High EPA:DHA Ratio with Placebo, Percentage of Responders

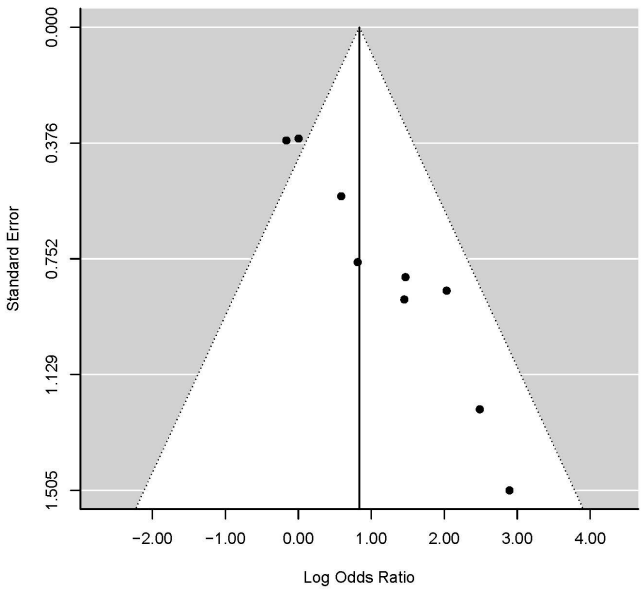


Figure E.6. Funnel Plot for Comparison of EPA and a High EPA:DHA Ratio with Placebo, Percentage of Remission

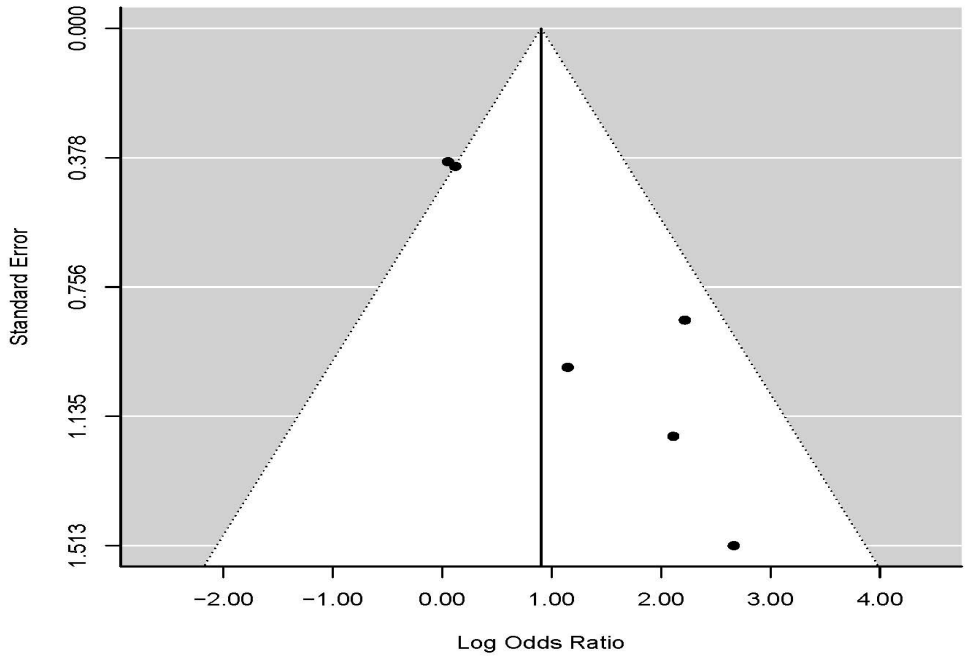
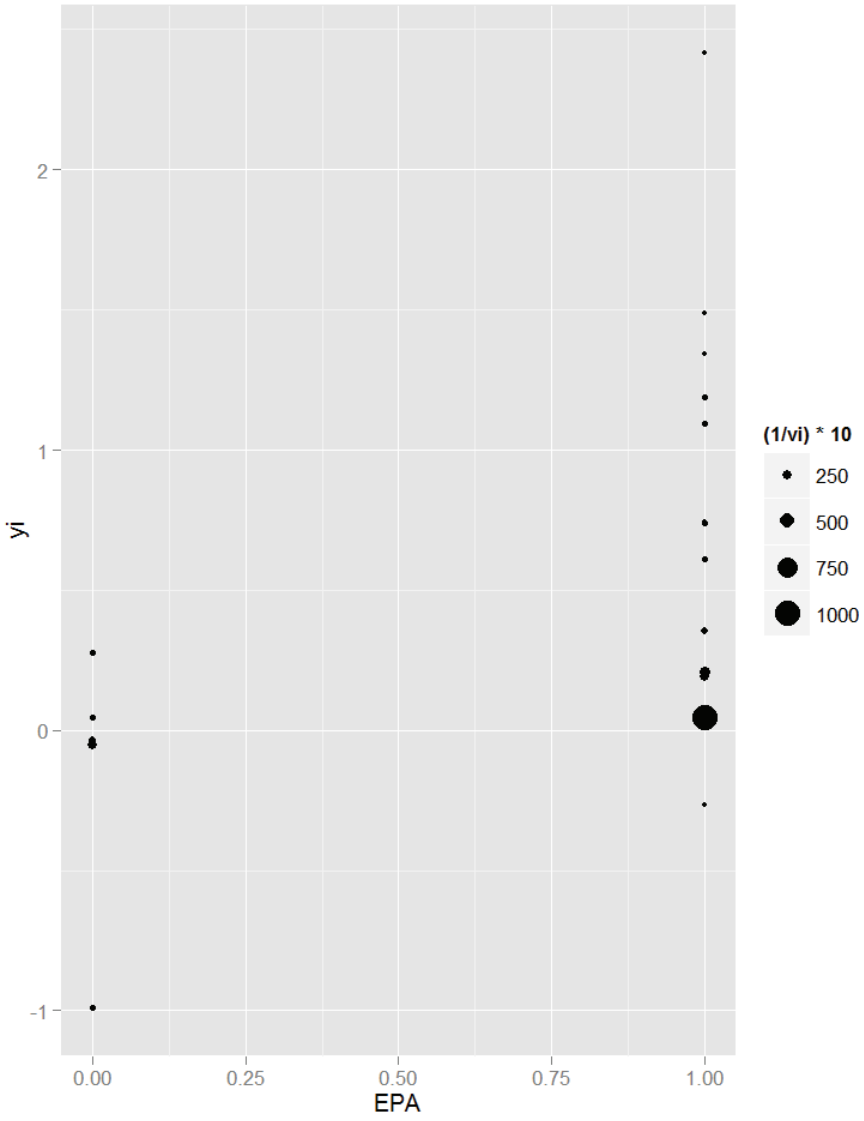


Figure E. 7. Scatter Plot for Comparison of EPA with DHA



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