A fishy depression treatment

Omega-3 fatty acids for depression in adults

Introduction

Depression is the leading cause of disability worldwide, with an estimated 350 million people suffering from this mood disorder. Major depressive disorder (MDD) is a type of depression defined as a state of extreme unhappiness and inability to feel pleasure lasting at least two weeks. Figure 1 shows a breakdown of major depression in the US.

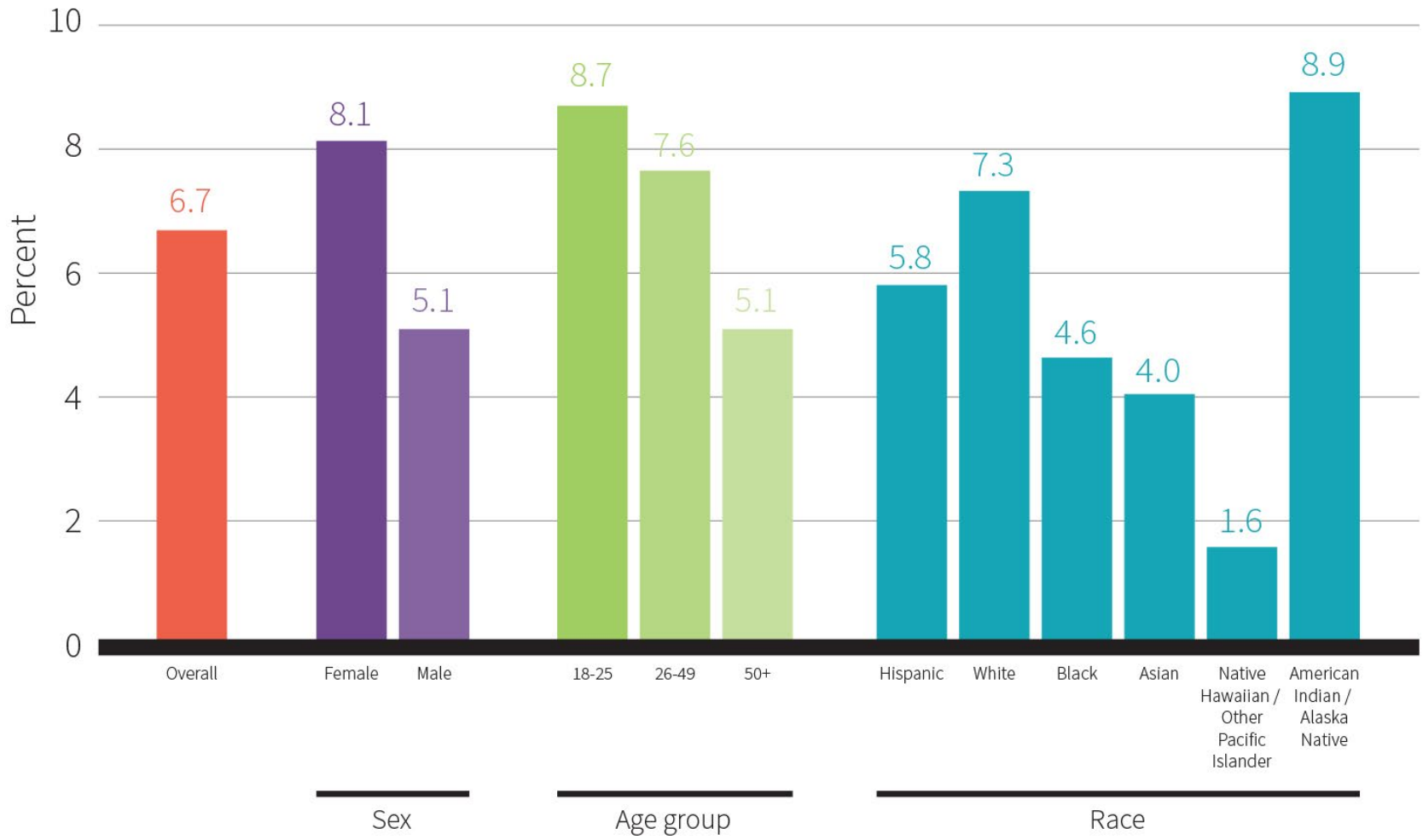
MDD can be very debilitating, has a high rate of recurrence, and often requires a complex mix of treatments. Comprehensive approaches to treating this affective disorder may include lifestyle interventions, therapy sessions, and the use of medications. In more difficult cases, electroconvulsive therapy, where electrical currents are sent through the brain, can be used to alleviate the symptoms of depression.

Increasingly, studies have examined the use of omega-3 polyunsaturated fatty acids (n-3) to treat depression. A link between n-3s and depression was suggested after the recognition of a population-wide reduction in Western dietary intakes of omega-3s being correlated with an increase in rates of depression. Some randomized controlled trials have shown benefits for symptoms of MDD among those who supplemented with n-3s.

The positive effects of n-3s on depression are thought to occur as a result of alterations to the cell membrane, cell to cell communication, and on inflammatory processes and neurotransmitter activity. These processes have all been implicated in the pathology of MDD.

However, not all investigations have reported beneficial effects and previous meta-analyses have found considerable variability among studies. The present study is the fourth update to the Cochrane Collaboration's review on omega-3 fatty acids for depression. To help reduce the variability seen in other reviews, this meta-analysis focuses solely on MDD in adults, not taking into account other types of depressive disorders or

Figure 1: Prevalence of major depressive episodes in the US in 2013



Source: SAMHSA, NIMH

younger populations. The objective of this review was to assess the effects of n-3s versus a comparator (e.g. a placebo or standard antidepressant treatment). To do this, the authors pool the results from multiple intervention studies and statistically analyze the data to see if there was a positive, negative, or neutral overall result.

Depression affects over 350 million people worldwide. Major depressive disorder (MDD) is defined as a state of extreme unhappiness and an inability to feel pleasure lasting at least two weeks. This meta-analysis examines the efficacy of n-3s versus placebo or standard depression treatment to alleviate the symptoms of MDD in adults.

Who and what was studied?

Only randomized controlled trials were included in this review. All suitable trials were included regardless of quality, but quantitative estimates of bias were recorded for each study. Observational and case-control studies were excluded to avoid an increased risk of bias in the results. Furthermore, only studies that enrolled participants with a formal diagnosis of major or unipolar depressive disorder from a trained clinician were incorporated. In an effort to make the results of this review as generalizable as possible, studies where participants had comorbidities (e.g. heart disease, anxiety) were included. This was done to obtain a sample that was representative of the MDD population, who have a high likelihood of existing comorbidities. Studies that had patients using adjunctive therapies were included for the same reason.

Depressive symptoms were assessed using validated measures like the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HDRS), which are commonly used to measure symptomatology. The HDRS, for example, is a 17 question survey that asks people to rate items like feelings of guilt, anxiety, agitation, and weight loss. These measures have been shown to reliably track and quantify symptoms of depression.

Adverse events were also recorded where possible, such as gastrointestinal distress or psychiatric events. Out of 575 potentially relevant records to the review, only 26 studies met the above inclusion criteria. In total, these

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studies included 1,458 participants. Only one of these trials compared n-3s to another antidepressant treatment. The rest used a placebo group as a control. At the time of publication, there were an additional 16 trials that were ongoing that could potentially be included in future updates of this review.

This review aimed to make the results of analyzed studies generalizable to a wide audience of adults with major or unipolar depressive disorder. Therefore, studies that included patients using multiple therapies and those with comorbidities, like anxiety, were included. Twenty-six studies with 1,458 participants were included in this review.

What were the findings?

The use of n-3s was shown to have an overall benefit for depressive symptomatology, but the effect was small to modest. In those patients that experienced a modest reduction in symptoms, there may be a clinical application for n-3s.

Adverse events were similar between placebo and intervention groups. Remission rates showed no statistical difference between groups, but there was a trend that favored n-3s for being able to reduce depression remission. The same positive trend for use of n-3s was seen in measures of quality of life. Interestingly, the results of the analyses were highly influenced by three large trials. The risk of bias in these trials was rated to be low, but

Assessing Bias in a Cochrane Review

When pooling together multiple studies into a meta-analysis, the results of the review can only be as valid as the data from which they draw on. In a Cochrane review, the authors will examine each included trial for six different areas of bias and give them a ranking of either low, high, or unclear risk of bias. These areas of bias, as defined by Cochrane, are as follows:

Selection bias – were the study participants randomly assigned to the various study groups to help ensure equal baseline characteristics, and did participants have any prior knowledge of the forthcoming group assignments?

Performance bias – was there adequate blinding of participants and research personnel involved in the study? When blinding is performed effectively, it can help ensure that each group receives equal time and attention from the investigators.

Detection bias – this bias examines if those who were assessing the outcomes of the trial were blinded as to which groups data they were assessing. Ensuring proper blinding in this area can be particularly important when assessing subjective outcomes, like how someone feels.

Attrition bias – withdrawals from a study can affect the overall outcome of the trial. This can cause the authors to exclude incomplete outcome data from the final analysis.

Reporting bias – when reporting outcomes, those with statistically significant findings are more likely to be reported than those that are not. This 'within-study publication bias' can skew results from individual studies.

Other sources of bias – there can be study-specific bias stemming from particular trial designs that must also be taken into account. For example, in a cross-over trial, where the same group receives both interventions at different periods, there may be a carry-over effect if the washout period was not long enough.

they contributed 26.9% of the data for the depressive symptomatology results. Figure 2 shows the risk of bias for all the included studies.

Although the authors included studies where participants had comorbidities (such as CHD, anxiety, and anorexia nervosa) they did perform analyses to determine if n-3s had a greater effect on participants with or without comorbidities. A positive effect was seen in both groups, although the effect ranged from negligible to modest. When comparing groups who were and were not receiving adjunctive therapy (like antidepressants, psychotherapy, or other therapies that may affect mood), the n-3 supplementation had a greater positive effect on those individuals who were not receiving adjunctive therapy.

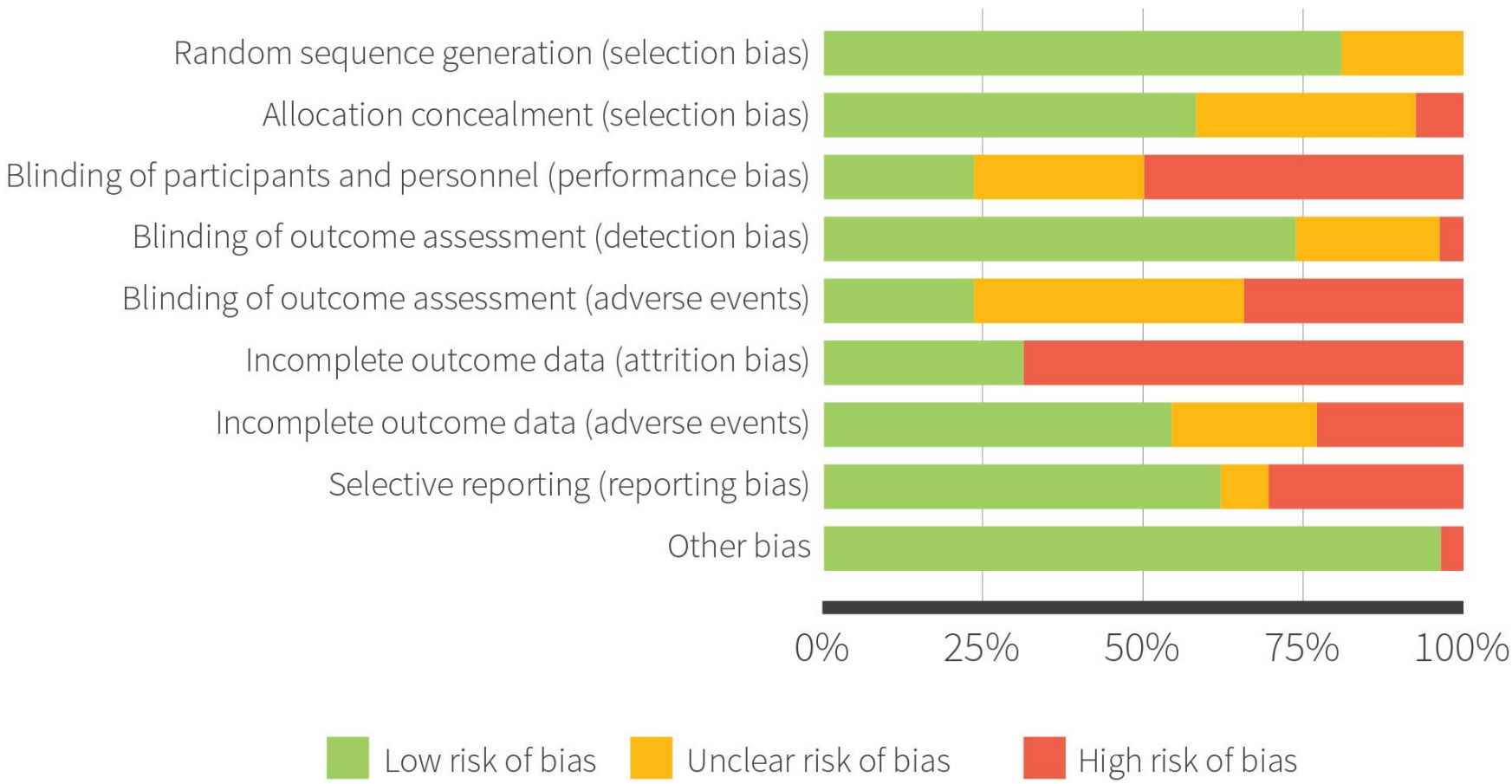
Only one study in the review compared n-3s to an antidepressant medication. In this case the selective serotonin reuptake inhibitor (SSRI) fluoxetine, commonly known as Prozac or Sarafem, was the comparator. Forty participants were recruited, 20 in each treatment arm, but 20% of the participants in each group did not complete the study. The results indicated that there was no difference in reducing symptoms of depression between treatments.

The ability of n-3s to ameliorate symptoms of depression are small to modest. Greater benefits may be experienced by people not currently receiving any therapy, although these benefits remain small. One study compared n-3s to a common antidepressant medication, fluoxetine (Prozac), and saw no difference in reducing depressive symptoms.

What does the study really tell us?

While the authors noted that n-3s may offer some limited clinical applications in treating depression, they are also careful to state that the quality of evidence was consistently rated as low to very low based on GRADE, a system that assess methodological flaws in a study.

Figure 2: Risk of biases in the included studies



Adapted from: Appleton et al. Cochrane Database Syst Rev. 2015 Nov.

An additional shortcoming is the heterogeneous nature of the study designs. They varied in participant types, interventions used, duration of supplementation period, and the range of outcomes examined. Further complicating the analyses was the wide variation in participants involved and interventions utilized. Differing background omega-3 status of subjects may have further confounded the results. N-3 supplementation may not have as beneficial an effect in an adult with MDD who already has sufficient levels of omega-3s.

As mentioned before, three trials contributed to 26.9% of the data examining n-3s and depressive symptomatology, and each of these were rated as having a low risk of bias. These trials all included participants with comorbidities, used an n-3 supplement with EPA and DHA, and ran for a duration of eight to ten weeks. When these three studies were examined by themselves, the authors found a negligible difference between n-3s and placebo. The implications here are that because the larger, more well-designed trials didn't really show an effect, it is possible that the overall slight trend in favor of n-3's are due to the other smaller trials included in the analysis that are more prone to bias.

The authors ended up concluding that, based on the presently available data, there is not enough high-quality evidence to determine the effects of n-3s as a viable treatment for MDD. While small to modest positive effects of n-3 supplementation were observed compared to placebo, the degree of this effect is unlike to have meaningful benefits to most people with depression. Additionally, there was not enough evidence available to assess potential negative side effects of supplementation. The authors state that more evidence is needed for examining the different findings that were seen between studies, mainly looking at individuals who improved with n-3s and why this may have occurred.

Most of the current evidence looking into n-3s and depression is of low or very low quality. This has led the authors of this review to conclude that there is not enough high quality data available to make a recommendation for or against n-3s at the moment. It is possible that some people may respond more favorably than others to supplementation, but future studies are needed to examine these differences.

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The big picture

This review has clarified the current state of the evidence on n-3s and depression. There have been many previous reviews on this topic, but early reviews tended to have a broader inclusion criterion for what was considered to be a depressive diagnosis, which included bipolar disorder, postpartum depression, and even studies of people with depressive symptoms but no formal diagnosis. More recent reviews, including the present one, have had tighter inclusion criteria.

To help elucidate the role of omega-3s in depression, more well-designed studies with large sample sizes would be needed to progress this line of research. Many studies are currently underway that may help to alleviate these issues. One important area of future research will be to compare n-3s to other antidepressant treatments, as it would give us an idea if n-3s are better or worse than what is currently available. Trials where n-3s are used as adjunctive therapies would be informative as well, and could show us if they act synergistically or antagonistically with depression medications.

The mechanisms by which n-3s may help in managing depression are not well understood at the moment either. Some potential ones are shown in Figure 3. It is thought that the beneficial effects of n-3s may occur through their incorporation into the cell membrane, which results in changes in structure and function. Incorporation can result in increased fluidity and permeability that can possibly aid with cell to cell transport and communication. N-3s may also play a role in forming a number of anti-inflammatory molecules. Future research into these mechanisms could assist in the development of treatments for depression.

The present meta-analysis has helped to clarify where the evidence currently stands for n-3s and depression. Larger, more well designed studies will be needed to alleviate some of the limitations currently present in the literature. Future trials looking into possible mechanisms of n-3s on depression could aid in developing new treatments.

Frequently asked questions

Why did this review just focus on MDD?

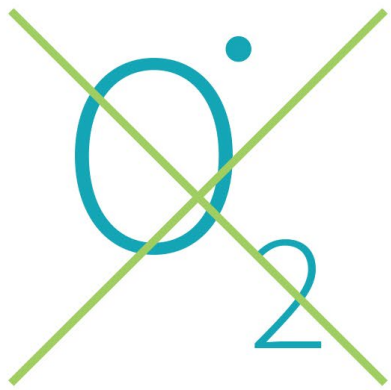
There are many different types of depression. In addition to major depressive disorder, there is persistent depressive disorder, psychotic depression, postpartum depression, seasonal affective disorder (SAD), and bipolar

Figure 3: Some possible ways in which n-3s may fight depression

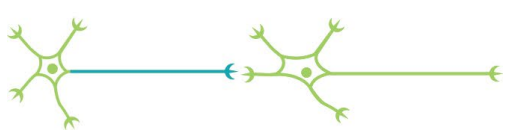
Reduced inflammation

Changes in neurotransmitters and receptors

Reduced oxidative stress



Increased neuroplasticity



Reference: Su et al. Expert Opin Investig Drugs. 2013 Dec.

> “Currently, there is not sufficient evidence to determine if omega-3s can play a role in the treatment of MDD.”

disorder. It is important to separate out these disorders into their distinct categories because the pathology, comorbidities, and treatments may range widely for each. By looking at just one form of depression, researchers can cut down on potential confounders that may disrupt the results of an analysis.

What role can nutrition play in fighting depression?
Disorders like MDD are complex and it is unlikely that one single treatment will work as a cure-all. It's more likely is that a multifaceted approach will yield the best results.

Regarding the topic addressed by this meta-analysis, the overall quality of one's fat intake may even be more important than specific omega-3 levels, although this topic hasn't been studied at length. Studies have shown a connection between depression and food quality, as people who eat more whole foods were less likely to get depression. A recent meta-analysis showed a correlation between high fruit and vegetable intake with decreased risk of depression as well. Neither of these studies established direct causation, but it is a reasonable assumption that eating a healthy diet of minimally processed foods may play a role in treating depression.

There is also emerging data looking into the role of the microbiota-gut-brain-axis and whether probiotics may be useful as a treatment. One trial demonstrated that probiotic interventions can “influence cognitive mechanisms that are known to determine vulnerability to mood disorders”. Another showed improvements on the Beck Depression Inventory after eight weeks of probiotic supplementation.

What should I know?

Currently, there is not sufficient evidence to determine if omega-3s can play a role in the treatment of MDD. More high quality data is needed to answer that question. As omega-3 fatty acids are an essential fatty acid, and they cannot be produced by our body, it is never a bad idea to ensure an adequate dietary intake. But, keep in mind that the evidence just doesn't support major improvements to your mood if you are an adult with MDD. ◆

So … omega-3 supplements aren't a panacea? Who'd a thunk. Discuss this topic at the ERD Facebook forum.