Trim the fat: the role of omega-3 fatty acids in psychopharmacology

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***Abstract*:** The American Psychiatric Association (APA) currently recommends the use of omega-3 fatty acid supplementation for depressive disorders, impulse-control disorders, and psychotic disorders in treatment guidelines. This review examines the evidence for efficacy of omega-3 fatty acids in depressive disorders, bipolar disorder, anxiety disorders, post-traumatic stress disorder (PTSD), and psychosis. Meta-analysis of randomized-controlled trials of omega-3 fatty acids for depression are inconclusive, with strong evidence of publication bias, sizable heterogeneity between included studies, and substantial methodological shortcomings in included trials. The large amount of heterogeneity in findings of RCTs of omega-3 fatty acids for unipolar depression is likely attributable to highly heterogeneous sample populations that are given different omega-3 supplements [which differ widely in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content, ratio, and dosage] as either adjunctive or monotherapy of other existing treatments, and then measure several different outcomes of depression symptomatology with likely incomplete blinding. Evidence of efficacy of omega-3 supplementation in treating psychosis, PTSD, anxiety, and bipolar mania is minimal. The current guidelines recommending the use of omega-3 fatty acids in adulthood psychiatric conditions should be revisited, especially given several recent negative studies examining the effects of omega-3 fatty acids for cardiovascular disease. Recommending likely ineffective treatment to patients, no matter how benign the side-effect profile, has opportunity cost (e.g. other more effective medications or therapies not being utilized) and likely affects patient compliance with other evidence-based treatments.

Keywords: depressive disorder, mood disorders, nutrition, omega-3 fatty acids, psychopharmacology, schizophrenia, supplements

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Introduction

Psychiatric disorders are characteristically chronic, with significant lifelong psychosocial morbidity, and are associated with increased mortality, specifically due to suicide and cardiovascular diseases.[1–3] The current psychopharmacological treatment algorithms have achieved only modest success, and the psychiatric disease burden is predicted to continue to increase in the upcoming decades.[4] As a result, researchers are exploring alternative treatments to improve outcomes. The evidence indicating that poor diet and nutritional deficiencies are important contributing factors to the psychopathology has prompted a focus on the use of nutritional supplements as monotherapies or adjunctive therapies.[5]

Omega-3 fatty acids are one of the most commonly prescribed supplements, and their use is predicted to rise, being projected to become a 4 billion dollar industry by the end of 2022.[6] They are considered beneficial for an array of physical illnesses, ranging from rheumatoid arthritis to coronary heart disease.[7] Thus, it is unsurprising that they are now being applied in psychiatry, as both a treatment of psychiatric symptoms and to lower risk of cardiovascular mortality.[8] As supplements, omega-3 fatty acids do not need to be

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tested and approved by the United States Food and Drug Administration (FDA) for efficacy and safety. Despite the FDA's policy regarding supplements, clinical practice should be dictated primarily by evidence, ideally from randomized clinical trials (RCTs) with clear end points and meta-analyses of such trials. This article reviews and discusses recent studies, trials, and meta-analyses to discuss whether there is enough evidence to justify recommending omega-3 supplements to patients.

The essentials of essential fatty acids: what, where, how, and why?

All fats play important roles in energy metabolism and body functions; however, the omega-6 precursor, linoleic acid (LA), and the omega-3 precursor, alpha-linolenic acid (ALA), are known as essential fatty acids as they cannot be synthesized in the body, thus making them a vital component of a healthy diet.[9] These are unsaturated fatty acids, that is, with double bonds between carbon atoms, as opposed to saturated fatty acids in which all the carbon atoms are 'saturated' with hydrogen atoms. Depending on the location of the double bond relative to the methyl end carbon (omega carbon), unsaturated fatty acids are categorized as omega-3 and omega-6 fatty acids.

Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are derived from alpha-linolenic acid (ALA). Fish is considered the primary source for omega-3 fatty acids, although they are also found in eggs, milk, and vegetables.[10] Plant oils such as sunflower, safflower, and corn oils are the main source of LA, which can be further metabolized to other omega-6 fatty acids such as gamma-linolenic acid (GLA) and arachidonic acid (AA).[11] Arachidonic acid can then be further converted into prostaglandins and leukotrienes, which are responsible for proinflammatory effects. In contrast, omega-3 fatty acids reduce the synthesis of the proinflammatory mediators by acting as competitive inhibitors to omega-6 fatty acids.[12]

Several sources suggest that humans evolved on a diet with an omega-6 to omega-3 fatty acid ratio (n–3: n–6 ratio) of approximately 1:1, whereas in the modern western diet the ratio is around 20:1.[13] This is due to the high quantities of omega-6 in popular foods. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, while increased omega-3 PUFA levels exert suppressive effects.[14] In addition to their anti-inflammatory and hypolipidemic effects, omega-3 fatty acids have been shown to affect serotonin and dopamine neurotransmission by altering the phospholipid composition, and thus the fluidity, of central nervous system cell membranes. These alterations modify the structure and function of membrane proteins.[15,16] Thus, the decrease in omega-3 fatty acids in the modern diet, and the skewed balance of fatty acids, can theoretically influence both somatic and psychiatric function through several mechanisms, and is considered detrimental to health.[17]

The therapeutic benefits of fish consumption, a primary source of omega-3 fatty acids, has been long recognized.[17] Perhaps the earliest mention of fish consumption as a therapy is in the Old Testament Book of Tobias, 'Then the angel said to him: Take out the entrails of the fish, and lay up his head, and his gall, and his liver for thee; for these are necessary for useful medicines'.[18] Historical and anecdotal evidence is reinforced by observations that show greater fish consumption is correlated with a lower prevalence of depression,[19–21] bipolar disorder,[22] and anxiety in the population,[23] and better outcomes in patients with schizophrenia.[24] The resurgence of interest in omega-3 supplementation as a potential treatment for psychiatric disorders resulted from the discovery that omega-3 fatty acid levels are reduced in the red blood cells of patients with depression,[25] bipolar disorder,[26] anxiety,[27] and schizophrenia.[28–30] Several double-blind placebo-controlled trials have studied the efficacy of omega-3 supplementation in mood disorders, anxiety, and schizophrenia, with mixed results. Despite the inconsistency in study outcomes, omega-3 fatty acid supplementation is now recommended by the American Psychiatric Association (APA).[8] The Omega-3 Fatty Acid Subcommittee assembled by the Committee on Research on Psychiatric Treatments of the APA advises that 'Patients with mood, impulse-control, or psychotic disorders should consume 1 g EPA + DHA per day. A supplement may be useful in patients with mood disorders (1–9 g per day).' [8]

Regardless of Biblical verses, ecological evidence, and plausible biological theories, steadily increasing sales of omega-3 supplements, and the endorsement by the APA clinical practice guidelines, should be based on the gold standard of evidence: RCTs and meta-analyses. The following sections review the current evidence and discuss the reasons why the omega-3 supplementation debate persists.

Epidemiological and tissue composition studies: causation, correlation, or confounders?

Population studies linking higher fish consumption with a lower prevalence of mood disorders and schizophrenia help support the hypothesis of the benefit of omega-3 fatty acids in psychiatry. Hibbeln and colleagues conducted comparisons on cross-national populations, and reported between 30 and 60 times higher prevalence rates of major depression,[31] postpartum depression,[32] and bipolar disorders[22] in countries with lower per capita fish consumption. Hedelin and colleagues found the risk of high-level psychotic-like symptoms were lower among women who ate fish three to four times per week compared with women who never ate fish.[33] However, these correlations are not consistent in schizophrenia or in mood disorders,[22,34,35] particularly when diet history questionnaires are used. This may be due to the various cultural, social, economic, and other factors confounding the simple correlation between disorders and fish consumption. The interference of confounding factors is further backed by the Albanese study, which showed that the link between fish consumption and depression disappeared when restricting the analysis to middle- and low-income countries, implying that the association could be explained by confounding demographic and lifestyle characteristics.[36] People without mental illnesses are more likely to have a better lifestyle, diet, and socioeconomic status, which is likely reflected in higher levels of omega-3 fatty acid consumption.

The preponderance of tissue compositional studies provides some more weight to the possible benefits of omega-3 fatty acids. They show decreased omega-3 fatty acid concentrations, specifically EPA and DHA, in red blood cell membranes of patients with depression,[25,26,37–41] bipolar disorder,[26,42] schizophrenia,[43–46] and anxiety disorders when compared with healthy controls.[27] However, it is essential to note that only two of the cited studies accounted for lifestyle and socioeconomic differences between the patient and control populations.[38,43] In addition, some findings could have been confounded by the effects of medication, diet, smoking, and storage artefacts.[47] Thus, this difference in levels implies only a correlation and not a causal relationship since it cannot be determined what came first: decreased omega-3 levels or the psychopathology. These studies aid in generating the hypothesis that omega-3 deficiency may contribute to mental illness and thus its supplementation may act as a possible treatment. Thus, they provide support for initiating RCTs to examine whether omega-3 fatty acid supplementation can decrease psychiatric symptoms.

RCTs and meta-analyses: what do they tell us?

Each different research methodology has its own advantages and yields a level of evidence quality. RCTs are known as the 'gold standard' of clinical research, offering the highest quality of evidence, as its design allows the minimization of several sources of biases at baseline. RCTs they offer information of temporal relations between the indication and the outcome. Only systemic reviews and meta-analyses are considered to offer a higher standard of evidence, as they amalgamate the outcomes of multiple RCTs.[48] Thus, nutritional psychiatry has turned to RCTs and meta-analyses in search of evidence of the benefits of omega-3 fatty acids. The following sections review and critically evaluate the validity of this methodology and its results. Table 1 synthesizes the results of previous meta-analyses conducted on the efficacy of omega-3 fatty acid supplementation for mood, anxiety and psychotic disorders.

Depressive disorders

Despite the ecological evidence associating low dietary intake of omega-3 fatty acids and depression, clinical trials examining the therapeutic effects of omega-3 supplements have shown inconsistent results. Thus, several meta-analyses have been conducted to uncover a common effect and possible sources of heterogeneity between trials. Earlier meta-analyses suggested a modest effect size (0.10–0.61), with a large degree of heterogeneity between

Table 1. Meta-analyses examining randomized-controlled trials of omega-3 fatty acids for mental disorders in adults.

Author	Year	k	Effect size	Significant	Heterogeneity	Publication bias	Population
Depression							
Appleton[49]	2006	12	0.13 SMD (95% CI: 0.01, 0.25)	Yes, but not clinically meaningful	Large, statistically significant	Present, no adjusted analysis	Any subjects with or without psychiatric or physical illnesses in trials which report depressive symptoms regardless of the primary outcome
Freeman[8]	2006	8	0.25 SMD (95% CI = 0.04, 0.44)	Yes, but not clinically meaningful	Large, statistically significant	Not assessed	Patients with unipolar or bipolar depression
Lin[50]	2007	10	0.61 SMD (95% CI = 0.21, 1.01)	Yes	Large, statistically significant	Present, no adjusted analysis	Patients with unipolar or bipolar depression
Martins[51]	2009	28	0.29 SMD, (95% CI: 0.12, 0.46)	Yes, but not clinically meaningful	Large, statistically significant	Present, minimal benefit when adjusted	Any subjects with or without psychiatric or physical illnesses in trials which report depressive symptoms regardless of the primary outcome
Kraguljac[52]	2009	13	Depressive symptoms 0.47 SMD (95% CI: 0.02, 0.92), mania symptoms 0.22 SMD (95% CI: –0.21, 0.65)	No	Large, statistically significant	Present, minimal benefit when adjusted	Subjects in randomized trials investigating the omega-3 efficacy in mood disorders including: BPD, MDD, and postpartum depression
Appleton[53]	2010	29	0.10 SMD (95% CI: 0.02, 0.17)	Yes, but not clinically meaningful	Large, statistically significant	Present, no adjusted analysis	Any subjects with or without psychiatric or physical illnesses in trials which report depressive symptoms regardless of the primary outcome
Sublette[54]	2010	15	EPA $\geqslant$ 60%: 0.53 SMD (95% CI: 0.28, 0.73), EPA $\leqslant$ 60% SMD –0.03 (95% CI: –0.20, 0.15)	Yes, only for EPA $\geqslant$ 60%	Present, magnitude not reported	Present, no adjusted analysis	Subjects whose primary complaint is a depressive episode with or without comorbid medical conditions
Martins[55]	2011	35	0.23 SMD (95% CI: 0.10, 0.36)	Yes, but not clinically meaningful	Large, statistically significant	Present, minimal benefit when adjusted	Any subjects with or without psychiatric or physical illnesses in trials which report depressive symptoms regardless of the primary outcome
Bloch and Hannestad[56]	2012	13	0.11 SMD (95% CI: –0.04, 0.26)	No	Large, statistically significant	Present, minimal benefit when adjusted	Subjects whose primary complaint is a depressive episode with or without comorbid medical conditions

(Continued)

Table 1. (Continued)

Author	Year	k	Effect size	Significant	Heterogeneity	Publication bias	Population
Giuseppe[57]	2014	11	0.56 SMD (95% CI: 0.20, 0.92)	Yes	Large, statistically significant	Not present, no adjusted analysis	Subjects with a DSM-defined diagnosis of MDD
Giuseppe[57]	2014	8	0.22 SMD (95% CI: 0.01, 0.43)	Yes, but not clinically meaningful	Moderate, statistically significant	Not present, no adjusted analysis	Subjects with depressive symptomatology but no diagnosis of MDD
Yang[58]	2015	8	0.65 SMD (95% CI: 0.18, 1.12)	Yes	Large, statistically significant	Not present, no adjusted analysis	Pregnant or nonpregnant women in trials which assess depressive symptoms regardless of primary diagnosis.
Appleton[59]	2015	26	0.30 SMD (95% CI 0.10, 0.50)	Yes, but not clinically meaningful	Present, magnitude not reported	Yes, no adjusted analysis	Subjects with MDD according to the DSM but excluding bipolar depression, perinatal or perimenopausal MDD or MDD secondary to other neuropsychiatric disorders.
Mocking[60]	2016	15	0.40 SMD (95% CI: 0.12, 0.68)	Yes	Large, statistically significant	Not present, no adjusted analysis	Subjects with MDD according to the DSM but excluding perinatal or perimenopausal MDD or MDD secondary to other neuropsychiatric disorders.
Schefft[61]	2017	10	0.19 SMD (0.00, 0.38)	Yes, but not clinically meaningful	Large, statistically significant	Present, no adjusted analysis	Any subjects with or without psychiatric or physical illnesses in trials which report depressive symptoms regardless of the primary outcome
Bai[62]	2018	9	0.20 SMD (95% CI: −0.06, 0.46)	No	Not reported	Not assessed	Subjects in trials that assess depressive symptoms in the elderly (age > 65 years)
Anxiety							
Kuan-Pin Su[63]	2018	19	0.37 SMD (95% CI: 0.03, 0.71)	Yes	Large, statistically significant	Not present, no adjusted analysis	Any subjects with or without psychiatric or physical illnesses in randomized or nonrandomized trials which report anxiety symptoms
Bipolar depression							
Kraguljac[52]	2009	13	Depressive symptoms 0.47 SMD (95% CI: 0.02, 0.92), mania symptoms 0.22 SMD (95% CI: −0.21, 0.65)	No	Large, statistically significant	Present, minimal benefit when adjusted	Subjects in randomized trials investigating the omega-3 efficacy in mood disorders including: BPD, MDD and postpartum depression

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Table 1. (Continued)

Author	Year	k	Effect size	Significant	Heterogeneity	Publication bias	Population
Sarris[64]	2010	5	Depressive symptoms 0.34 SD (95% CI: 0.035, 0.641), mania symptoms 0.20 SD (95% CI: −0.037, 0.433)	Only for depressive symptoms	Moderate, statistically significant for depressive symptoms	Not present, no adjusted analysis	Children and adults in randomized trials investigating omega-3 efficacy in bipolar depression (type 1 and 2)
Giuseppe[65]	2014	3	0.74 SMD (95% CI: 0.38, 1.10)	Only for depressive symptoms	Minimal, not significant	Not assessed	Adults in randomized trials investigating omega-3 efficacy in bipolar depression (type 1 and 2)
Perinatal Depression							
Jans[66]	2010	7	0.03 SMD (95% CI: −0.13, 0.18)	No	Not significant	Not present, no adjusted analysis	Pregnant or postpartum women in trials that assess depressive symptoms regardless of the primary outcome
Giuseppe[57]	2014	3	0.24 SMD (95% CI: −0.73, 1.21)	No	Not reported	Not assessed	Pregnant women with MDD as the primary diagnosis and outcome
Schizophrenia							
Freeman[8]	2006	3	2.76 SMD (95% CI: −1.15, 6.37)	No	Not reported	Not assessed	Adults with schizophrenia as the primary diagnosis and outcome
Fusar-Poliand Berger[67]	2012	4	0.24 SMD (95% CI: −0.03, 0.51)	No	Not significant	Not present, no adjusted analysis	Adults with schizophrenia as the primary diagnosis and outcome
Attention deficit hyperactivity disorder							
Bloch and Qawasmi[68]	2011	10	0.31 SMD (95% CI: 0.16–0.47)	Yes	Not significant	Not present, no adjusted analysis	Children in omega-3 supplementation trials that target ADHD symptoms (diagnosed or undiagnosed, with or without comorbid conditions) and used a validated rating scale to measure ADHD severity during the trial.
Gillies[69]	2012	5	−0.17 SMD (95% CI: −0.38, 0.03)	No	No	Not assessed	Children with ADHD
Edmund[70]	2013	9	0.17 SMD (95% CI: 0.01, 0.34)	Yes, but not clinically meaningful	Not reported	Not assessed	Children with a diagnosis of ADHD or that met accepted criteria for clinical levels of symptoms on validated ADHD rating scales given both omega-3 and omega-6 supplements.

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Table 1. (Continued)

Author	Year	k	Effect size	Significant	Heterogeneity	Publication bias	Population
Puri and Martins[71]	2014	18	−0.19 SMD (95% CI: −0.3, −0.09)	Yes, but not clinically meaningful	No	Yes, significance lost after adjusted analysis	Children with ADHD
Hawkey and Nigg[72]	2014	16	0.26 SMD (95% CI: 0.15, 0.37)	Yes	Moderate, statistically significant	Yes, SMD decreased to clinically unmeaningful 0.16 [95% CI: 0.03, 0.28] after adjusted analysis	Children with ADHD
Chang[73]	207	7	0.38 SMD (95% CI: 0.20, 0.56)	Yes	No	Not reported	Children with ADHD
Autism							
James[74]	2011	2	Social interaction 0.82 SMD (95% CI: −2.84, 4.48) Communication 0.62 SMD (95% CI: −0.89, 2.14) Stereotypy 0.77 SMD (95% CI: −0.69, 2.22) Hyperactivity 3.46 SMD (95% CI: −0.79, 7.70)	No	No	Not assessed	Children and adults diagnosed with ASD by established diagnostic criteria or standardized instruments.
Horvath[75]	2017	5	Lethargy 1.98 SMD (95% CI: 0.32, 3.63) Externalising −6.22 SMD (95% CI: −10.9, −1.59) Social skills −7 MD (95% CI: −13.62, −0.38)	Yes, improvement of lethargy and worsening of externalising behavior and social skills.	No	Not assessed	Children diagnosed with ASD by established diagnostic criteria or standardized instruments.
Mazahery[76]	2017	4	Repetitive restricted behaviors −1.08 SMD (95% CI: −2.17, −0.01) Social skills −1.96 SMD (95% CI: −3.5, 0.34)	Yes	Large, statistically significant	Not assessed	Children and adults diagnosed with ASD by established diagnostic criteria or standardized instruments.
Cheng[77]	2017	6	Hyperactivity −2.69 SMD (95% CI: −5.36, −0.02) Lethargy −1.97 SMD (95% CI: −3.57, −0.37) Stereotypy −1.07 SMD (95% CI: −2.11, −0.03) Inappropriate speech −0.2 SMD (95% CI −0.63, 0.23) Irritability 0.02 SMD (95% CI: −0.35, 0.38)	Yes, only for hyperactivity, lethargy and stereotypy and clinically not meaningful	No	Not present, no adjusted analysis	Children diagnosed with ASD by established diagnostic criteria or standardized instruments.

studies and evidence of publication bias.[8,49,50,52,53,57] However, most of these meta-analyses did not adjust their results to account for publication bias, and included studies that examined depressive symptoms in patients with other primary disorders, such as bipolar disorder, schizophrenia, obsessive-compulsive disorder, personality disorders, or chronic fatigue syndrome, which is likely to increase heterogeneity between trials. In addition, trials which report depressive symptoms as a secondary measure are more prone to publication bias, since secondary measures are often only reported by authors if statistically significant.

These issues were addressed in the Bloch and Hannestad meta-analysis, which only included studies where depression was the primary indication, and adjusted for publication bias using the trim-and-fill method.[56] They found that omega-3 supplementation had a small and insignificant effect on depression [SMD = 0.11, 95% confidence interval (CI): –0.04, 0.26 $p = 0.14$, fixed effects model] and with significant heterogeneity between studies. After correcting for publication bias, nearly all the effect of omega-3 fatty acids was eradicated (SMD = 0.01, 95% CI: –0.13, 0.15, fixed effects model) and the results remained insignificant. Higher depression severity at baseline, shorter trial duration, and lower trial quality were associated with greater efficacy. In fact, trials that included subjects with more severe depression tended to be of lower quality, with fewer subjects (thus more prone to publication bias), and employed completer rather than intention-to-treat (ITT) analysis. Thus, it is difficult to tease apart whether there was a true correlation, or these associations were the result of confounding factors.

The dosage of EPA or DHA, and whether it was administered as monotherapy or as an adjunct to medication, did not significantly influence efficacy. However, in a similar meta-analysis by Mocking, depressive symptoms showed significant improvement with omega-3 supplementation (SMD = 0.398, 95% CI: 0.114, 0.682, $p = 0.006$, random effects model), especially for higher doses of EPA and in patients taking antidepressants.[60] Random effects models are less conservative when confronting possible publication bias as they give greater weight to smaller trials where selective publication is more likely to occur. Earlier publication year was also associated with better omega-3 supplementation outcome. There are several factors that could account for this. The requirement for public registration of trials and their primary outcome is relatively recent, resulting in lower publication bias in later trials. In addition, earlier trials were of lower quality, with methodological issues such as potential unblinding due to the fishy aftertaste of early omega-3 preparations.[65] This theory is further reinforced by the association of shorter trial duration with a greater response since the placebo effect is known to wear off with time.[78] Later formulations of omega-3 supplements have masked this taste and result in better blinding. It is possible that these earlier, lower quality studies with blinding issues are driving the measured effect size rather than the actual efficacy of the supplementation.

Bipolar disorder

As with depression, RCTs investigating the effect of omega-3 supplementation on bipolar depression have shown contradictory results. Most, including the largest omega-3 supplementation for BPD study to date ($n = 116$)[79] show no significant improvement in symptomatology.[80–83] In contrast, Stoll and colleagues, reported efficacy of omega supplementation over placebo for depressive, but not manic, symptomatology in 30 patients.[84] Another three-arm study (ethyl-EPA 1 g/day, 2 g/day or placebo) of 75 patients with bipolar disorder[85] found that if the two active arms were combined for analysis, they showed efficacy over placebo. However, it is worth noting the disproportion of psychiatric medication use: at baseline, 51% of patients in the active groups were on lithium and 49% on antidepressants compared with 34.6% and 26.9%, respectively, in the placebo group. In sum, all RCTs are limited by small sample sizes, or by the association of omega-3 supplementation with conventional BPD treatment.

A meta-analysis of six RCTs found that omega-3 supplementation in bipolar disorder was associated with statistically significant moderate effect (0.34, $p = 0.029$) in depressive, but not manic, symptoms.[64] There was moderate heterogeneity between studies on the outcome of depressive symptoms ($I^2 = 30\%$; $p = 0.21$), but not on the outcome of manic symptoms ($I^2 = 0\%$; $p = 0.98$). Meta-regression analysis between sample size and effect size, however, revealed that studies with smaller sample sizes had larger effect sizes ($p = 0.05$), consistent with possible publication bias. Thus, the same limitations mentioned for the RCTs of omega-3 fatty acids in unipolar depression may have influenced the results of the meta-analysis of the bipolar disorder literature as well.

Since both depression and bipolar disorders have ecological evidence correlating them to decreased omega-3 intake, it stands to reason that suicidality, highly comorbid with both, might show a similar correlation.[86,87] Thus, their deficiency has been implicated as a contributing factor to suicide risk, with supplementation being considered protective. However, this is not supported by study data, which have shown no statistical difference in omega-3 levels of those engaged in suicidal behavior and controls.[88]

Perinatal and postpartum depression

The antidepressant potential of omega-3 fatty acids is of particular interest in perinatal depression because omega-3 fatty acids are considered safe during pregnancy, unlike certain antidepressant medications. In fact, due to increased metabolic demand for omega-3 fatty acids during pregnancy,[89] it is recommended that women consume two or more portions of fish weekly, which approximates to the consensus guidelines of a minimum of 200 mg of DHA per day, in order to optimize obstetrical and fetal outcomes.[90] However, despite the increased need for omega-3 fatty acids during pregnancy, dietary intake during pregnancy is even more diminished in the US, especially after the FDA issued mercury advisories regarding fish intake during pregnancy.[91] Thus, if effective, omega-3 supplements could be highly desirable as safe mono- or adjunctive antidepressants therapy that potentially provides additional perinatal benefits.

Studies examining the relationship with seafood intake and perinatal depression have given mixed results, with some demonstrating an inverse correlation,[92] and others not showing any relationship.[93] A prospective study of more than 54,000 Danish women found that, although there was an association between lower dietary intake and the risk of developing perinatal depression, fish intake was also strongly associated with potentially confounding sociodemographic factors.[94] Tissue compositional studies have shown lower levels of omega-3 fatty acid indices and an increased n–6:n–3 ratio during pregnancy are significantly associated with perinatal depression.[41] These observational studies are subject to the same issues with confounding as discussed earlier for depression. Thus, despite this association, RCTs assessing fatty acid supplementation have shown inconsistent and inconclusive effects, with only two small trials out of a current total of 11 showing significant efficacy.[95] Unsurprisingly, meta-analyses of these RCTs did not find omega-3 supplementation more effective than placebo in the treatment or prevention of perinatal depression.[57,66]

Schizophrenia

Several RCTs have investigated the effects of omega-3 supplementation in schizophrenia, with mixed results. Some have shown efficacy in decreasing the Positive and Negative Syndrome Scale (PANS) score,[96–98] and others found no significant effect at all.[99–101] There have also been studies looking at possible use of omega-3 supplements to prevent transition to psychotic disorders in high risk populations. A RCT with 81 adults found that omega-3 fatty acid supplements reduced the risk of progression to psychotic disorders by 22.6%.[102] However, another much larger RCT with 304 participants was unable to replicate these findings and found no difference between omega-3 supplements and placebo.[100] While RCTs have given contradictory results, all meta-analyses have consistently concluded that omega-3 supplementation does not significantly alleviate symptoms of schizophrenia. A Cochrane review of eight studies of omega-3 supplementation in patients with schizophrenia found no significant improvement in the PANS score.[103] Omega-3 supplementation did not decrease tardive dyskinesia symptoms as measured by the Abnormal Involuntary Movement Scale. Another meta-analysis including 335 patients with schizophrenia failed to show any beneficial effects of EPA augmentation on psychotic symptoms.[66] Freeman and colleagues found that omega-3 supplementation did not improve the PANS total score. Unlike the meta-analyses of omega-3 efficacy in other mental disorders, there was no significant heterogeneity between studies, and all effect sizes were similar.[8]

Anxiety

Decreases in EPA and DHA have been found in the RBC membranes of nondepressed patients with social anxiety in comparison with normal controls.[27] Like in the depression studies, no inference can be drawn regarding causation, other than the fact that decreased intake or decreased uptake of omega-3 fatty acids into RBC membranes is associated with social anxiety.[104] It is unknown whether similar decreases occur in other anxiety disorders, as is how any changes in omega-3 PUFA levels may be correlated with other confounding factors such as socioeconomic class.[105] Greater deficits in EPA and DHA were found in

the plasma of depressed patients with comorbid anxiety in comparison with depressed without comorbid anxiety patients and healthy controls.[54]

In terms of RCTs, most trials involving mood disorders have not investigated anxiety symptoms, or have specifically excluded patients with anxiety, despite the high comorbidity between anxiety and mood disorders. There have been RCTs that suggest omega-3 supplementation decreases in anxiety symptoms in substance abusers,[106] patients with acute myocardial infarctions,[107] and healthy medical students facing exams.[108] However, all these studies were limited by small sample sizes.

To date, there has only been one meta-analysis on the efficacy of omega-3 fatty acids in the reduction of anxiety. While it showed a significant effect (k = 19; Hedges g = 0.37; 95% CI, 0.08–0.67; $p = 0.01$), it included nonplacebo-controlled trials, studies in which subjects had a primary diagnosis other than anxiety, and in which the primary outcome measure was not anxiety, utilized per-protocol numbers when intent-to-treat analysis was unavailable, and did not control for publication bias. In addition, there was significant heterogeneity in the results (Cochran Q = 179; $df = 18$; $I^2 = 90\%$; $p < 0.001$).[109] Due to the issues addressed, current literature on the effects of omega-3 supplements on anxiety should be regarded with scepticism.

Post-traumatic stress disorder

Epidemiological studies have yielded contradictory results regarding the presence of a relation between erythrocyte membrane fatty acid concentrations and post-traumatic stress disorder (PTSD) symptoms. A study on 95 participants found lower levels of DHA and eicosatrienoic acid in participants with PTSD symptoms compared with healthy controls.[110] However, when adjusting for sociodemographic and dietary factors, only DHA remained significantly lower. A major limitation in this study is that it did not screen for trauma exposure in the healthy controls. Due to small effect sizes and limited effect of alterations authors recommended further investigation of the assumed role of FA metabolism and its mechanisms in PTSD before implementing any further FA supplementation studies.

A 12-week RCT in Japan found that omega-3 supplementation in accident survivors resulted in higher erythrocyte EPA levels and lower heart rate, both at rest and when shown script-driven imagery, compared with placebo controls.[63,111,112] However, there was no difference in skin conductance or the clinician-administered PTSD scale (CAPS) scores.[63,111,112] Another very small open-label trial ($n = 6$) found no PTSD symptom improvement after omega-3 supplementation, and had to be severely curtailed in response to patient complaints of adverse effects.[113]

There are not enough RCTs to conduct meta-analyses on the efficacy of omega-3 fatty acids in PTSD. Given the sparsity of evidence, it would be a reach to consider omega-3 fatty acids a 'nutritional-armor' preventing or mitigating symptoms of PTSD.[114]

Borderline personality disorder

Borderline personality disorder (BPD) is usually treated with psychotherapy; however, it can be supplemented with pharmacotherapy to manage associated mood and anxiety symptoms. There have been a few trials that evaluated efficacy of omega-3 supplementation in decreasing BPD symptoms. Zanarini demonstrated a significant decrease in aggression and depression in those given 1 g/day ethyl EPA versus those on placebo after 8 weeks.[115] However, the low sample size ($n = 30$) and small differences in baseline values (–0.8 for Modified Overt Aggression Scale and –1.5 for MADRS) cast doubts on the validity and utility of the results. The same issues arise for the other two trials by Hallahan,[116] and Bellino,[117] which showed small significant changes in small sample sizes of BPD patients. Taking into account the high risk of bias due to blinding issues, attrition bias, and publication bias associated with omega-3 supplementation, currently, there is little evidence to recommend omega-3 fatty acids in the treatment of BPD, especially when compared with the efficacy of currently available medication.[118]

Attention deficit hyperactivity disorder

While current treatments such as psychostimulants are generally quite effective in the treatment of attention deficit hyperactivity disorder (ADHD), a substantial proportion of children with ADHD, approximately 30%, do not exhibit significant benefit on stimulants.[119] Therefore, alternative treatments are still needed for ADHD. Deficiency in omega-3 fatty acids has been considered as one of the pathogenetic mechanisms of ADHD,[120] thus omega-3 supplements could be a potential alternative. This is supported by the fact that children with

ADHD have lower essential fatty acid levels than healthy children, and essential fatty acid deficiency negatively correlates with ADHD symptoms.[121] Surprisingly, case–control studies have shown no differences or higher dietary intake of omega-3 fatty acids in ADHD.[120,122–124] RCTs have shown heterogenous results, with some showing benefit in clinical symptoms and cognitive performance and others no improvement.[125–129] Similarly, there have been several meta-analyses, some that show benefit and others that do not.[68–73,130] Potential causes of conflicting results are heterogenous populations of both children and adults,[71] including subjects with diagnosis other than ADHD,[71,72] and mixed interventions such as including omega-3 supplements with other supplements.[69,70] Regardless, omega-3 fatty acids are likely, at best, modestly effective for the treatment of ADHD, with a treatment benefit that is substantially less than other stimulant and nonstimulant treatments for ADHD.

Autism

A meta-analysis of 15 RCTs found that those with Autism Spectrum Disorder (ASD) had lower DHA, EPA, arachidonic acid, and total n–3:n–6 ratio than normal controls.[131] This could be due to genetic causes or could be environmental since children with ASD show higher food selectivity and consume less omega-3 than typically developing children.[132] In either case, it is plausible that omega-3 supplementation might be beneficial and could potentially ameliorate ASD symptoms, especially when taking into account the role of fatty acids in neural development. To date, the results of RCTs and the five subsequent meta-analyses have been inconsistent.

In the meta-analysis by Bent and colleagues, published in 2009, the authors set broad inclusion criteria incorporating all omega-3 trials of any type, dose, and duration that addressed both the core or associated symptoms of ASD.[133] Six studies were identified; one RCT, four open-label trials and one case-study; no significant evidence to support clinical recommendations was found. In 2011, a Cochrane review by James, Montgomery and Williams[74] included only two RCTs and assessed social interaction, communication, stereotypy, and hyperactivity.[74] The authors reached the same conclusion as the review by Bent and colleagues.[133] In 2017, three more meta-analyses on the effects of omega-3 supplementation in ASD were published.[75,77,131] Mazahery included four RCTs, and found small but significant improvements in social interaction and repetitive and restricted interests and behaviors, and no effects on communication, hyperactivity, or irritability. However, they used a fixed effects model, the results of which cannot be extrapolated to the general population,[134] and they did not assess the presence of publication bias. In contrast, Horvath and colleagues,[75] and Cheng and colleagues,[77] did utilize a random effects model. Although Horvath and colleagues identified five trials, only two of those were included for the assessment of treatment outcomes [i.e. change in Aberrant Behavior Checklist (ABC)].[75] Apart from a small significant improvement in the lethargy subscale, they found no significant improvements on most subscales of the ABC. In fact, the Behavioral Assessment System for Children parents' ratings indicated significant worsening of both externalizing behaviors and social skills. Thus, the authors concluded that supplementation of omega-3 fatty acids did not benefit patients with ASD. Cheng and colleagues identified six trials and found small significant improvements in hyperactivity, lethargy, and stereotypies, and no significant effects on global functioning or social interactions. Thus, even when the meta-analyses found significant differences between the omega-3 and placebo groups, there has been no consistency on which symptoms are affected and whether they are exacerbated or ameliorated. The only consistent conclusion drawn by the authors was that, to date, there is not sufficient evidence that omega-3 fatty acid supplementation improves either the core or associated symptoms of ASD.

RCTs and meta-analyses: gold standard or lead weight?

While RCTs and meta-analyses are the established 'gold standard' informing evidence-based medicine, when interpreting and applying their results it is essential to consider their limitations within the context of the field of research. The sparse, inconsistent, and contradictory results of omega-3 supplementation RCTs, and the persistently high heterogeneity in the meta-analyses, speak to certain complexities specific to omega-3 supplements and nutritional psychiatry research that need to be addressed in order to successfully advance this field.

RCTs and the compounded complexities of psychiatric and omega-3 supplement research

Unlike other medical specialities that rely on biological tests, psychiatric diagnosis depends on the reporting of a cluster of symptoms that meet

predefined psychiatric criteria.[135] These diagnostic definitions are imprecise, as they group together patients with overlapping, or completely disparate, symptoms, different aetiologies (ranging from environmental trauma to genetic susceptibility), severities, and comorbidities within the same heterogeneous sample. In addition, the subjective self-reporting measures are more susceptible to bias and placebo response than objective biological measures.[136] Studies are relatively small, generally involving, at most, a few hundred subjects. Treatment effect sizes are usually small and easily obfuscated by spontaneous recovery and placebo response rates. There is consistent evidence of selected or distorted reporting in RCTs.[135] Thus, RCTs in psychiatry may have a bias in design, recruitment, patient populations, data analysis, and presentation of findings.

The difficulties of nutrition research add another layer of complexity to psychiatric RCTs. In contrast to serious deficiencies, the effects of modest changes in nutrient intake are difficult to study reliably. Larger effect sizes are more conceivable for complex lifestyle patterns that sum the effects of multiple nutrients and behaviors than as a result of increasing a single nutrient in the diet.[137] Additionally, protective nutritional combinations vary with age, environmental exposure, genetic, and metabolic profiles. Given that these and the nutritional variables are correlated, as well as the complex associations of eating patterns with varying social and behavioral factors that also affect health, no current dataset has sufficient information to address the confounding associations. In such situations, where the effect size is small, even minimal confounding can create noise that drowns out any genuine effect, and meta-analyses just add spurious precision to the noise. Disentangling the potential influence on health outcomes of a single dietary supplement from the extensive confounding variables is challenging, if not impossible. As with psychiatric research, nutrition RCTs usually have small sample sizes and utilize unreliable and inconsistent measures that often tend to have selective reporting bias. The dietary consumption of the supplement being studied is difficult to control, or capture, with the questionnaire methods used by most studies.

Added to this, RCTs of omega-3 fatty acid supplements face a few unique challenges. Firstly, omega-3 fatty acids supplements containing both EPA and DHA have been used separately and combined, in various doses and ratios in trials. This variable complicates the selection of the specific components to be evaluated. For example, in certain meta-analyses, subgroups of EPA $\geqslant$ 60% and EPA $\leqslant$ 60% were selected since a difference was noted between their efficacy. This *post hoc* grouping, based on arbitrary cut off dosage percentages, may lead to significant findings where there are none, inadvertently fishing for spurious cures.[138,139]

Secondly, omega-3 fatty acid supplements are vulnerable to oxidation, and are affected by dietary and consumptive practices.[140] Investigators attempt to control for this by excluding smokers and people who already consume high levels of omega-3 in the diet[141,142]; however, this is not by any means adequate since self-reporting is not reliable and cannot cover every potential factor. Another potential solution could be to use biological measures to ascertain fatty acids levels, although more sophisticated measurements based on biochemical, web, camera, mobile, or sensor tools have not necessarily shown a reduction in bias.[143]

This, unfortunately, leads on to the third challenge posed by omega-3 fatty acids. Unlike biological markers such as cholesterol or glucose, there are no standardized methods for measuring or clearly defined optimal levels of fatty acids. There are multiple species of fatty acids that can be measured in multiple lipid pools (red blood cells, white blood cells, whole blood, plasma), where they are found in varying proportions,[144] and serum levels may not reflect levels in the brain, which, in turn, may not reflect changes in symptomatology.[140] Since EPA (which has anti-inflammatory activity) and AA were found to compete as substrates, the idea that omega-3 fatty acids were anti-inflammatory and omega-6 fatty acids were proinflammatory became commonly accepted.[145] Thus, a ratio of omega-3 to omega-6 (n–3:n–6) was suggested to represent the body's potential inflammatory response to insult.[146] As increased inflammatory states have been found to play a role in the pathophysiology of depression,[147] bipolar disorder,[148] schizophrenia,[149] and cardiovascular disorders,[147] increasing the 'good' omega-3 fatty acids and lowering the 'bad' omega-6 fatty acids could be beneficial.

However, it has recently been discovered that the biochemistry of fatty acids and their metabolites is much more nuanced, with both omega-3 and omega-6 having proinflammatory and anti-inflammatory activity, and neither is 'all good or all

bad'.[150] In fact, higher levels of linoleic acid have been associated with reduced inflammatory status,[151–153] and there is now a large body of research that shows neutral or beneficial effects of dietary intake or blood levels of linoleic acid on risk for cardiovascular disease.[154–156] These revelations have led to questioning the usefulness of a ratio 'where the good is divided by the good'.[157] In RCTs, the components of the n–3:n–6 ratio are rarely defined, and depend on how many fatty acids are quantified in a given study. Dietary advice to lower this ratio is equally ambiguous and problematic. Not only does it make the incorrect, implicit presumption of metabolic equivalence of fatty acids within the same class, there at least five ways to lower the ratio, each with different resulting biochemistry and consequences.[145] Thus the ratio is imprecise, nonspecific, based on invalid assumptions, and not conducive for use in RCTs or when giving dietary advice. Unsurprisingly, calls have been made to abandon its use altogether.[157–159]

Meta-analyses of omega-3 RCTs: weighted averages of expert opinions or effect sizes?

Combining the results of individual studies by conducting a meta-analysis increases the number of participants, thereby increasing statistical power. However, omega-3 RCTs have methodological differences that present special challenges for meta-analyses, thus weakening the argument for combining their results. As discussed, these RCTs contain highly heterogeneous populations that are given either adjunctive or monotherapy of omega-3 supplements, differing widely in EPA and DHA content, ratio and dosage, and, finally, measure outcomes by self-reports or questionably meaningful biological tests that also vary from study to study. In these cases, combining studies increases variability in findings that can reduce statistical power, drowning out the real effect with the variability; thus, a null result may reflect heterogeneity rather than the absence of a signal. In this situation, instead of focusing on the summary of effect size, meta-analyses may be better employed to explore the heterogeneity of results, elucidating potential causes for different results using subgroup analyses. Sensitivity analyses, which systematically remove lower studies from the analysis, sometimes help by focusing, for example, on similar higher-quality studies. However, this can also be a problem since the nutrition literature can easily be shaped by investigators who report nonprespecified results that are possible to analyze in very different ways, giving different outcomes. One possible example of this could be the *post hoc* selection of the $\geqslant$ 60% EPA trials subgroup, which resulted in giving a moderate effect size for depression,[138] when a previous meta-analysis showed no significant EPA dose-dependent efficacy.[56] Consequently, meta-analyses can easily become weighted averages of 'expert opinions' instead of 'effect sizes' if prespecified selection and outcome criteria are not adhered to.[137]

The verdict: fish oil or snake oil?

Whether epidemiological, biological, RCT, or meta-analysis, all interventional research is ultimately conducted to answer one question: to prescribe or not to prescribe? The APA recommends the use of omega-3 fatty acid supplementation despite conceding that 'results remain inconclusive in most areas of interest in psychiatry'.[8] The reasoning presented is that they appear to have negligible risks and some potential benefit in unipolar depression. In addition, they add that the potential protective cardiovascular benefits may be particularly beneficial as smoking, obesity, and the metabolic side effects of psychotropic medication contribute to increased cardiovascular mortality in the psychiatric population.

While it is granted that there are plausible biological mechanisms and observational studies that support a role of omega-3 fatty acids in psychopathology, unfortunately, current evidence from RCTs and meta-analyses is inconclusive given the high heterogeneity and inconsistency of findings. The most common adverse effects are diarrhoea, flatulence, and elevated LDL-C levels.[160] In high doses, some studies have shown omega-3 fatty acids to interfere with clot formation and thus increasing epistaxis, bleeding gums, and even hemorrhagic stroke.[161–164] Therefore, the use of greater than 3 g daily should be monitored by a physician due to the risk of bleeding.[8] Adding further ambiguity to omega-3 fatty acids is that, since they are supplements, they are not regulated or controlled by the FDA and do not need to satisfy their safety or efficacy criteria. The manufacturers produce many variations of EPA and DHA ratios and dosages of different quality, none of which have shown conclusive evidence of being effective. As for the cardiovascular benefits, most recent RCTs and meta-analyses show no evidence of any change in cardiovascular outcomes. The most recent being a meta-analysis of 10 trials

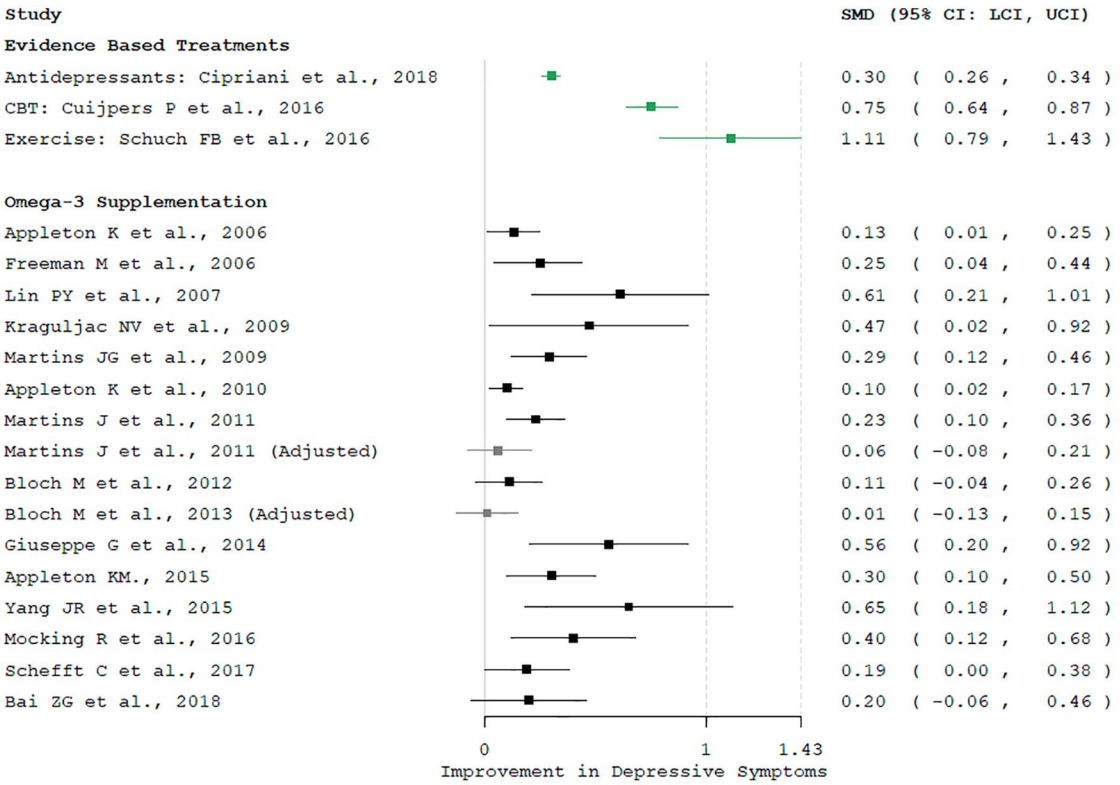

Figure 1. Compares the estimated benefits of omega-3 fatty acids on depressive symptoms in published meta-analysis compared with the measured benefits of other evidence-based treatments for depressive disorders.

with 77,917 participants that demonstrated that omega-3 supplementation for an average of 4.4 years had no significant association with reductions in fatal or nonfatal coronary heart disease or any major vascular events.[165] Among many researchers in the field, the status omega-3 supplementation has fallen from 'effective' to 'no proof of effectiveness' to, recently, 'proof of no effectiveness'.[166]

Psychiatric disorders and long-term therapy (such as with supplements and most psychiatric treatments) are already associated with decreased compliance. Adding omega-3 supplements could further decrease compliance, which is inversely correlated to the number of prescribed medications,[167] possibly due to additional cost and a more complex regimen. In addition, focusing on the effects of supplements or any additional pills of dubious effects takes attention away from making lifestyle changes or engaging in other psychotherapeutic interventions that may be of real benefit. Figure 1 emphasizes this point by comparing the measured benefits of omega-3 fatty acid supplementations in meta-analyses to those of other available, evidence-based interventions, using depression as an example. In conclusion, it does not seem beneficial to prescribe any intervention regardless of how minimal its adverse effects are unless there is conclusive evidence of its benefit. This is not the case for omega-fatty acid supplementation. In its stead, recommending therapy,[168] medication,[169] exercise,[170] and a healthier diet with two or more servings of fish (as per the Omega-3 Fatty Acid Subcommittee recommendations) would be preferred in most cases.[8]

Future directions

Observational and epidemiological studies are insufficient to provide definitive evidence regarding the efficacy of omega-3 supplementation for mental health conditions. Simply put, potential confounding by socioeconomic status, lifestyle characteristics (such as exercise) and culture background cannot be ruled out. These observational studies provide good evidence to investigate the efficacy of omega-3 fatty acids in RCTs. The results of RCTs of omega-3 trials in

psychiatric disorders suggest that omega-3 fatty acids likely work somewhere between minimally to not at all. Further methodological issues with the underlying trials (heterogeneity in populations, omega-3 pill content, blinding issues, non-standardized biological measures, utilization of non-ITT analyses etc.) combined with probable publication bias in the literature, suggest the benefits are overstated. To make significant strides in nutritional research of mental health disorders there would need to be 'mega-trials' with much larger sample sizes (like in the study of cardiovascular disease) in order to detect these modest benefits. It is difficult to justify the significant expenditure of such trials based on the available results from RCTs. Another approach would be to target mental health populations particularly likely to benefit from supplementation in terms of baseline intake, genetic, or biological risk factors. Unfortunately, this strategy has not been very successful thus far, as our knowledge regarding who might particularly benefit from omega-3 fatty acid supplementation is thin. Future trials will also be more successful if they can minimize the influence of lifestyle and nutritional patterns. This could be accomplished by recruiting study populations where these factors are fairly uniform, such as those found in the army, monasteries, and prisons (only in the absence of obvious ethical implications).

Comparison studies of EPA and DHA could be conducted to illuminate any differences in their efficacy, followed by optimal dose-finding trials if successful. Incorporating more objective measures of neuropsychological performance (such as executive functioning), biochemical levels, and neuroimaging techniques will minimize falsely inflated effects, such as those due to placebo response and investigator biases. They will also shed a light on possible mechanisms of action. Identifying and agreeing upon a standardized, reliable, and meaningful measure of omega-3 fatty acids is essential to link changes in subjective symptomatology to omega-3 supplementation. Harris recommends RBC EPA + DHA content instead of n–3:n–6 as a possible contender, which is responsive to changes in EPA and DHA intake and has shown to provide independent predictive information for a variety of diseases.[145] This is also important since differences in genetics and physiology result in individual variability in blood omega-3 levels after receiving a fixed dose.[171] In addition, changes in blood levels do not necessitate changes in neurophysiology.

Neuroimaging can be employed to investigate any changes in neuronal membrane fluidity or integrity that may be associated with omega-3 blood levels as well as decreased symptomatology. Preliminary studies have linked omega-3 supplementation to increased T2 relaxation time, indicating greater membrane fluidity,[81] and increased N-acetyl aspartate, a marker of neuronal integrity[80]; however, the sample sizes were small and neither were able to show any symptom improvement. It is unknown whether the decrease in peripheral omega-3 fatty acids seen in psychopathology arises from dietary deficiencies, metabolic aberrations, or an interaction of both. Genome-wide association studies and epigenetics could contribute to our understanding of this pathogenesis as some research suggests the possibility of genetic variation that influences the extent to which individuals require omega-3 fatty acids.[104]

Meta-analyses, especially those involving nutrition, impact health policy. They carry considerable weight in the media and the public, and thereby could result in potential harm if misinterpreted. Thus, the peer-review process must regulate this to ensure that certain standards of meta-analytic procedures are maintained. This could include review by both editors with knowledge of meta-analysis, and those who are experts in the subject being examined; requiring confirmation by the authors of the original studies that their data were accurately reported; requiring authors to share their data, analysis, and other methodological specifics to allow reproducibility; and prioritizing meta-analyses utilizing original primary outcomes over those using secondary outcomes or published summary data; justifying and adhering to prespecified selection and outcome criteria; and (6) scrutiny of potential conflicts of interest in meta-analyses and the included studies. This could be enabled by a permanent financial disclosure registry.[172] This is crucial since the food industry is cognisant of the impact of science-driven headlines, and has a history of investing in RCTs and meta-analyses. A review of 111 industry-funded studies showed that the funding source was significantly correlated to study results and conclusions; similarly, examining the conflicts of interests of many omega-3 fatty acid papers reveals that they are no exception to the rule.[173] Even in the absence of funding, allegiance bias exists amongst researchers; this too can be minimized by the recommended steps.

Nutrition is a complex and nuanced field that is cursed with oversimplified provocative headlines that resonate and capture the public attention. It is therefore vital that researchers and scientists take a more proactive part in disseminating research to the public so that it is not sensationalized by the media or selectively reported by the supplement industry. Omega-3 fatty acid supplementation for cardiovascular disease is a cautionary tale in this regard as it is much harder to contradict a practice once it is accepted. In 2002, the AHA endorsed omega-3 fatty acids for the secondary prevention of heart disease.[174] Since then, from January 1, 2005, until December 31, 2012, a total of 9 out of 10 RCTs and 5 out of 6 meta-analyses published in leading journals have reported no cardiovascular benefit of omega-3 fatty acids.[175] These publications have resulted in several news stories, but neither of these have had much effect on the use of supplements, as 10% of adults in the US still take omega-3 supplements, most commonly for heart disease.[166] In fact, between 2007 and 2012, US omega-3 supplement sales have increased from $425 million to $1043 million.[175] It is understood that, in order to counter an established practice, research needs to overcome both researcher's and clinician's biases.[176] However, in the situation of over-the-counter supplements, public perception may be a greater challenge. Only 10% of those taking omega-3 supplements were advised by medical specialists. Other barriers to discouraging use may be anecdotal evidence, over the counter availability, low cost, positive news reports, assumptions of being natural thus safe, and selective evidence or advertisements by the supplement industry.[177]

Recommending potentially ineffective treatments, and taking additional potentially ineffective medicine, has significant costs for our patients, even if those pills do not produce significant side-effects. When patients take omega-3 fatty acids in addition to other evidence-based medications for their mental health conditions, increasing the number of medicines consumed likely reduces overall compliance and the medications have an economic cost. Potentially even more problematic, patients often take omega-3 supplements instead of other evidence-based treatments or lifestyle modifications that may be more likely to help their overall mental and physical health. Of course, treatment decisions need to take into account not only the current evidence-base for efficacy but also patient preferences and values. From a public health and research perspective, it may be more prudent to use scarce resources to develop novel treatments for mental disorders that improve overall outcomes rather than expending more funds to tinker with omega-3 formulations to determine the optimal combination with minimal to no efficacy.

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