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EXPERT OPINION

Omega-3 polyunsaturated fatty acids for major depressive disorder

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Introduction: Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) are not synthesized by the human body; they must be derived from dietary sources and they have been known to be involved with neurological, cardiovascular, cerebrovascular, autoimmune and metabolic diseases, and cognitive disorder as well as mood disorders.
Areas covered: A number of epidemiological and preclinical studies have proven the potential benefit and critical role of omega-3 PUFA in the development and management of major depressive disorder (MDD). In addition, recently independent clinical trials and meta-analyses have also provided superidority of omega-3 PUFA over placebo as monotherapy or augmentation agent in the treatment of MDD. This article presents a brief overview of the evidence to date about the clinical application and biological mechanisms of omega-3 PUFA in the treatment of MDD.
Expert opinion: Given the potential action mechanism, clinical benefits and currently available clinical trial data, omega-3 PUFAs may deserve greater attention and wider application for treatment of MDD. However, the practical utility of omega-3 PUFA as one of promising alternative agent for treatment of MDD still have many questions unresolved to be fully addressed in near future.

Keywords: clinical trial, efficacy, major depressive disorder, omega-3 polyunsaturated fatty acids, safety

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1. Background

Major depressive disorder (MDD) is a chronic, recurrent and serious mental illness, and it is also associated with high morbidity and mortality, significant economic burdens, decrease in personal and work productivity, high suicide rates and substantial impairments in the quality of life [1-3]. Despite a numerous antidepressants with different action mechanism are currently available in the market, the clinical efficacy in terms of remission and response in the treatment of MDD is still disappointing to both clinicians and patients, evidenced by a number of well-controlled, industry-sponsored and investigator-initiated clinical trials as well as large practical clinical trials [4,5]. Approximately 30% of MDD patients remit with initial antidepressant treatment, whereas a chance of recurrence significantly increases with subsequent treatment failures. Hence, most treatment guidelines propose various treatment approaches for patients with inadequate treatment response or treatment failure [4]. Among such different treatment strategies, augmentation to current antidepressant is commonly used to enhance the efficacy of initial antidepressant or to produce a synergistic effect with current antidepressant [6,7]. Although, the clinical benefit of augmentation agents such as atypical antipsychotics has been recently demonstrated, we need more innovative and safe agents other than currently available

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Article highlights.

- Approximately 30% of MDD patients remit with initial antidepressant treatment, whereas a chance of recurrence significantly increases with subsequent treatment failures.
- The beneficial effects of omega-3 PUFA in depression are proven in preclinical studies of animal and cellular models. Omega-3 PUFAs are associated with preventive and reductive effects of depression-like behaviors in animal models.
- Currently available clinical trials have suggested that omega-3 PUFAs would be effective and tolerable for treating patients with depression.
- Despite need of more proven clinical trial data, omega-3 PUFAs may be another viable treatment option for patients who have shown poor treatment response or intolerability to currently exsting antidepressants, who have failed to have any benefits from other next treatment option, or who are not able to be treated with antidepressant.
- More clinical trial data with adequate sample size and advanced-study design will be mandatory to prove the effects and safety of omega-3 PUFAs in the treatment of depression.

This box summarizes key points contained in the article.

augmentation agents, when considering such augmentation agents' adverse events (AEs) (e.g, atypical antipsychotics' tardive dyskinesia and lithium's nephrotoxicity) [8]. In fact, there has been some progress in trials of unique augmentation agents based on their pharmacological profile [9,10].

In this context, one of essential nutrients, omega-3 polyunsaturated fatty acid (omega-3 PUFA), may be one of intriguing therapeutic agents in the treatment of depression [11]. There are two main types of PUFAs in the human body, the omega-6 (n-6) series derived from cis-linoleic acid (LA, 18:2) and the omega-3 (n-3) series derived from α-linolenic acid (ALA, 18:3). Omega-3 PUFAs (e.g, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) and omega-6 PUFAs (e.g, arachidonic acid (AA)) are important constituents of all cell membranes and are essential for survival of humans and other mammals. Omega-3 PUFA cannot be synthesized efficiently in the human body; hence, they have to be obtained from the diet and are, thus, called essential fatty acids (EFAs) [12].

The deficit of omega-3 PUFA has been reported to be associated with neurological, cardiovascular, cerebrovascular, autoimmune and metabolic diseases [13-16], dementia [17], bipolar disorder [18,19] and depression [20,21]. The preclinical studies revealed that omega-3 PUFAs are linking to neurophysiologic and neurochemical functions of depression [15,22-24]. In addition, the clinical studies from double-blind randomized clinical trials and systemic meta-analyses have shown the potential application to use omega-3 fatty acids in the treatment of clinical depression [17,25,26], especially for special populations of children [27] or pregnant women [28] with MDD. However, it is yet to be determined whether the efficacy of omega-3 PUFAs' antidepressant effects are dependent on specific patient types or on specific formula and ratio of DHA and EPA [29-31].

This article is to provide a brief overview of the evidence to date about the clinical application and biological mechanisms of omega-3 PUFA in MDD.

2. Literature selection

A search of the studies used the key terms "omega-3 PUFA" from the databases (PubMed and MedLine) and Web resources. The studies searched were verified for publication in English peer-reviewed journals. We also used reference lists from identified articles and reviews to find additional studies. No date constraint was utilized. Randomized, placebo-controlled clinical trials were principally considered for this review. Open-label studies and case reports, and studies regarding other than depression were not included. Proceedings of the scientific meetings were also searched for paper and poster presentations. Literature search and verification were handled first by one of the authors (S.M.W.) and then independently reassessed by (K.S. and C.U.P.). All relevant studies meeting a scope of the present review purpose were selected based on the consensus among the authors. Systematic/meta-analytic reviews improve the reliability and accuracy of the conclusions based on the data selection criteria and search methods, however, the results are often inconsistent and require careful appraisal and interpretation. Clinicians need to integrate such review results with clinical expertise, updated studies, clinical experiences and the patient's preferences [32]. In this context, narrative review may also provide useful clinical points for specific topic since such reviews.

3. Basic experimental rationale (action mechanism)

The beneficial effects of omega-3 PUFA in depression are further supported in preclinical studies of animal and cellular models. Omega-3 PUFAs are associated with preventive and reductive effects of depression-like behaviors in animal model in rats [33-36]. In addition, the level of brain DHA is negatively correlated to the immobility time and is positively correlated to the swimming time [35]. Although the biological mechanisms underlying the antidepressant effects of omega-3 PUFAs are yet to be addressed, we summarize a few possible explanations:

i) Neurotransmitter regulations: The change in omega-3 PUFA concentrations in the brain, induced by chronic deficiency in dietary omega-3 PUFAs, could lead to an increase in serotonin 2 (5-HT_2) and decrease in dopamine 2 (D_2) receptor density in the frontal cortex [37-42]. The upregulation of $5\text{-HT}_{2A/C}$ receptors and downregulation of dopamine receptors are thought to play a role in the pathophysiology of depression [43]. Further, high cerebrospinal fluid concentration of 5-hydroxy-indoleacetic acid (5-HIAA), a metabolite of serotonin and an indicator of brain serotonin

turnover, has been shown to be associated with high plasma concentration of omega-3 PUFAs among healthy subjects [44]. Biochemical studies have also shown that omega-3 PUFAs increased CSF 5-HIAA concentration and somatotrophin release [45], which are commonly associated with the improvement of depressive symptoms.

ii) Anti-inflammation and anti-oxidation effects: The inflammation theory of depression has been supported from several lines of evidence including increasing inflammatory biomarkers in clinical depressed patients and the observed behavioral changes related to inflammatory changes [46,47]. Inflammation induce depression-like behaviors [48] and signal transductions [49] and neuroendocrine [48,50] changes linking to depression. Omega-3 PUFAs are anti-inflammatory and therefore could be beneficial in depression and several inflammation-related physical diseases [14,23,24,36,51,52]. According to the recent trial, omega-3 PUFAs can also lower inflammation (measured by changes in interleukin-6 and TNF-α) in healthy middle-aged and older adults who were sedentary and overweight, and thus could have broad health benefits [53].

iii) Neuroplasticity effects: Various chronic antidepressant treatments increase adult hippocampal neurogenesis [54-56], and animal studies suggest that the behavioral effects of chronic antidepressants may be mediated by an induction of neuroplasticity and neurogenesis in the brain [56]. In a small clinical study, EPA supplementation has been shown to increase cortical concentrations of *N*-acetyl aspartate, a putative marker of neuronal integrity and function, thereby protecting against excitotoxic apoptosis [57]. In addition, preclinical studies have shown that omega-3 PUFAs promote hippocampal neurogenesis in adult animals [58-60]. Moreover, omega-3 PUFAs may modulate neurotrophins [61-65], which might be a direct mechanism to mediate neurogenesis and antidepressant effects [61].

iv) Arachidonic acid cascade: The "Arachidonic acid cascade" has been identified as one of the mechanisms of mood stabilization [66] and has been supported by empirical evidences, including the higher ratio of AA to DHA [18,67,68] and hyperactivity of its major metabolic enzyme phospholipase A2 (PLA2) in patients with mood disorders [69,70], the inhibitory effect on PLA2 activity of mood stabilizers [71-74], and the therapeutic effect of omega-3 PUFAs in mood disorders [18,26,75]. Despite the exact interaction between omega-3 PUFAs and arachidonic cascade, possible mechanisms of having low membrane AA and DHA in mood disorders, may include reduced availability of PUFAs, reduced cellular uptake of PUFAs, deficient incorporation of PUFAs into membrane phospholipids, deficient activity of both enzyme (desaturase or enlongase), or excessive removal by membrane lipid peroxidation [18,76].

v) Oxidative stress: It has been proposed that oxidative stress may also play a major pathophysiological link with mood disorders [77]. Factors that may contribute to increased oxidative stress in mood disorders include increased gluco-oxidation, increased formation of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide, and antioxidant deficiencies [78,79]. There is considerable evidence that a diet enriched with EPA and DHA protects against multiple medical diseases involving anti-oxidation pathways defects [78,80,81]. In fact, administration of omega-3 PUFA was found to be beneficial on serum triglycerides, HDL-cholesterol, lipid peroxidation and anti-oxidant enzymes, which have been continuously replicated in patients with diabetes [82-84] as well as mood disorders [77,85].

vi) Clinical findings: It has been observed that societies with a high consumption of fish in their diet appear to have a lower prevalence of MDD, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality and all-causes mortality [44,86,87] implying a protective effect of omega-3 PUFAs in medical and psychiatric disorders, although the evidence is not clear-cut and contradictory findings are also presented [88]. Consistent with the epidemiological finding, it is found that patients with MDD have lower levels of omega-3 PUFAs in tissues of blood [21] and brain [52]. The deficits in omega-3 PUFA levels have been reported in other populations with mood disorders, including lower DHA and total omega-3 PUFAs in postpartum depression [89]; lower DHA and EPA in social anxiety disorder [90]; and lower DHA and AA in bipolar disorders [18]; even in recovered depressed patients [7].

4. Clinical evidence

4.1 Efficacy

In consistent to the case-control studies of PUFA levels in human tissues, omega-3 PUFAs have been reported to be effective in the treatment of MDD.

A number of independent clinical trials [26-28,91-99] have reported an antidepressant effect of PUFAs, although other studies failed to demonstrate the superiority of omega-3 PUFA over placebo [100-108]. Briefly, as for monotherapy trials, the reduction of various primary endpoints from baseline to the endpoints (e.g, Hamilton Depression rating scale and Montgomery Asberg Depression Rating scale, etc.) ranged approximately from 23 to 56% in the treatment with omega-3 PUFA, while it was from 17 to 46% in the treatment with placebo, with magnitude of differences (2 to 21%, omega-3 PUFA vs. placebo) between the two treatment groups.

When it comes to augmentation trials, the reduction of various primary endpoints from baseline to the endpoints ranged approximately from 3 to 60% in the treatment with omega-3 PUFA, while it was from -3 to 56% in the treatment with placebo, with magnitude of differences (-13 to 31%, omega-3 PUFA vs. placebo) between the two treatment groups.

Six meta-analytic researches were conducted by four independent groups [17,20,25,30,31,109]. However, among such

meta-analysis, three previous meta-analyses from two groups did not support the antidepressant effects of omega-3 PUFA when heterogeneous populations (e.g, community samples) were included [29,104,110]. The negative findings need to be interpreted with caution because of a few limitations, such as pooling heterogeneous populations, using different mood assessments, and implementing different intervention methods [30,31,111]. **Tables 1** and **2** summarize the clinical efficacy of omega-3 OUFAs as a monotherapy or augmentation therapy for the treatment of MDD. In addition, omega-3 PUFA's adjunctive mood-stabilizing effects on bipolar disorder were demonstrated in a 4-month, randomized controlled study [112]. In the results, omega-3 PUFA treatment significantly prolonged the remission period than the placebo group. The omega-3 PUFA was also more likely to have better treatment outcomes in most other secondary measures than the placebo group. In our reexamination of the data reported by Stoll *et al,* we found that all "noncompleted" cases (3 out of 14 cases) in the omega-3 group developed a manic episode, whereas the depressive symptoms in all but 1 of the noncompleted cases (10 out of 16 cases), in the placebo group worsened. This observation suggests that omega-3 PUFA could prevent depression but not mania in patients with BD [70]. Despite the uneven quality of published studies, recent meta-analytic evidence strongly supports the adjunctive use of omega-3 to treat bipolar depression. However, the study regarding effectiveness of omega-3 PUFA in the acute manic phase of bipolar disorder is still lacking. To date, only two small double-blind placebo-controlled trial was published and did not support omega-3 PUFAs' anti-manic effects [113,114]. Future large-scale, double-blind, placebo-controlled trials are needed.

4.2 Safety and tolerability

In numerous clinical studies, omega-3 PUFAs have been shown to be well tolerated for patients with chronic medical illnesses, mental disorders and in pregnant women [20,115,116]. Adverse reactions are rare; if occur, they usually involve belching or eructation or perhaps fish taste [117]. It has been suggested that the potential anti-thrombotic effect of omega-3 PUFAs may theoretically increase the risk for bleeding. Clinical trials have shown high-dose omega-3 PUFAs consumption to be safe, even when concurrently administered with other agents that may increase bleeding, such as aspirin and warfarin [115]. According to Harris's systematic review on 19 available clinical trials with n-3 PUFAs supplementation for patients with high risk of bleeding (n = 4397) [118], the risk for clinically significant bleeding is "virtually nonexistent" Another potential safety concern is the susceptibility of omega-3 fatty acids to undergo oxidation [119], which may contribute to patient intolerance and potential toxicity [120-122]; however, the conclusions are highly inconsistent. Adding antioxidant vitamin E to omega-3 PUFAs is the common way to reduce oxidation and rancidity, to maintain freshness, and to increase shelf life [123]. The concurrent use of vitamin E with omega-3 PUFAs may also overcome the potential risk of oxidative stresses [123-127]. However, most of the published studies have shown either no change in oxidation [126,128-135], or decreasing oxidation [84,136-143].

Since omega-3 PUFAs may have antidepressant effects, another possible adverse effect is drug-induced mania. Until now, there is only one case report to show that omega-3 PUFAs could induce hypomania [144]. It is recommended to perform comprehensive assessments on manic symptoms for patients receiving omega-3 PUFAs in future clinical trials.

5. Expert opinion

A mounting evidence suggests the inadequate response and remission rates after treatments with different antidepressants. A number of newer and older medications including lithium, triiodothyronine (TH), creatine monohydrate, scopolamine, buspirone, dopamine agonists, S-adenosyl-L-methionine (SAM-e) and stimulants [10,145-149] have been investigated as a monotherapy or augmentation treatment for depressed patients after inadequate clinical improvement with antidepressants treatment or from the beginning of treatment. However, among such alternative agents, majority of studies with lithium, SAM-e, TH, buspirone, scopolamine, dopamine agonists and stimulants have significant methodological issues (few controlled trials, formulation of agents and small samples, etc.) and also produced inconsistent results yet.

In addition, although some atypical antipsychotics including aripiprazole, quetiapine XR and olanzapine plus fluoxetine have received the official approval as augmentation agent for MDD and treatment-resistant depression [7,150], the treatment outcomes are not satisfactory yet in terms of remission and full recovery, and there are major safety issues of antipsychotics such as potential risks for developing movement disorders, drug interactions and metabolic disturbance in patients with MDD. Based on such critical safety issues from other agents and overall clinical benefit considering efficacy and safety profile, omega-3 PUFA may be one of putative promising agent for the treatment of MDD. Based on currently available clinical trials with omega-3 PUFA, most such trials involved a small number of patients but were largely well designed. The most convincing evidence for beneficial effects of omega-3 PUFA should be in the treatment of mood disorders. Many meta-analyses of trials involving patients with MDD and bipolar depression also provided some evidence that omega-3 PUFA treatment may potentially decrease depressive symptoms [17,20,25,30,31,109].

Despite well-controlled clinical trials and systematic meta-analyses which have demonstrated the potential utility of omega-3 PUFA in the treatment of MDD [20,26-28,31,91-97,116], it is not clearly shown whether the efficacy of omega-3 PUFAs' antidepressant effects should be potentially different for specific subtypes of MDD (anxious vs. non-anxious, atypical vs. nonatypical, etc.).

Table 1. Summary of double-blind, placebo-controlled (with or without active comparisons) clinical trials of omega-3 (monotherapy) in depressive disorder.

Study	Subjects characteristics	W3 type and dose (g/day)	No. of patients (ω/placebo)*	Duration (weeks)	Primary outcome measure	Baseline mean of primary outcome measure		Endpoint mean of primary outcome measure		Other remarks
						ω (SD)	placebo (SD)	ω (SD)	placebo (SD)	
da Silva [97]	MDD with Parkinson's disease	0.72 g EPA+ 0.36 g DHA	6, 8/7, 8‡ (**ω**, **ω** +ST/placebo, placebo+ST)	12	MADRS	NA	NA	NA	NA	MADRS mean change (baseline-endpoint) statistically higher only in **ω** and **ω** +ST groups (for both, $p < .005$) No statistical difference between groups SMD = 0.42 (95% CIs, -0.57, 1.41)
Freeman [100]	Perinatal women with MDD (+ supportive psychotherapy)	1.1 g EPA+ 0.8 g DHA	28/23	8	HDRS EPDS	18.86 (3.43) 17.11 (3.75)	17.43 (2.19) 15.83 (3.63)	12.82‡‡ (5.48) 10.96‡‡ (5.92)	9.91‡‡(4.74) 8.09‡‡ (4.96)	SMD = -0.35 (95% CIs = -0.90, 0.21)
Jazayeri [96]	MDD	1 g EPA	16,16, 16 (**ω**, **ω** +FLU, FLU)	8	HDRS	29.94 (4.9) 31.6§ (5.8)	29.3¶ (6.5)	NA	NA	Statistical difference in HDRS mean change (baseline-endpoint) in all groups (for all $p < 0.05$) SMD = 0.86 (95% CIs = 1.72, 8.07) **ω** +FLU groups significantly higher than FLU or **ω** alone groups in mean endpoint HDRS (for all $p < 0.01$)
Lespérance [101]	MDD	1.05 g EPA+ 0.15 g DHA	214/218	8	IDS-SR_{30}	43.3 (8.88)	43.8 (8.75)	30.93 (12.12)	32.26 (12.16)	IDS-SR_{30} mean change (baseline-endpoint) within group not analyzed. SMD = 0.35 (95% CIs = -0.20, 2.84)
Lucas [102]	Depressive symptoms	1.05 g EPA+ 0.15 g DHA	59/61	8	PGWB	55.9 (12.1)	52.5 (11.1)	68.3‡‡ (15.9)	63.8‡‡ (18.6)	SMD = -0.67 (95% CIs = -1.42, 0.09)

*Number of intent-to-treat patients, unless otherwise stated.

‡Number of patients for per-protocol analysis.

§Mean values for W3+fluoxetine group.

¶Mean values for fluoxetine group.

#p <. 05, **p <. 01, ‡‡p <. 001 vs baseline.

§§p <. 05, ¶¶p <. 01,##p <. 001 vs placebo.

ω: Omega-3; AD: Antidepressant; BDI: Beck depression inventory; CDI: Children's depression inventory; CDRS: Children's depression rating scale; CGI: Clinical global impression scale; DASS: Depression, anxiety and stress scales; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; EPDS: Edinburgh postnatal depression scale; FLU: Fluoxetine; HDRS: Hamilton depression rating scale; IDS-SR_{30}: Self-report inventory of depressive symptomatology; MADRS: Montgomery–Åsberg depression rating scale; MDD: Major depressive disorder; NA: Exact number not available; PGWB: Psychological general well-being; ST: Sertraline; SMD: Standardized mean difference.

Table 1. Summary of double-blind, placebo-controlled (with or without active comparisons) clinical trials of omega-3 (monotherapy) in depressive disorder (continued).

Study	Subjects characteristics	W3 type and dose (g/day)	No. of patients (ω/placebo)*	Duration (weeks)	Primary outcome measure	Baseline mean of primary outcome measure		Endpoint mean of primary outcome measure		Other remarks
						ω (SD)	placebo (SD)	ω (SD)	placebo (SD)	
Marangell [103]	MDD	2 g EPA	18/17	8	MADRS	25.3 (5.5)	27.2 (4.0)	15.4§§ (8.3)	22.7 (9.7)	MADRS mean change (baseline-endpoint) within group was not analyzed. MADRS mean change (baseline-endpoint) between group was not significant (**ω**, -8.1 vs placebo, -5.8; p =.43) SMD = 0.33 (95% CIs = -0.34, 1.00)
Mischoulon [92]	MDD	1 g EPA	16/19	8	HDRS-17	21.6 (2.7)	20.5 (3.6)	13.9** (8.9)	17.5 (7.5)	No statistical difference between groups in HDRS-17 mean change (baseline-endpoint), response (**ω**, 38% vs placebo, 21%), and remission (**ω**, 25% vs placebo, 16%) rates SMD = 0.74 (95% CIs = 0.05, 1.43)
Nemets [93]	Childhood MDD (age 6 – 12)	0.4 EPA+ 0.2 DHA	10/10	16	CDRS, CDI, CGI	NA	NA	NA	NA	**ω** group showed higher mean changes (baseline-endpoint) of CDRS, CDI, and CGI (for all, p <. 001) SMD = 2.03 (95% CIs = 0.91, 3.16) on VDRS
Rees [108]	Perinatal women with MDD	1.64 g EPA+ 0.41 g DHA	13/13	6	EPDS HDRS MADRS	17.3 (2.7) 19.7 (4.8) 30.2 (6.4)	16.5 (2.3) 9.0 (3.5) 29.2 (4.4)	8.5‡‡ (5.5) 7.9‡‡ (5.1) 13.5‡‡ (8.6)	9.0‡‡ (5.2) .7‡‡ (5.1) 15.1‡‡ (7.5)	SMD = 0.73 (95% CIs = -0.07, 1.52)

*Number of intent-to-treat patients, unless otherwise stated.

‡Number of patients for per-protocol analysis.

§Mean values for W3+fluoxetine group.

¶Mean values for fluoxetine group.

#p <. 05, **p <. 01, ‡‡p <. 001 vs baseline.

§§p <. 05, ¶¶p <. 01,##p <. 001 vs placebo.

ω: Omega-3; AD: Antidepressant; BDI: Beck depression inventory; CDI: Children's depression inventory; CDRS: Children's depression rating scale; CGI: Clinical global impression scale; DASS: Depression, anxiety and stress scales; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; EPDS: Edinburgh postnatal depression scale; FLU: Fluoxetine; HDRS: Hamilton depression rating scale; IDS-SR_{30}: Self-report inventory of depressive symptomatology; MADRS: Montgomery–Åsberg depression rating scale; MDD: Major depressive disorder; NA: Exact number not available; PGWB: Psychological general well-being; ST: Sertraline; SMD: Standardized mean difference.

Table 1. Summary of double-blind, placebo-controlled (with or without active comparisons) clinical trials of omega-3 (monotherapy) in depressive disorder (continued).

Study	Subjects characteristics	W3 type and dose (g/day)	No. of patients (ω/placebo)*	Duration (weeks)	Primary outcome measure	Baseline mean of primary outcome measure		Endpoint mean of primary outcome measure		Other remarks
						ω (SD)	placebo (SD)	ω (SD)	placebo (SD)	
Rogers [104]	Mild to moderate depression	0.63 g EPA+ 0.85 g DHA	109/109	12	DASS depression subscale	10.9 (6.1)	11.0 (5.5)	8.4 (8.0)	9.6 (7.3)	SMD = -1.02 (95% CIs = -2.83, 0.81)
Su [28]	MDD in pregnant women	2.2 g EPA+ 1.2 g DHA	17/16	8	HDRS-21	22.3 (5.0)	22.3 (3.9)	9.9¶¶ (4.3)	14.6 (4.8)	HDRS change (baseline-endpoint) within group was not analyzed ω group had significantly higher response rate (W3, 62% vs. placebo, 27%; p <. 05) SMD = 1.01 (95% CIs = 0.28, 1.74)
Khajehnasiri [98]	≥ 10 in BDI score	0.36 g EPA +0.24 g DHA	34/34/34/34 VitC+ ω/ω/VitC/ placebo		BDI score	Mean change = 6.3 ± 6.8§§		Mean change = 2.3 ± 5.9		SMD = 0.68 (95% CIs = -0.6, 8.6)
Mozurkewich [99]	9 – 19 in EPDS score or history of depression	1.06 g EPA +0.274 g DHA/ 0.9 g DHA +0.18 g EPA/ placebo	42/42/42	Full-term and up to 8 weeks post parum	BDI scores	NA		NA		No differences among groups Three endpoints at 26 – 28 weeks, 34 – 36 weeks and at 6 – 8 weeks' postpartum

*Number of intent-to-treat patients, unless otherwise stated.
‡Number of patients for per-protocol analysis.
§Mean values for W3+fluoxetine group.
¶Mean values for fluoxetine group.
#p <. 05, **p <. 01, ‡‡p <. 001 vs baseline.
§§p <. 05, ¶¶p <. 01,##p <. 001 vs placebo.
ω: Omega-3; AD: Antidepressant; BDI: Beck depression inventory; CDI: Children's depression inventory; CDRS: Children's depression rating scale; CGI: Clinical global impression scale; DASS: Depression, anxiety and stress scales; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; EPDS: Edinburgh postnatal depression scale; FLU: Fluoxetine; HDRS: Hamilton depression rating scale; IDS-SR_{30}: Self-report inventory of depressive symptomatology; MADRS: Montgomery–Åsberg depression rating scale; MDD: Major depressive disorder; NA: Exact number not available; PGWB: Psychological general well-being; ST: Sertraline; SMD: Standardized mean difference.

Table 2. Summary of double-blind, placebo-controlled clinical trials (adjunctive therapy to established antidepressant only).

Study	Subjects characteristics	W3 type and dose (g/day)	No. of patients (ω/placebo)*	Duration (weeks)	Primary outcome measure	Baseline mean of primary outcome measure		Endpoint mean of primary outcome measure		Other remarks
						ω (SD)	placebo (SD)	ω (SD)	placebo (SD)	
Bot [105]	MDD with diabetes mellitus	1 g EPA	13/12	12	MADRS	26.3 (8.2)	26.4 (8.7)	14.8[#] (6.9)	11.6[#] (9.1)	
Carney [106]	MDD with coronary heart disease	0.93 g EPA+ 0.75 g DHA	62/60	10	BDI-21	28.1 (8.7)	29.0 (9.2)	16.1 (10.2)	14.8 (9.7)	No group differences in remission (**ω**, 28.3% vs placebo, 27.4%; p =.91) and response (**ω**, 47.7% vs placebo, 49.0; p =.88) rates SMD = -0.77 (95% CIs = -4.5, 2.0)
Grenyer [107]	MDD	0.6 g EPA+ 2.2 g DHA	40/43	16	HDRS, BDI	NA NA	NA NA	NA NA	NA NA	Statistical difference in HDRS and BDI mean changes (baseline-endpoint) in both groups (for both p <. 0001) No group differences in endpoint mean HDRS (p =.651) and BDI (p =.424) SMD = –.09 (95% CIs = -0.50, 0.33)
Peet [94]	MDD despite adequate AD treatment	1 g, 2 g, 4 g EPA	15, 15, 14/15	12	HDRS-17	19.9[‡] (NA)	20.3 (NA)	10.0[‡] (NA)	14.2 (NA)	HDRS mean change (baseline-endpoint) within group was not analyzed. 1 g EPA group only had significantly higher endpoint mean HDRS than placebo (p <. 05) SMD = 0.26 (95% CIs = -0.28, 0.80)
Silvers [175]	MDD	0.6 g EPA+ 2.4 g DHA	40/37	12	HDRS-short form	11.5 (5.3)	12.4 (5.4)	11.2 (NA)	12.8 (NA)	SMD = -0.06(95% CIs = -0.51, 0.39)
Su [26]	MDD	4.4 g EPA+ 2.2 g DHA	14/14	8	HDRS-21	22.5 (3.9)	22.1 (3.9)	8.9[#§] (3.7)	15.7 (3.2)	HDRS mean change (baseline-endpoint) within placebo group was not analyzed SMD = 1.87 (95% CIs = 0.83, 2.91)
Gertsik [95]	MDD	0.9 g EPA + 0.2 g DHA	20/22	9	HDRS-21	25.3 (4.4)		10[#,¶¶] (NR)	17[¶¶] (NR)	significantly greater improvement in HDRS total scores beginning at week 4 [¶¶]SMD = 1.47 (95% CIs = 3.75, 9.24)

*Number of intent-to-treat patients, unless otherwise stated.

[‡]Mean values for 1 g EPA only.

[§]p <. 05, [¶]p <. 01, [#]p <. 001 vs baseline.

**p <. 05, [‡‡]p <. 01,[§]p <. 001 vs placebo.

[¶¶]The mean was estimated manually from the figure of the original study and standard deviation for calculation of SMD was set with 4.4 from the baseline values.

ω: Omega-3; AD: Antidepressant; BDI: Beck depression inventory; DHA: Docosahexaenoic acid; EPA: Eicosapentenoic acid; HDRS: Hamilton depression rating scale; MADRS: Montgomery–Åsberg depression rating scale; MDD: Major depressive disorder; NA: Exact number not available; NR: Not reported.

Further, substantial differences have been reported in the prevalence, symptom manifestation, developmental mechanisms, patients' recognition and treatment of MDD across different ethnicities [151]. Hence investigation of whether any differences would exist for specific target depressive symptoms between Western and Asian populations in the use of omega-3 PUFA should be also intriguing.

Another issue is what type of formula and the ratio of DHA and EPA should be the optimal for the treatment of MDD [29-31]. In fact, most clinical trials with omega-3 PUFA for MDD adopted different formula and ratio of DHA and EPA and potential differences in efficacy and safety by different ratios in DHA and EPA has not been fully elucidated yet. There have been some differences in the role of DHA and EPA. DHA is the predominantly major fatty acid component of brain phospholipids and is essential for normal brain development [152]. According to a recent study, interestingly, a 1% increase in plasma DHA was associated with ~ 60% decrease of depressive symptoms [153]. In addition, EPA and DHA had significant differences in the production of interferon-γ (IFN-γ) [154]. EPA has been known to cause a higher decrease in the production of IFN-γ, which is associated with the development of depression [96]. According to a recent meta-analysis [155], EPA was proposed to be more beneficial than DHA in the treatment of depression; however, such a finding has not been confirmative since subsequent studies have shown opposite results [28,35,85]. Based on currently existing literatures, more research is required to determine the relative importance of EPA and DHA in the development and treatment of depression, and this issue should be more clearly investigated to place the exact ratio in omega-3 PUFA for establish a standardized formulation [156].

In the efficacy trials, another critical point is that some investigators [102,104] did not apply firm diagnosis of MDD based on formal criteria. This point is important since the baseline severity of MDD should be one of significant moderator of the antidepressant effect of omega-3 PUFA supplementation as proposed in the previous research [29]. As the sample size of researches with omega-3 PUFA are relatively small, meta-analysis may be possible solution to detect more reliable efficacy of omega-3 PUFA with increase of sample power adding currently all available studies together. In this context, such diagnostic issues may substantially impact and deviate the treatment outcomes as providing conflicting meta-analytic results among researchers [29,31].

Early improvement in depressive symptoms with antidepressant treatment may predict a favorable treatment outcome [157-162]. Studies on the association between the onset time of antidepressant response and the probability of response have yielded some intriguing findings, although debates still continue. Therefore, future studies will need to investigate the influence of early treatment effect of omega-3 PUFA on the later clinical outcomes may exist in the longer term treatment of MDD.

Polymorphisms in the cytochrome P450 2D6 (CYP2D6) gene are a major cause of pharmacokinetic variability in humans, and sufficient evidence suggests ethnic differences in metabolism of psychotropics between Asian and Western populations [163,164]. However, omega-3 PUFA lacks this unwanted pharmacokinetic issues influencing on development of adverse events and thereby more universal and predictable treatment outcomes as well as favorable tolerability across different ethnicities. Interestingly, cross-cultural population differences in fish intake and serum omega-3 PUFA levels have been consistently reported even in same ethnic group; according to a recent study, the percentage of total serum fatty acids contributed by omega-3 PUFA was approximately 3.5 times higher in rural Japanese than in Japanese Americans [165]. When compared with Caucasian Americans, such difference increased up to five times. In fact, the average daily North American intake of EPA/DHA has been approximately 130 mg, significantly short compared to the recommended dose of 900 mg/d by the American Heart Association [165,166]. In fact, mortality from coronary heart disease is much lower in Japan than in the United States. It has been well-known that population differences in fish intake and serum omega-3 fatty acid levels may contribute to the population difference in the risk of coronary heart disease [165]. Similarly, it should be also interesting whether or not the basal level of PUFAs may influence on differential effects of omega-3 PUFA in the treatment of MDD between Western and Asian population.

Omega-3 PUFA may be also promising in the treatment of special populations with depression. We firstly reported a successful treatment with omega-3 PUFA in a pregnant woman with MDD [167]. Our subsequent 8-week, double-blind, placebo-controlled study showed that monotherapy with omega-3 PUFA was associated with significant improvement of depressive symptoms and a higher response rate in pregnant women with depression [28]. Most importantly, omega-3 PUFA are safe and well tolerated in depressed women during pregnancy and postpartum periods [14,168,169]. However, the recent study failed to demonstrate a preventive effect on depressive symptoms during pregnancy or postpartum [99]; hence, further well-designed, subsequent studies with a large sample should be mandatory to draw definite conclusion on this field.

In addition, omega-3 PUFA have been shown to be effective and safe for children with depression [93]. Further, supplementation of omega-3 PUFA was also found to decrease risks of suicidality [19,170,171], to improve depressive symptoms in MDD associated with the menopausal transition [22], and to diminish aggression in women with borderline personality disorder [172]. The efficacy of omega-3 PUFA has been also tested in Tourette's disorder [173] and posttraumatic stress disorder [174], demonstrating a significant clinical benefit and safety for such patients. These results mat extend the role of omega-3 PUFA into a wider area of psychiatric disorders.

In conclusion, omega-3 PUFAs are neuro-protective, anti-inflammatory and the agent has proven promising efficacy for treatment of MDD. Omega-3 PUFA may be also beneficial for children and pregnant women, as well as those patients with comorbid cardiovascular diseases or metabolic disorders, who may be at greater risks of adverse effects from antidepressants, antipsychotics and mood stabilizers. The cost of omega-3 PUFA is relatively modest as compared to many psychiatric treatments and other over-the-counter natural products; hence, such overall cost-benefit ratio may endorse the incorporation of omega-3 PUFA into psychiatric treatment algorithms. Given the potential benefits and safety, omega-3 PUFAs deserve greater attention and wider application. However, the practical utility of omega-3 PUFA as one of promising alternative agent for treatment of MDD still have unresolved questions to be fully addressed in near future in adequately powered, well-controlled clinical trials (i.e, sample size, comparison issues in global benefits with other currently available agents, proper dose, and more better treatment option of omega-3 PUFA such monotherapy vs. augmentation). The premise of omega-3 PUFA appears prudent but the actual promise of the agent as antidepressant should fully depend on future studies.

Declaration of interest

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