

Review

Omega-3 Fatty Acids and Mood Disorders: A Critical Narrative Review

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Abstract

Background: In recent decades, interest has grown in the link between lipid metabolism and mental health. Omega-3 fatty acids (EPA and DHA) play a crucial role in brain function, neuroplasticity, and emotional regulation. Deficiency or an imbalanced omega-6/omega-3 ratio, typical of Western diets, has been associated with an increased risk of mood disorders, such as major depression and bipolar disorder. **Objective:** This review critically synthesizes neurobiological and clinical evidence on the role of omega-3s in mood disorders, assessing mechanisms, randomized controlled trials, and meta-analyses, with a focus on inflammatory biomarkers and their integration into a personalized psychiatry framework. **Methods:** A narrative review of epidemiological studies, randomized controlled trials (RCTs), meta-analyses, and experimental research was conducted, evaluating mechanistic pathways (synaptic, inflammatory, neuroplastic, and redox) and clinical moderators (particularly inflammatory markers and dietary lipid profiles). **Results:** Consistent evidence indicates that EPA-enriched formulations ($\geq 60\%$) exert antidepressant effects, particularly in patients with elevated inflammatory markers (CRP, IL-6, TNF- α). In contrast, DHA-only preparations show limited efficacy, and outcomes vary depending on dietary omega-6/omega-3 balance. However, the literature remains heterogeneous in design, sample size, and biomarker stratification, which limits generalizability and contributes to conflicting findings across studies. **Conclusions:** While omega-3 fatty acids represent promising adjunctive interventions for mood disorders, methodological weaknesses and inconsistent formulations hinder definitive conclusions. Future research should prioritize biomarker-guided, precision-based approaches to clarify therapeutic efficacy and optimize clinical use.



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1. Introduction

Mood disorders, including major depressive disorder (MDD), bipolar disorder, and persistent depressive disorder, are among the leading causes of disability and global disease burden, significantly impairing psychosocial functioning and quality of life [1,2]. Despite the widespread use of pharmacological and psychotherapeutic treatments, a significant

proportion of patients—particularly those with treatment-resistant depression or chronic subtypes—fail to achieve full remission, experience frequent relapses, or develop adverse effects [3,4].

In response to these limitations, nutritional psychiatry has gained increasing interest as an adjunctive or integrative approach. In particular, omega-3 polyunsaturated fatty acids (PUFAs)—notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—have demonstrated potential in the modulation of mood regulation, neuroplasticity, and inflammatory signaling [5–7]. Omega-3 PUFAs are critical structural and functional components of neuronal membranes and play a key role in synaptic integrity, neurotransmitter dynamics, neuroinflammatory control, and redox balance [8,9].

Although omega-3 fatty acids can be synthesized endogenously (including in the brain), this occurs only in limited amounts—estimated to meet roughly 15% of physiological requirements. Therefore, sufficient intake through dietary sources such as oily fish (e.g., salmon, sardines), krill oil, or supplementation is essential [1]. Deficiency in omega-3 fatty acids has been associated with altered brain function, elevated pro-inflammatory cytokine levels, and increased vulnerability to affective dysregulation [8,10].

Accordingly, growing evidence suggests that omega-3 interventions—particularly EPA-enriched formulations—may offer greater efficacy in specific subgroups, such as those with elevated inflammatory biomarkers [4,6,11]. The current scientific discourse is increasingly moving toward a biomarker-driven, precision-based model that integrates nutritional, immunological, and psychiatric variables for optimal care [11,12].

In recent years, the concept of precision psychiatry has emerged as a promising paradigm for addressing heterogeneity in mood disorders, particularly in treatment-resistant depression (TRD). By integrating biological, inflammatory, and metabolic biomarkers into clinical decision-making, this approach aims to tailor interventions to individual pathophysiological profiles, moving beyond the traditional symptom-based model. Such biomarker-guided frameworks align with the growing recognition that treatment resistance may reflect distinct neurobiological subtypes, rather than a single uniform entity. Within this context, omega-3 fatty acids represent a valuable case study in the translational shift toward biologically informed, personalized treatment strategies [13] as reported in Table 1.

Table 1. “Overview of Mechanistic Pathways Linking Omega-3 Fatty Acids to Mood Regulation” (Include synaptic function, inflammation modulation, neurotransmitters, and neurotrophic factors in one infographic).

Mechanism	Biological Effect	Impact on Mood
Synaptic Function	↑ Membrane fluidity, ↑ Neurotransmitter release (5-HT, DA)	Improved emotional regulation
Inflammatory Pathways	↓ IL-6, ↓ TNF-α, ↓ Microglial activation	Reduced neuroinflammation
Neuroplasticity	↑ BDNF expression, ↑ Hippocampal neurogenesis	Enhanced resilience, cognition
Oxidative Stress	↓ ROS, ↑ Antioxidant defenses	Lower cellular stress, mood stability
Overall Mood Regulation	System-wide neuromodulation	↓ Depressive symptoms, ↑ Cognitive function

Abbreviations: 5-HT = serotonin; DA = dopamine; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; BDNF = brain-derived neurotrophic factor; ROS = reactive oxygen species.

This critical narrative review aims to:

- Examine the neurobiological mechanisms linking omega-3 fatty acids to mood regulation;
- Critically evaluate findings from randomized clinical trials (RCTs) and meta-analyses on their efficacy in mood disorders;
- Assess how inflammatory biomarkers and dietary lipid profiles may moderate treatment response;
- Propose an integrative, personalized model of psychiatric care based on current translational and clinical evidence.

1.1. Inflammation, Lipidomics, and the Neurobiology of Depression

Recent research has highlighted the central role of lipid dysregulation in the pathogenesis of depressive disorders, particularly through mechanisms of neuroinflammation and microglial dysfunction. Some studies emphasize how lipid peroxidation and the accumulation of oxidized lipids can trigger an immune response in the brain, impairing synaptic function and reducing neuronal plasticity [14,15]. This chronic inflammatory state has been observed both in patients with major depressive disorder and in animal models, where ferroptosis—a form of lipid-dependent cell death—has emerged as a potentially involved pathway in depressive symptomatology [16,17]. In parallel, alterations in brain phospholipid metabolism, as demonstrated by Wang et al. (2025), contribute to microglial dysregulation and blood–brain barrier impairment, both of which are key features in bipolar depression [18].

1.2. Diet, Lipid Profiles, and Depressive Risk

Another recurring theme is the connection between diet, lipid metabolism, and depressive risk, with particular attention to the plasma lipid profile. Findings reported indicate that individuals with major depressive disorder (MDD) often show significant alterations in triglycerides, LDL/HDL cholesterol, and free fatty acids [14,19]. These abnormalities are not merely consequences of depression but may contribute to a self-perpetuating inflammatory–metabolic cycle. Within this framework, targeted nutritional interventions—such as the ketogenic diet—have shown promise in improving both lipid profiles and affective symptoms in individuals with metabolic syndrome [20]. Moreover, traditional herbal-based interventions like *Xiaoyao San* appear to reduce hepatic lipid accumulation while simultaneously alleviating depressive symptoms, suggesting a strong interplay between hepatic lipid metabolism and mental health [21].

1.3. Therapeutic Implications and Clinical Perspectives

The clinical implications of these findings open new horizons in metabolic psychiatry, suggesting that depression treatment should include inflammatory and lipid profile assessments as predictors of therapeutic response. Targeted interventions that modulate lipid metabolism—whether nutraceutical, dietary, or pharmacological—could become essential components of a more integrated therapeutic approach. For example, the administration of bioactive compounds such as melatonin, extracellular vesicles (EVs), or plant-derived molecules has demonstrated the capacity to restore lipid balance and reduce cerebral oxidative stress, thereby improving depressive-like behaviors in experimental models [22,23]. Finally, the growing interest in lipid and immunometabolic biomarkers paves the way for personalized medicine, where depression treatment is no longer guided solely by clinical symptomatology but also by measurable, modifiable biological profiles [24].

1.4. Methods

This study employed a narrative review design with elements of a semi-systematic approach to enhance transparency and reproducibility. A structured search of the literature was conducted using the PubMed, Scopus, and Web of Science databases. The search

covered publications from January 2000 to September 2025, combining the following keywords and Boolean operators: “omega-3 fatty acids” OR “EPA” OR “DHA” AND “depression” OR “mood disorders” OR “bipolar disorder” OR “neuroinflammation”.

Studies were included if they met the following criteria:

- (1) peer-reviewed original research (human or experimental);
- (2) randomized controlled trials (RCTs), meta-analyses, epidemiological, or mechanistic studies;
- (3) publications in English addressing the relationship between omega-3 fatty acids and mood disorders or related neurobiological mechanisms.

Exclusion criteria comprised case reports, conference abstracts, non-English papers, and studies not reporting psychiatric or neurobiological outcomes.

Although primarily narrative in nature, this review applied a semi-systematic selection and synthesis process to identify consistent findings, highlight methodological weaknesses, and summarize mechanistic and clinical insights relevant to precision psychiatry and biomarker-guided treatment.

2. Neurobiological Mechanisms of Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential components for maintaining brain structure and function. These long-chain fatty acids are incorporated into neuronal membranes, where they influence multiple processes crucial to emotional regulation, neuroplasticity, and inflammatory control [6].

EPA and DHA exert antidepressant-like effects through interconnected biological pathways that link cellular processes to measurable biomarkers and clinical outcomes (Table 2). In brief, omega-3s:

1. Enhance synaptic membrane fluidity and receptor mobility within lipid rafts, facilitating efficient neurotransmission—particularly in serotonergic (5-HT) and dopaminergic (DA) circuits implicated in mood regulation [8,13,25];
2. Modulate neuroinflammatory signaling by reducing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), thereby lowering C-reactive protein (CRP) levels and attenuating microglial activation, a key driver of neuroimmune dysregulation in depression [5,7];
3. Promote neuroplasticity through the upregulation of brain-derived neurotrophic factor (BDNF), supporting neuronal survival, dendritic branching, and hippocampal neurogenesis—mechanisms associated with improved cognitive flexibility and resilience [10];
4. Reduce oxidative stress by neutralizing reactive oxygen species (ROS) and enhancing endogenous antioxidant defenses, mitigating cellular injury and redox imbalance [26,27].

Collectively, these pathways converge on quantifiable biomarkers—CRP, IL-6, TNF- α , BDNF, and ROS—that mediate the observed antidepressant effects of omega-3s. Decreases in inflammatory and oxidative markers, together with increases in BDNF levels, consistently correlate with symptom improvement and treatment response across clinical studies.

Thus, the neurobiological and clinical dimensions of omega-3 efficacy are intrinsically connected: modulation of these biomarkers provides a mechanistic bridge between molecular effects and patient outcomes, reinforcing a precision psychiatry framework in which biomarker-guided supplementation can optimize therapeutic benefit, particularly for individuals with inflammation-driven or treatment-resistant depression [7,12,28].

Table 2. Neurobiological Mechanisms of Omega-3 Fatty Acids in Mood Regulation.

Mechanism	Biological Effect	Impact on Mood
Synaptic Function	↑ Membrane fluidity, ↑ Neurotransmitter release (5-HT, DA)	Improved emotional regulation
Inflammatory Pathways	↓ IL-6, ↓ TNF-α, ↓ Microglial activation	Reduced neuroinflammation
Neuroplasticity	↑ BDNF expression, ↑ Hippocampal neurogenesis	Enhanced resilience, cognition
Oxidative Stress	↓ ROS, ↑ Antioxidant defenses	Lower cellular stress, mood stability
Overall Mood Regulation	System-wide neuromodulation	↓ Depressive symptoms, ↑ Cognitive function

Abbreviations: 5-HT = serotonin; DA = dopamine; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; BDNF = brain-derived neurotrophic factor; ROS = reactive oxygen species.

3. Inflammation as a Moderator of Treatment Response

A growing body of evidence suggests that systemic inflammation acts as a critical moderator in determining the clinical efficacy of omega-3 fatty acid supplementation, particularly eicosapentaenoic acid (EPA). Patients with elevated levels of inflammatory biomarkers—such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)—appear to derive greater therapeutic benefit from omega-3 treatment compared to non-inflamed individuals [5].

This has led to the identification of a clinically relevant subtype often referred to as “inflamed depression”, characterized by treatment resistance, fatigue, psychomotor slowing, and elevated immune-inflammatory activity. For this population, conventional antidepressants frequently show limited efficacy, whereas EPA-predominant omega-3 interventions appear to offer significant symptom reduction, especially when the EPA content exceeds 60% of the total formulation [7].

Findings across multiple randomized controlled trials and biomarker-stratified analyses have consistently shown that:

- EPA concentrations ≥60% are significantly more effective in patients with baseline inflammation, particularly those with CRP > 3 mg/L or elevated IL-6/TNF-α [13];
- Non-inflamed patients, by contrast, often experience no meaningful clinical benefit, highlighting the importance of biological stratification [11];
- Biomarker-guided supplementation strategies not only improve treatment precision but also help avoid unnecessary interventions and reduce interindividual variability in outcomes [7,12].

These results support a precision psychiatry framework, in which inflammatory status functions as a predictive biomarker, guiding clinicians in the selection of candidates most likely to respond to omega-3 augmentation. This biomarker-based approach aligns with broader efforts to tailor psychiatric interventions according to individual biological profiles, rather than relying solely on syndromic diagnosis.

From a clinical standpoint, integrating inflammatory biomarkers into treatment algorithms could enhance therapeutic decision-making in everyday practice. Simple and widely available assays—such as C-reactive protein (CRP) or interleukin-6 (IL-6) testing—may help clinicians identify patients more likely to benefit from EPA-enriched omega-3 supplementation. For example, individuals with CRP levels above 3 mg/L or evidence of low-grade systemic inflammation could be prioritized for adjunctive omega-3 therapy, whereas non-inflamed patients might be guided toward alternative interventions. Such biomarker-informed strategies represent a feasible step toward precision psychiatry, bridging translational research and personalized clinical care, as you can see in Table 3.

Table 3. Comparison Between Inflammatory and Non-Inflammatory Depression in Response to Omega-3 Treatment.

Feature	Inflamed Depression	Non-Inflamed Depression
CRP/IL-6/TNF-α levels	Elevated	Normal or low
Clinical symptoms	Fatigue, psychomotor slowing, anhedonia	Cognitive symptoms, sadness
Response to EPA	Significant (especially ≥60%)	Minimal or none
Optimal dose range	1–2 g/day	Unclear
Need for adjunctive treatment	High (often treatment-resistant)	Varies
Recommended testing	Baseline inflammation profile (blood test)	Optional

Abbreviations: CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; EPA = eicosapentaenoic acid.

4. Clinical Evidence: RCTs and Meta-Analyses

Over the past two decades, numerous randomized controlled trials (RCTs) and meta-analyses have evaluated the therapeutic potential of omega-3 polyunsaturated fatty acids (PUFAs) in major depressive disorder (MDD), bipolar depression, perinatal mood disturbances, and treatment-resistant depression (TRD) [2,4,7]. The collective evidence indicates that EPA-dominant formulations (≥60%) yield superior antidepressant efficacy, particularly when used as adjunctive treatments alongside conventional pharmacotherapy [5]. In contrast, DHA-only formulations have shown inconsistent or limited benefit, suggesting distinct neurobiological contributions of each fatty acid [6,8].

A smaller subset of monotherapy trials, where omega-3s were administered without concurrent antidepressants, reported mixed results—often showing modest improvement or significance only in patients with elevated inflammatory markers. This distinction underscores the importance of treatment context and baseline biological state in interpreting efficacy outcomes.

As detailed in Table 4, optimal dosing of EPA typically ranges from 1 to 2 g/day, though benefits have been observed at 500 mg/day in inflammation-driven subgroups [8,9]. In line with previous sections, patients with elevated CRP, IL-6, or TNF-α consistently show greater symptom reduction with EPA-enriched supplementation, supporting a biomarker-guided, precision psychiatry approach [11].

However, methodological heterogeneity—including variability in sample size, diagnostic criteria, treatment duration, and particularly the use of biologically active placebos such as olive or sunflower oil—complicates cross-trial comparisons and may attenuate true effect sizes [2,8,29]. Despite these limitations, recent systematic reviews and meta-analyses converge in supporting the clinical utility of EPA-rich formulations, especially in adjunctive therapy for TRD, bipolar depression (depressive phase), and perinatal mood disorders [30,31].

Overall, the accumulated evidence positions omega-3 fatty acids—especially EPA—as evidence-based adjuncts in the management of mood disorders within a personalized, inflammation-informed clinical framework.

Table 4. Selected Meta-Analyses and RCTs on Omega-3 Efficacy in Depression.

Study (Year)	Design	Main Finding	Omega-3 Type	Population
Grosso et al. (2014) [3]	Meta-analysis (RCTs)	Significant effect, esp. as adjunct	EPA ≥ 60%	General MDD
Martins (2009) [5]	Meta-analysis	EPA effective, DHA is not	Separated EPA/DHA	MDD

Table 4. Cont.

Study (Year)	Design	Main Finding	Omega-3 Type	Population
Mocking et al. (2016) [6]	RCT + Meta-analysis	Inflammation moderates EPA response	EPA	MDD with/without inflammation
Liao et al. (2021) [32]	Meta-analysis	EPA ≤ 1 g/day most effective	EPA ≥ 60%	MDD
Rapaport et al. (2016) [4]	RCT	EPA > placebo in high-CRP patients	EPA	Treatment-resistant MDD
Okereke et al. (2021) [2]	RCT (JAMA)	No effect, in general, population over 5 years	Mixed (low EPA)	Older adults (preventive)
Wu et al. (2024) [12]	RCT	Significant improvement with EPA monotherapy	EPA 2 g/day	Adults with MDD
Suneson et al. (2024) [30]	RCT	Matched treatment better in inflamed subgroup	EPA	Inflammatory depression

Abbreviations: RCT = randomized controlled trial; RCTs = randomized controlled trials; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CRP = C-reactive protein; MDD = major depressive disorder; JAMA = Journal of the American Medical Association.

5. The Role of Omega-6/Omega-3 Ratio in Diet

While much of the clinical literature has focused on the effects of omega-3 supplementation in mood disorders, increasing attention is being directed toward the dietary ratio of omega-6 to omega-3 fatty acids, which may represent an equally important determinant of inflammatory tone and affective stability [8,33]. In ancestral human diets—particularly those of hunter-gatherer societies—this ratio was estimated to be approximately 1:1, favoring a balanced eicosanoid profile and anti-inflammatory homeostasis. However, in modern Western dietary patterns, the ratio has shifted dramatically, often exceeding 15:1 or even 20:1, largely due to the widespread consumption of seed oils such as soybean, corn, and sunflower oils, which are rich in omega-6 linoleic acid [8,26].

This excessive omega-6 intake drives the synthesis of pro-inflammatory eicosanoids, promotes chronic low-grade systemic inflammation, and has been linked to the pathogenesis of depression, cardiovascular disease, and neurodegenerative conditions [6,13,34]. From an epidemiological standpoint, several studies have demonstrated that:

- Higher omega-6/omega-3 ratios are positively correlated with increased depression severity, elevated CRP levels, and a greater incidence of mood disorders [2,33].
- Populations adhering to Mediterranean or traditional Japanese diets, which are rich in omega-3s and low in processed seed oils, consistently exhibit lower prevalence of mood disturbances and greater emotional resilience [13,30].
- Reducing the dietary ratio to below 5:1—through increased omega-3 intake and reduced omega-6 consumption—may enhance the effectiveness of antidepressant treatments and improve response to nutritional interventions [8,26].

These findings suggest that omega-3 fatty acids should not be evaluated in isolation but rather within the context of overall fatty acid balance. A ratio-based dietary model encourages a holistic nutritional strategy aimed at limiting pro-inflammatory omega-6 sources while promoting anti-inflammatory omega-3 consumption, ultimately creating a biochemical environment more conducive to mood stability and therapeutic response.

Beyond correlational evidence, several population-based and interventional studies support the clinical relevance of dietary ratio correction. Large epidemiological cohorts, such as the SUN and PREDIMED trials, have shown that adherence to Mediterranean-style

diets—characterized by a lower omega-6/omega-3 ratio—was associated with significantly reduced depressive symptoms and greater psychological well-being. Similarly, controlled nutritional interventions reducing the ratio below 5:1 have been linked to measurable improvements in mood and perceived stress within weeks of dietary adjustment (see Table 5) [35–37]. These findings suggest that optimizing the dietary lipid profile may represent a feasible, non-pharmacological strategy to complement standard treatments for mood disorders.

Table 5. Omega-6/Omega-3 Ratio in Diet and Its Impact on Mental Health.

Diet Type	Omega-6/Omega-3 Ratio	Inflammatory Status	Mood Disorder Risk
Ancestral (hunter–gatherer)	~1:1	Low	Very low
Mediterranean diet	~3:1 to 5:1	Balanced	Low
Japanese diet	~4:1	Balanced	Low
Modern Western diet	15:1 to 20:1	High	High (↑ depression, ↑ anxiety)
Vegan/vegetarian (typical)	Often > 10:1	Variable (high LA intake)	Moderate to high

Abbreviations: LA = linoleic acid; ↑ indicates increased risk or higher levels.

5.1. Toward a Precision-Based Integration of Omega-3 Fatty Acids in Mood Disorder Treatment

The accumulated evidence from preclinical, neurobiological, and clinical research supports a context-dependent role for omega-3 fatty acids—particularly eicosapentaenoic acid (EPA)—in the treatment of mood disorders [6,8,9]. Through their actions on inflammation, neurotransmission, neuroplasticity, and oxidative stress, omega-3s have emerged as promising adjunctive therapies, especially in patients unresponsive to standard antidepressants [5,7]. Yet, marked interindividual variability persists, underscoring the need for personalized, biomarker-driven approaches.

Consistent moderators of clinical efficacy include systemic inflammation (CRP, IL-6, TNF-α), EPA:DHA ratio, dietary lipid balance, and clinical phenotype (e.g., treatment-resistant or high-inflammation depression) [11,12,33]. However, progress has been slowed by methodological inconsistencies across trials, such as small samples, short durations, variable dosing, and the use of biologically active placebos [2].

Future research should prioritize large-scale, biomarker-guided randomized controlled trials (RCTs) that incorporate:

- systematic biomarker stratification (CRP, IL-6, TNF-α, omega-3 index);
- standardized EPA-predominant formulations and dosage ranges;
- integration of nutritional counseling to optimize omega-6/omega-3 balance; and
- assessment of longitudinal outcomes in early and preventive psychiatry settings.

Such biologically informed, precision-oriented designs may finally clarify the true therapeutic potential of omega-3 fatty acids and establish their place in personalized mood disorder care.

5.2. Limitations of the Literature

Despite encouraging findings, the current evidence base remains constrained by heterogeneous designs, small sample sizes, short treatment durations, and lack of biomarker stratification, all of which limit comparability and generalizability [32,38]. Publication bias, inconsistent outcome measures, and biologically active placebos may further overestimate treatment effects.

To advance the field, future investigations must adopt standardized protocols, ensure adequate power and duration, and embed biomarker-based stratification within trial

design. Multicenter, large-scale RCTs are essential to validate efficacy across subtypes, refine optimal EPA:DHA formulations, and confirm the clinical utility of inflammatory and lipid biomarkers as predictive tools.

Until such evidence emerges, omega-3 supplementation should be viewed as a promising but still evolving adjunctive strategy, best applied within a precision psychiatry framework that integrates biological profiling, dietary modulation, and personalized treatment planning.

5.3. Translational Perspective

While the current evidence base is marked by heterogeneity and methodological shortcomings, the cumulative data on omega-3 fatty acids provide valuable insights that should guide clinical practice, preventive strategies, and future guideline development. A consistent theme across meta-analyses is the superior efficacy of EPA-predominant formulations compared to DHA-predominant ones, particularly at dosages around 1 g/day. This specificity suggests that clinical recommendations should move beyond generic calls for “omega-3 supplementation” and instead emphasize the EPA dose and ratio, aligning with recent guideline updates that advocate a minimum 2:1 EPA:DHA ratio for therapeutic purposes. Moreover, genetic and Mendelian randomization studies support a causal role of EPA in major depressive disorder (MDD), reinforcing the rationale for targeted supplementation strategies rather than broad population-based interventions [39,40].

From a clinical perspective, omega-3s are attractive as adjunctive treatments given their favorable safety profile and biological plausibility. In bipolar disorder, preclinical and clinical evidence links omega-3 supplementation with neuroprotective and neurogenic effects mediated in part by brain-derived neurotrophic factor (BDNF) signaling [41]. Although large-scale RCTs are still required, the available evidence suggests that EPA- and DHA-rich formulations may serve as effective mood stabilizer adjuncts in depressive phases, with potential benefits for cognitive and inflammatory pathways. Similarly, comprehensive reviews have highlighted the importance of integrating omega-3 supplementation into a personalized medicine framework, whereby baseline inflammatory status, omega-3 index, and comorbid metabolic factors are assessed before recommending treatment [42,43].

On a policy level, authoritative bodies have already recognized the potential role of omega-3s. The American Psychiatric Association (APA) recommends 1 g/day of combined EPA and DHA for patients with mood, impulse-control, or psychotic disorders, highlighting their role as a low-risk adjunct to standard therapies. However, recent critiques urge that such guidelines be refined to avoid overgeneralization and to ensure that recommendations reflect the most effective formulations and patient populations [7,44]. Beyond psychiatry, Mendelian and epidemiological evidence support the consideration of omega-3s in public health initiatives, particularly dietary policies aimed at reducing the omega-6:omega-3 imbalance characteristic of Western diets. Such policies could include promoting regular consumption of oily fish, fortifying foods with EPA and DHA, or developing synthetic analogs designed to optimize bioavailability and stability [45,46].

Taken together, these findings underscore the importance of embedding omega-3 research within a translational continuum, bridging molecular insights with clinical and population-level applications (see Table 6). In the short term, clinicians should consider EPA-predominant omega-3 supplementation as an adjunctive option for patients with depressive disorders, particularly those with high inflammatory markers or poor dietary omega-3 intake. In the longer term, refining guidelines to specify effective formulations, incorporating biomarker-driven personalization, and adopting preventive nutritional policies may ensure that the potential benefits of omega-3 fatty acids extend beyond individual patients to broader public health impact.

Table 6. Clinical Highlights—Key Take-Home Messages.

Area	Key Point
Efficacy	EPA ($\geq 60\%$ of formulations) consistently shows antidepressant effects; DHA alone is not effective.
Target patients	Strongest response observed in patients with elevated inflammation (CRP, IL-6, TNF- α).
Dosage	Clinical efficacy at 1–2 g/day EPA; benefits may appear at 500 mg/day in inflamed subgroups.
Dietary context	Western diets with omega-6/omega-3 ratio $> 15:1$ blunt treatment response; Mediterranean/Japanese patterns (3–5:1) support emotional resilience.
Precision psychiatry	Biomarker-guided stratification (inflammation, lipid profile) is essential to optimize outcomes.
Safety	Favorable tolerability profile, suitable as an adjunctive option in treatment-resistant or recurrent mood disorders.

Abbreviations: EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CRP = C-reactive protein; IL-6 = interleukin-6; TNF- α = tumor necrosis factor-alpha.

6. Conclusions

Omega-3 polyunsaturated fatty acids—particularly eicosapentaenoic acid (EPA)—represent a biologically plausible and evidence-supported adjunctive intervention in the management of mood disorders. Their therapeutic potential stems from multifaceted mechanisms involving membrane fluidity, neurotransmitter modulation, anti-inflammatory signaling, and neuroplasticity enhancement. Among these domains, systemic inflammation has emerged as the most consistent moderator of treatment response, with EPA-enriched formulations showing the strongest antidepressant effects in patients presenting with elevated inflammatory biomarkers such as CRP, IL-6, and TNF- α .

However, translation into clinical practice remains limited by the heterogeneity of study designs, populations, supplement compositions, and outcome measures. The variable efficacy of DHA-only preparations, the critical role of EPA concentration ($\geq 60\%$), and the influence of the dietary omega-6/omega-3 ratio all highlight the need for context-aware, personalized application rather than uniform supplementation strategies.

This review supports a biomarker-guided, precision-based framework for omega-3 use in psychiatry, emphasizing:

- Rigorous patient stratification based on inflammatory profiles;
- Use of EPA-predominant formulations at clinically effective dosages (1–2 g/day, or tailored to biomarker thresholds);
- Integration of dietary and lifestyle counseling aimed at restoring lipid homeostasis.

Importantly, omega-3 supplementation should be viewed not as a replacement for standard antidepressant therapy but as a complementary approach that enhances treatment efficacy and targets underlying biological dysfunctions. Within this multimodal, precision-oriented model, nutritional psychiatry can contribute meaningfully to individualized care—bridging molecular science and clinical practice to improve outcomes in mood disorder treatment. As emphasized by Fiorillo et al. (2025), advancing toward multimodal

and biomarker-guided treatment paradigms is essential for addressing the persistent burden of treatment-resistant depression, within which nutritional and metabolic strategies such as omega-3 supplementation may play a key complementary role [13].

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