Polyunsaturated Fatty Acids and Recurrent Mood Disorders: Phenomenology, Mechanisms, and Clinical Application

Erik Messamore[1,2], **Daniel M. Almeida**[3], **Ronald J. Jandacek**[4], and **Robert K. McNamara**[1,*]

[1]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH 45219-0516

[2]Lindner Center of HOPE, Mason, OH, USA

[3]Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45224 United States

[4]Department of Pathology, University of Cincinnati, Cincinnati OH 45237, USA

Abstract

A body of evidence has implicated dietary deficiency in omega-3 polyunsaturated fatty acids (*n*-3 PUFA), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the pathophysiology and etiology of recurrent mood disorders including major depressive disorder (MDD) and bipolar disorder. Cross-national and cross-sectional evidence suggests that greater habitual intake of *n*-3 PUFA is associated with reduced risk for developing mood symptoms. Meta-analyses provide strong evidence that patients with mood disorders exhibit low blood *n*-3 PUFA levels which are associated with increased risk for the initial development of mood symptoms in response to inflammation. While the etiology of this *n*-3 PUFA deficit may be multifactorial, *n*-3 PUFA supplementation is sufficient to correct this deficit and may also have antidepressant effects. Rodent studies suggest that *n*-3 PUFA deficiency during perinatal development can recapitulate key neuropathological, neurochemical, and behavioral features associated with mood disorders. Clinical neuroimaging studies suggest that low *n*-3 PUFA biostatus is associated with abnormalities in cortical structure and function also observed in mood disorders. Collectively, these findings implicate dietary *n*-3 PUFA insufficiency, particularly during development, in the pathophysiology of mood dysregulation, and support implementation of routine screening for and treatment of *n*-3 PUFA deficiency in patients with mood disorders.

*Corresponding Author: Robert K. McNamara, Ph.D., Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson Street, Rm. 3306, Cincinnati, OH 45218-0516, PH: 513-558-5601, FX: 513-558-4805, robert.mcnamara@uc.edu.

1. Introduction

Major mood disorders including major depressive disorder (MDD) and bipolar I disorder are
characterized by a dysregulation in emotional homeostasis. Specifically, MDD is typically
associated with recurrent and protracted episodes of depression and bipolar I disorder is
characterized by recurrent episodes of both mania as well as depression. The initial onset of
MDD most frequently occurs during adolescence and young adulthood [1], and the initial
onset of mania, and by definition bipolar I disorder, most frequently occurs during childhood
and adolescence [2]. Depressive symptoms frequently precede the initial onset of mania
[3,4] and are associated with increased risk for developing mania in the offspring of bipolar
parents [5]. Moreover, the high rate of attention deficit hyperactivity disorder (ADHD) in
youth with bipolar disorder, and lower age at onset of mania in patients with co-occurring
ADHD, are consistent with ADHD being risk factor for mania [6]. In addition to significant
psychosocial impairment, MDD and bipolar I disorder are associated with elevated rates of
cardiometabolic risk factors [7,8] and excess premature mortality [9,10] compared with
general population estimates.

Over the past three decades there has been extensive research devoted to identifying genetic
risk factors associated with mood disorders. However, to-date a robust and consistent pattern
has yet to emerge suggesting that the etiology is polygenic and multifactorial. Indeed,
subtotal heritability estimates and monozygotic twin discordance rates indicate that non-
genetic factors also confer significant vulnerability [11,12]. For example, a meta-analysis of
community-based twin studies of MDD yielded a heritability estimate of 0.37, indicating
that approximately two thirds of the liability is attributable to environmental factors [13].
While there is strong evidence for familial transmission of bipolar disorder [14–16], non-
genetic factors shared within families may also contribute to risk transmission [17]. There is
also growing evidence that early environmental factors can impact gene expression patterns
through epigenetic modifications (i.e., DNA methylation)[18]. Because environmental risk
factors are amenable to modification, developing a clearer understanding of their role in the
etiology of mood disorders may provide new insights to guide and inform early intervention
strategies.

One candidate environmental risk factor that is amenable to modification is the habitual diet.
Evidence has emerged over the last three decades which suggests that the fatty acid
composition of the habitual diet may be relevant to the pathophysiology and potentially
etiology of mood disorders. Cross-national and cross-sectional epidemiological surveys,
longitudinal prospective cohort studies, prospective intervention studies, and basic science
research have provided converging evidence implicating omega-3 (*n*-3) polyunsaturated fatty
acids (PUFA) insufficiency, and associated increases in the *n*-6/*n*-3 PUFA ratio, in the
pathophysiology of mood disorders. The goals of this review are to provide an overview of

epidemiological and clinical research investigating the role of these PUFAs in mood disorders, discuss plausible mechanisms mediating dietary PUFA composition and mood dysregulation, and then consider strategies to translate this evidence into clinical practice.

2. PUFA Biochemistry

As background, the PUFA family includes n-3 and n-6 fatty acids. Ubiquitous dietary sources of the plant-derived n-3 PUFA precursor α-linolenic acid (18:3n-3) include flaxseed, linseed, canola, soy, and perilla oils, and sources of the plant-derived n-6 PUFA precursor linoleic acid (18:2n-6) include safflower, soy, and corn oils. These plant-derived PUFAs are considered 'essential' because they cannot be formed endogenously and therefore require procurement through the diet. The biosynthesis of n-3 PUFAs, including eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), and n-6 PUFAs including arachidonic acid (20:4n-6), from their plant-derived precursors requires a series of common and competitive microsomal desaturation and elongation reactions [19](Fig. 1). Enzymes regulating PUFA biosynthesis include delta-6 desaturase (*FADS2*) and delta-5 desaturase (*FADS1*) and elongases *(e.g., ELOVL5).* Desaturase enzymes are regulated by multiple factors including gonadal hormones [20–24], insulin [25], single nucleotide polymorphisms [26], as well as epigenetic (i.e., DNA methylation) modifications induced by dietary fatty acids [27,28]. The final synthesis of DHA is catalyzed by multiple enzymes within peroxisomes [29], and heritable defects in peroxisome biogenesis genes are associated with impaired DHA synthesis as well as other lipid and neurological abnormalities [30]. Nevertheless, it has been estimated that only 24 percent of the variability in levels of EPA and DHA arise from heritable factors [31]. Therefore, n-3 and n-6 PUFA biosynthesis is complex and involves both heritable genetic as well as non-genetic factors.

Extant evidence from human studies suggest that the biosynthesis of n-3 and n-6 PUFAs from plant-derived fatty acid precursors is extremely inefficient [32–35]. This may be due in part to the fact that n-3 and n-6 PUFA biosynthesis are mediated by common and competitive enzymatic reactions. Indeed, translational evidence indicates that the balance of linolenic acid to α-linolenic acid in the diet is an important determinant of n-3 and n-6 PUFA biosynthesis [36–39]. Dietary intake of preformed n-3 or n-6 PUFAs is more effective for increasing their levels in peripheral or central tissues than is enzyme-mediated biosynthesis from short-chain precursors [40–44]. Preformed n-6 PUFAs including arachidonic acid can be obtained directly from animal-based foods including beef, chicken, and eggs, and preformed n-3 PUFAs can be obtained directly from fatty cold water fish, including salmon, trout, tuna, as well as fish oil and algal-derived supplements. Therefore, both n-3 and n-6 PUFA content as well as the ratio of linolenic acid to α-linolenic acid in the habitual diet are important determinants of PUFA biostatus.

In addition to being incorporated into cellular phospholipid membranes, the n-6 PUFAs including arachidonic acid and n-3 PUFAs including EPA and DHA also serve as precursors for immune-inflammatory signaling modulators (Fig. 1). Phospholipid-bound arachidonic acid can be mobilized via calcium-dependent cytosolic isoform of phospholipase A_2 (cPLA$_2$), and free arachidonic acid is a substrate for cyclooxygenase (COX)-mediated biosynthesis of prostaglandins (i.e., PGH$_2$) and thromboxanes, as well as lipoxygenase

(LOX)-mediated biosynthesis of leukotrienes and lipoxins. COX-generated PGH_2 is converted to PGE_2 via PGE synthase, and PGE_2 stimulates the biosynthesis of down-stream pro-inflammatory cytokines including interleukin-6 (IL-6) at the level of transcription [45–48]. In contrast, EPA competes with arachidonic acid for metabolism by COX enzymes, and COX and LOX metabolites of DHA and EPA (i.e., D- and E-series resolvins) have potent inflammation-resolving properties [48–52]. Therefore, EPA+DHA and arachidonic acid have opposing effects on immune-inflammatory signaling cascades, and a shift in their ratio may contribute to dysregulated inflammatory signaling homeostasis [53].

3. Associations with mood disorders

3.1. Observational studies

Cross-national evidence indicates that habitual fish intake is correlated with breastmilk [54] and blood [55] n-3 PUFA biostatus. For example, in the U.S., where annual seafood consumption is approximately 2-fold lower than in Japan [56], erythrocyte EPA+DHA levels are approximately fifty percent lower [57,58] and breastmilk DHA levels approximately 5-fold lower [54] compared with Japanese levels. Cross-national epidemiological surveys have observed a significant inverse correlation between per capita fish or seafood consumption and lifetime prevalence rates of MDD [59,60], postpartum depression [61], and bipolar spectrum disorders [62]. A retrospective study found that shifts away from fish-based to Western diets in Arctic communities were associated with increased rates of seasonal affective disorder, depression, suicide, and cardiovascular disease [63]. Moreover, a longitudinal prospective study of 4,856 adults residing in the U.S. found that greater linoleic acid intake was associated with increased risk of depression in men but not women during the 10.6 year follow-up period [64]. Within the U.S., it has been estimated that over the last century there has been a gradual increase in the consumption of linoleic acid and a corresponding decline in α-linolenic acid and n-3 PUFAs [65]. It will therefore be of interest to retrospectively evaluate whether this increase in n-6/n-3 PUFA ratio was associated with increased prevalence rates of mood disorders in the U.S. during this period.

Cross-sectional studies further suggest that higher intake of fish (as well as fruit, vegetables, and whole grains) is associated with a reduced depression risk [66]. For example, a cross-sectional survey of 21,835 adult and elderly subjects from Norway found that subjects who ingested cod liver oil on a daily basis (EPA: ~300–600 mg/d; DHA: ~300–600 mg/d) were 30 percent less likely to have depressive symptoms than non-users after adjusting for multiple possible confounding factors [67]. In view of evidence that the initial onset of mood disorders frequently occurs during the peri-adolescent period [1,2], it is notable that surveys have found that a large percentage of adolescents residing in Western countries consume low quantities of n-3 PUFA in their habitual diet which may be associated with depressive symptoms and cardiometabolic risk factors [68–77]. While findings from dietary surveys provide general support for an inverse association between n-3 PUFA intake and the prevalence of depressive symptoms in the general population, collinear cultural, socioeconomic, and/or genetic variables may mediate or moderate this association [78].

3.2. PUFA biostatus

Because estimating dietary fatty acid intake based on retrospective recall may be prone to errors and biases, and the *n*-3 PUFA composition in different types of fish varies widely, an alternative and more objective approach is to investigate fatty acid levels in blood and tissues. For example, erythrocyte (red blood cell) phospholipid membrane EPA+DHA levels are positively correlated with habitual dietary fish intake frequency [58], and increase in a linear dose-dependent manner following long-term fish oil supplementation [79]. Using this approach, several cross-sectional studies conducted in different countries have investigated blood fatty acid levels in patients with mood disorders. A meta-analysis of fourteen cross-sectional studies comprising n=648 depressed patients and n=2,670 healthy control subjects observed significant blood (plasma, erythrocyte) deficits in EPA and DHA, but not arachidonic acid or total *n*-6 PUFA, in patients with depressive symptoms [80]. Similarly, a meta-analysis of 6 cross-sectional studies comprising n=118 bipolar I disorder patients and n=147 healthy controls found significant erythrocyte deficits in DHA, and to a lesser extent EPA, in patients with bipolar I disorder [81]. In the latter study levels of linoleic acid and arachidonic acid were not different, and extant evidence also suggests that saturated and monounsaturated (i.e., oleic acid) fatty acid levels are not abnormal in patients with mood disorders. While the majority of these studies were conducted in adults, other studies have similarly found that pediatric and adolescent patients with MDD [82,83] or bipolar I disorder [84,85] also exhibit erythrocyte EPA and/or DHA deficits compared with healthy youth. Together, these findings provide strong evidence for an association between mood disorders and low EPA and/or DHA biostatus, as well as associated increases in the *n*-6/*n*-3 PUFA ratio.

Recent evidence further suggests that *n*-3 PUFA deficits coincide with, and may precede, the initial onset of mood symptoms. For example, robust erythrocyte DHA deficits were observed in mediation-naïve first-episode manic patients that were diagnosed with bipolar I disorder [86]. Moreover, asymptomatic adolescents who are at increased risk for developing mood disorders i.e., they have with a biological parent with bipolar I disorder [15], exhibit erythrocyte EPA+DHA levels that are intermediate between first-episode manic patients and offspring of parents with no family history of psychiatric illness [85]. Furthermore, adolescent offspring of bipolar parents with depressive symptoms or MDD, i.e., at ultra-high risk for developing bipolar I disorder [5], exhibit erythrocyte EPA+DHA deficits that are significantly lower than adolescents with no personal or family history of psychiatric illness [85]. These findings suggest that low EPA+DHA biostatus coincides with the initial onset of mood symptoms and may be associated with symptom progression in high-risk youth.

Some fatty acid composition studies [84,87,88] but not others [83,85,86,89] have observed an inverse correlation between blood *n*-3 PUFA levels, or positive correlations with the *n*-3/*n*-6 PUFA ratio (i.e., arachidonic acid/EPA), and depression or manic symptom severity within groups of patients. The latter discrepancies may be due in part to uniformity in mood symptom severity scores and more robust inverse correlations between manic and depressive symptom severity and blood *n*-3 PUFA levels are observed when both healthy controls and patients with a wider range of symptom severity are included [85]. Moreover, a recent study found that the inverse association between EPA+DHA levels and depressive symptoms was

only observed in subjects with elevated oxidative stress biomarkers [90]. It is also notable that a large percentage of bipolar patients have a history of psychotic symptoms [91] and a meta-analysis of case-control studies observed significant erythrocyte DHA as well as arachidonic acid deficits in first-episode psychosis patients [92]. The latter finding suggests that arachidonic acid deficits may distinguish risk for psychosis versus MDD or bipolar disorder. Furthermore, there is a high rate of ADHD in youth with bipolar disorder [6], and a meta-analysis found that youth with ADHD also exhibit robust EPA+DHA deficits [93]. These findings suggest that n-3 PUFA deficits are not uniquely associated with mood symptoms, and are also associated with a broader range of psychiatric symptoms frequently exhibited by patients with mood disorders.

While prospective longitudinal studies are required to evaluate whether low EPA+DHA biostatus can serve as a reliable prognostic indicator of risk for 'endogenous' mood dysregulation, recent evidence suggests that low n-3 PUFA biostatus increases risk for the initial onset of mood symptoms elicited by 'exogenous' pro-inflammatory signaling cascades [94]. Specifically, prospective studies have found that lower baseline DHA levels, or a higher ratio of arachidonic acid to EPA+DHA, are a significant predictor of depression development in initially non-depressed hepatitis C patients during treatment with interferon-α (IFN-α)[95–97]. Additionally, during IFN-α treatment hepatitis C patients with a higher baseline ratio of arachidonic acid to EPA+DHA are also at increased risk for developing core symptoms of bipolar I disorder including anger and irritability [98]. In view of evidence that a subset of patients with mood disorders exhibit elevated biomarkers of inflammation [53], these prospective findings suggest that low EPA+DHA biostatus may also increase risk for 'endogenous' mood dysregulation in response to a natural pro-inflammatory challenge (e.g., viral infection). While there is currently nothing known about DHA and EPA metabolite levels (i.e., D- and E-series resolvins) in patients with mood disorders, research is warranted to evaluate whether impaired biosynthesis of D- and E-series resolvins secondary to DHA +EPA deficits contribute to mood dysregulation by creating a chronic low-grade pro-inflammatory state.

Other cross-sectional studies have investigated fatty acid levels in postmortem brain tissue. The most abundant n-3 PUFA found in mammalian brain gray matter is DHA, which comprises approximately 12% of total fatty acid composition, whereas EPA is rapidly oxidized and consequently comprises <1% of total brain fatty acid composition [99]. Preliminary evidence suggests that mammalian erythrocyte and cortical gray matter DHA levels are positively correlated under steady state dietary conditions [41,100]. Although several case-control studies have investigated the fatty acid composition of regional postmortem gray matter from patients with mood disorders, some studies but not others have observed DHA deficits in patients with MDD or bipolar I disorder [101–113]. These equivocal results may be due in part to the challenges and limitations associated with the postmortem approach [114], and additional research is needed to understand the relationship between blood and cortical DHA levels in patients with mood disorders. An alternative approach is to investigate relationships between n-3 PUFA intake and biostatus and neurophysiological variables in living patients using neuroimaging [115]. As discussed in great detail below, emerging evidence suggests that DHA biostatus is associated with

different measures of cortical structural and functional integrity in brain regions repeatedly implicated in the pathophysiology of mood disorders.

In view of evidence that mood disorders are associated with elevated rates of cardiometabolic risk factors [7,8] and excess premature mortality attributable in part to cardiovascular-related disorders [9,10], it is also relevant that low erythrocyte EPA+DHA biostatus is associated with cardiometabolic risk factors including elevated triacylglycerol and C-reactive protein levels [116,117] as well as risk for sudden cardiac death [118–121]. Moreover, suicide is a primary cause of excess premature mortality in patients with mood disorders [9,10], and low erythrocyte DHA biostatus was found to be a significant predictor of future suicidal attempts in medication-free MDD patients [122], and blood *n*-3 PUFA deficits are observed in suicidal patients [123,124]. Therefore, *n*-3 PUFA deficits exhibited by patients with mood disorders may also contribute risk for premature mortality secondary to suicide and cardiometabolic disorders.

4. Etiological mechanisms

While extant evidence suggests that mood disorders are associated with blood deficits in *n*-3 PUFA, but not *n*-6 PUFA, understanding the etiological variables that contribute to blood *n*-3 PUFA deficits may have implications for treatment and prevention. Candidate etiological mechanisms including impaired biosynthesis, elevated lipid peroxidation, psychotropic medication effects, and dietary *n*-3 PUFA insufficiency, are discussed in greater detail below (Fig. 2).

4.1. Impaired biosynthesis

Reductions in the expression or function of the microsomal and peroxisomal enzymes that mediate EPA and/or DHA biosynthesis from α-linolenic acid would be anticipated to lead to robust deficits in blood EPA and DHA levels [29,125,126]. However, extant evidence suggests that mood disorders are not associated with deficits in other major *n*-3 PUFAs including docosapentaenoic acid (DPA, 22:5*n*-3) or *n*-6 PUFA including arachidonic acid [80,81]. This fatty acid signature would suggest that EPA+DHA deficits cannot be attributed to impaired microsomal desaturase and elongase activity. This is also supported by a recent genotyping study which did not observe an association between common single-nucleotide polymorphisms in *FADS1* or *FASD2* genes and depression or suicidality in MDD patients [127]. However, DNA methylation in the *Elovl5* gene was found to be associated with depression and suicidality [128], and abnormalities in *FADS1* and *FADS2* mRNA expression have been observed in the postmortem prefrontal cortex of patients with mood disorders [129–131]. Recent evidence further suggests that patients with mood disorders do not exhibit impaired peroxisomal function despite exhibiting robust DHA deficits [132]. While additional research is needed to better characterize the role of genetic and epigenetic factors in the *n*-3 PUFA deficits observed in patients with mood disorders, existing evidence suggests that impaired biosynthesis does not represent a major etiological mechanism.

4.2. Lipid peroxidation

Mood disorders are associated with elevated indices of oxidative stress [133,134] which may also contribute to erythrocyte membrane EPA and DHA deficits. For example, incubation of erythrocytes from healthy control subjects with hydrogen peroxide decreased EPA and DHA composition to levels observed in MDD patients [135]. Moreover, deficiencies in oxidative defenses (i.e., vitamin E, alpha-tocopherol) are associated with increased susceptibility of erythrocyte *n*-3 PUFA to oxidative degradation [136], and erythrocyte EPA+DHA composition is positively correlated with plasma vitamin E concentrations [137]. Different case-control studies have separately found that MDD patients exhibit significantly lower serum vitamin E concentrations [138] and elevated indices of oxidative stress [133]. However, other evidence suggests that erythrocyte EPA+DHA deficits exhibited by patients with mood disorders are dissociable from biomarkers of lipid peroxidation [139]. For example, first-episode manic patients exhibit *lower* indices of lipid peroxidation [140] *and* lower erythrocyte EPA+DHA levels [85,86] compared with healthy controls. Nevertheless, additional studies are warranted to investigate whether antioxidant supplementation can increase EPA+DHA levels in patients with mood disorders to evaluate causality.

In view of the high rate of cigarette smoking among patients with mood disorders [141,142], it is also relevant that studies have found that cigarette smoking is associated with elevated indices of erythrocyte lipid peroxidation [143], and is also inversely correlated with plasma EPA+DHA and arachidonic acid concentrations [144]. However, other studies have found that cigarette smoking is not correlated with erythrocyte EPA+DHA levels among healthy male and female adults [57,58], and cross-sectional studies that specifically investigated the contribution of cigarette smoking to erythrocyte EPA+DHA status in patients with mood disorders did not observe an association [86,145]. Furthermore, robust erythrocyte EPA +DHA deficits have been observed in patients that reported to have never smoked cigarettes [86]. These findings suggest that elevated lipid peroxidation secondary to cigarette smoking cannot uniformly account for the EPA+DHA deficits observed in patients with mood disorders.

4.3. Psychotropic medications

Another potential etiological factor that may contribute to *n*-3 PUFA deficits in mood disorder patients is chronic exposure to psychotropic medications, including mood-stabilizers, antidepressants, or antipsychotics. Indeed, many of the case-control studies observing *n*-3 PUFA deficits in patients with mood disorders employed medicated patients. However, EPA+DHA deficits have been observed in chronically medicated, medication-withdrawn, and medication-naïve patients [85,86,89]. Moreover, in a prospective study it was found that erythrocyte DHA deficits observed in first-episode bipolar patients at medication-free baseline were not altered following 52 weeks treatment with lithium [86]. Additional evidence suggests that erythrocyte EPA and/or DHA deficits are present in medication-free [85,89] as well as selective serotonin reuptake inhibitor (SSRI)-treated [83] MDD patients. Furthermore, chronic treatment with the SSRI fluoxetine, which resulted in clinically-relevant plasma concentrations, did not significantly alter rat erythrocyte EPA +DHA levels under controlled dietary conditions [146]. In contrast, chronic treatment with the atypical antipsychotics risperidone or quetiapine significantly *increased* erythrocyte

DHA composition in rats under controlled dietary conditions [147,148]. However, 52 week treatment with quetiapine did not significantly alter erythrocyte DHA deficits observed in medication-free bipolar patients at baseline [86]. Taken collectively, extant translational evidence would suggest that the blood EPA+DHA deficits observed in mood disorder patients cannot be wholly attributed to chronic exposure to psychotropic medications.

4.4. Dietary *n*-3 PUFA insufficiency

Several lines of evidence suggest that the *n*-3 PUFA deficit observed in patients with MDD or bipolar disorder are attributable to dietary *n*-3 PUFA insufficiency. This is directly supported by evidence that patients with mood disorders consume less EPA+DHA in their habitual diet [84,149,150]. Perhaps most compelling is the observation that dietary supplementation with fish oil significantly increases erythrocyte EPA+DHA levels in patients with mood disorders [83,151,152]. The latter finding additionally suggests that patients can efficiently absorb EPA+DHA from the gut and incorporate these fatty acids into erythrocyte membranes. In contrast, dietary supplementation with flax oil (a rich source of α-linolenic acid) does not significantly increase erythrocyte DHA levels in youth with bipolar I disorder [153], a result also observed in healthy subjects [42]. While greater intake of linoleic acid would have the potential to decrease *n*-3 PUFAs in patients with mood disorders [36], extant evidence suggests that patients with mood disorders do not exhibit elevated blood linoleic acid or *n*-6 PUFA levels compared with healthy subjects [80,81]. Therefore, while the etiology of the EPA+DHA deficits observed in patients with mood disorders may be multifactorial, extant evidence suggests that increasing dietary EPA+DHA intake is sufficient to correct this deficit.

5. *n*-3 PUFA supplementation studies

There has been considerable interest in evaluating whether *n*-3 PUFA supplementation has acute psychotherapeutic effects in patients with mood disorders. Over the past 20 years, numerous open-label and placebo-controlled *n*-3 PUFA supplementation trials have been conducted, and more recently several independent meta-analyses have been performed on placebo-controlled trials. While there have been discrepancies among the results of placebo-controlled trials, independent meta-analyses have reported a modest but statistically significant advantage of *n*-3 PUFA interventions over placebo for reducing depression symptom severity in patients with MDD [154–157] or bipolar disorder [155,158]. Controlled and open-label trials have also found that *n*-3 PUFA supplementation, administered either adjunctively or as monotherapy, significantly reduce depression and manic symptom severity in pediatric and adolescent patients [83,151,152,159]. Secondary analyses suggest that a larger EPA/DHA ratio has greater antidepressant efficacy [157], and a recent study found that higher EPA+DHA biostatus at baseline, which was associated with higher endpoint EPA+DHA biostatus following *n*-3 PUFA supplementation, was associated with increased antidepressant efficacy in depressed coronary heart disease patients [160]. Emerging evidence from controlled and open-label trials further suggests that *n*-3 PUFAs may augment the therapeutic efficacy of SSRI medications [83,161–164] and may be protective against adverse cardiometabolic [165–168] and hepatic [169,170] side-effects associated with second generation antipsychotic medications. Additional evidence suggests that increasing

n-3 PUFA biostatus may be protective against the initial onset of depressive symptoms in hepatitis C patients during treatment with IFN-α [171], and to reduce suicidality in MDD patients [164]. Although extant evidence suggests that n-3 PUFA supplementation may have acute antidepressant and/or mood-stabilizing effects, large-scale controlled trials will be required to confirm and extend this body of evidence.

6. Neuropathophysiological mechanisms

Translational studies have elucidated several plausible biological mechanisms that may mediate the association between low n-3 PUFA status and mood dysregulation (Fig. 2). Consistent with a neurodevelopmental etiology, the initial onset of mood disorders frequently occurs during childhood and adolescence [1,2], a developmental period associated with the rapid cortical accrual of DHA [100] and both regressive (i.e., synaptic pruning) and progressive (i.e., myelination) cortical maturational processes [172–174]. Rodent neurodevelopmental studies have provided critical insight into the role of dietary n-3 fatty acids in normal brain development, and have the advantage of systematic and selective manipulation of n-3 fatty acid intake while controlling myriad potentially confounding variables that can impact clinical research. Additionally, converging evidence from neuroimaging studies is providing clarification regarding brain regions and neuropathological biomarkers associated with mood disorders, and more recently, associations between these biomarkers and n-3 PUFA biostatus.

6.1. Rodent studies

In brief, rodent studies have demonstrated that deficits in brain DHA accrual during perinatal development are associated with perturbations in neurogenesis [175,176], neuroblast migration [177,178], neurotrophic factor expression [179,180], and synaptogenesis [181]. Deficits in cortical DHA accrual during perinatal development are also associated with elevations in peripheral [182] and central [183,184] pro-inflammatory signaling cascades which have been found in separate studies to be down-regulated by mood-stabilizer medications [185]. Moreover, greater cortical DHA levels increase resilience to neurodegenerative processes associated with inflammation [186], lipid peroxidation [187,188] and glutamate excitotoxicity [189–191], and promotes neurovascular coupling [192]. Rodent studies also suggest that perinatal n-3 PUFA deficiency leads to long-standing alterations in neurotransmitter systems, including dopamine [193–195] and serotonin [196,197], and neuroendocrine systems, including corticosterone [198] and melatonin [199], implicated in mood regulation. n-3 PUFA deficiency also leads to elevated behavioral indices of depression, aggression, and anxiety [198,200,201] whereas dietary fish oil fortification decreases depression-like behavior [202,203]. These and other rodent findings suggest that n-3 PUFA deficiency during perinatal development can recapitulate key neuropathological, neurochemical, and behavioral features associated with mood disorders.

6.2. Clinical neuroimaging studies

There is emerging consensus from neuroimaging evidence that mood disorders are associated with abnormalities in connectivity between the prefrontal cortex and limbic emotional structures mediated in part by frontal white matter pathology [204–214]. Frontal

lobe connectivity with limbic structures is mediated in part by the uncinate fasciculus and superior longitudinal fasciculus, prominent white matter tracts that develop during gestation and undergo significant maturation during childhood and adolescence. Accumulating evidence suggests that *n*-3 PUFAs promote cortical white matter microstructural integrity [215], and a recent study found that fish oil supplementation increased white matter microstructural integrity and decreased depressive symptom severity in MDD patients [216]. Moreover, perinatal *n*-3 PUFA deficiency in monkeys [217], or low erythrocyte DHA biostatus in typically developing children [218], are both associated with reduced functional connectivity within prefrontal cortical networks. These preliminary findings suggest that lower *n*-3 PUFA intake and biostatus may contribute to reduced functional connectivity within prefrontal cortical networks.

The third trimester of human gestation is a period associated with the initial formation of connections between brain regions including the uncinate fasciculus and superior longitudinal fasciculus [219], and preterm birth, which leads to deficits in third trimester cortical DHA accrual [220–222], is associated with both decreased white matter tract integrity and reduced connectivity within frontal lobe cortical networks [223–232]. In view of the high rate of ADHD in youth with bipolar disorder, it is relevant that preterm birth and/or low birth weight is associated with increased risk for developing ADHD in childhood [233–235] and mood, anxiety, and psychotic disorders during adolescence and young adulthood independent of multiple confounding variables including maternal history of psychiatric illness [236–239]. While these associations suggest that DHA deficits during critical neurodevelopmental periods may contribute to suboptimal frontal lobe cortical network maturation, it is not currently known whether early deficits in cortical DHA accrual directly contribute to frontal lobe cortical network pathology in patients with mood disorders.

Evidence from neuroimaging studies also suggest that *n*-3 PUFA intake and biostatus is associated with cortical structural integrity over the lifespan [240–245]. For example, greater habitual dietary *n*-3 PUFA intake [240] and erythrocyte EPA+DHA composition [245] are associated with larger hippocampal volumes among healthy adults. It is relevant, therefore, that hippocampal gray matter volume deficits are among the most consistent and robust neurostructural abnormalities observed in patients with MDD [246]. Furthermore, greater habitual dietary *n*-3 PUFA intake is associated with larger amygdala volumes among healthy adults [240], and structural imaging studies have consistently observed smaller amygdala volumes in children and adolescents with bipolar I disorder [247]. Near-infrared spectroscopy [248,249], functional magnetic resonance imaging (fMRI)[250,251], and magnetic resonance spectroscopy (^{1}H MRS) studies [252–254], further suggest that higher *n*-3 PUFA intake or biostatus promote cerebrovascular efficiency and neuronal integrity. As observed in *n*-3 PUFA deficient rodents [183], recent neuroimaging evidence suggests that depression is also associated with increased microglial activation indicative of neuroinflammation [255]. While this preliminary neuroimaging evidence supports a potential link between low *n*-3 PUFA status and the abnormalities in cortical structure and function observed in patients with mood disorders, additional research is needed to establish this link and elucidate whether these abnormalities can be prevented with early *n*-3 PUFA intervention.

7. Clinical applications

In the previous sections we reviewed a body of translational evidence which suggests that *n*-3 PUFA deficiency, particularly during perinatal development, may represent a modifiable risk factor for neuropathophysiological processes implicated in mood disorders. Together these and other data provide a compelling rationale to begin to translate this body of evidence into clinical practice in an effort to optimize treatment and improve long-term health outcomes for patients. Below we briefly discuss existing screening and treatment resources and general guidelines required for implementation in psychiatric practice.

7.1. Screening for *n*-3 PUFA deficiency

Blood fatty acid analysis by gas-liquid chromatography can provide a valid measure of a patient's fatty acid biostatus [256]. As discussed in greater detail previously, erythrocyte EPA+DHA composition, termed the 'omega-3 index', has been widely characterized as a risk biomarker in the context of coronary heart disease [121,257]. In this regard, erythrocyte EPA+DHA composition of 4% of total fatty acids has been suggested to represent an appropriate criterion for defining a state of '*n*-3 PUFA deficiency' warranting corrective intervention. Based on cross-sectional evidence that patients with mood disorders commonly exhibit erythrocyte EPA and/or DHA deficits [80,81], and are at increased risk for cardiovascular-related disease [9,10], erythrocyte EPA+DHA composition of 4% may also be considered undesirable in the context of psychiatric practice. It is notable that one study found that 90 percent of adolescents with SSRI-resistant MDD exhibited erythrocyte EPA +DHA composition of 4% [83]. Importantly, there are currently laboratories that specialize in determining the fatty acid composition of whole blood obtained from a finger prick, a sampling method that is highly amenable to routine clinical practice. As proof-of-concept, beginning in mid-2014 measurement of whole blood fatty acid levels was implemented as part of the routine laboratory assessment at a university-affiliated mental health care center. To date fatty acid levels have been collected from over 100 patients with mood and anxiety disorders. Our initial results suggest that the rate of whole blood EPA+DHA levels of 4 percent of total fatty acid composition in patients is significantly greater than the general U.S. population (75% vs. 25%)[258]. Therefore, analogous to routine cholesterol testing routine testing for *n*-3 PUFA deficiency is currently feasible within the context psychiatric clinical practice.

7.2. Treating *n*-3 PUFA deficiency

As discussed, dietary supplementation with *n*-3 PUFA formulations (i.e., fish oil) is efficacious for the treatment of EPA+DHA deficits observed in patients with mood disorders. Prescription ethyl ester EPA+DHA (Lovaza® in the US, Omacor® in Europe, GlaxoSmithKline), purified ethyl ester EPA containing no DHA (Vascepa®, Amarin Corporation), and a free versus ethyl ester EPA+DHA formulation (Epanova®, AstraZeneca) have been approved by the U.S. FDA for the treatment of hypertriacylglycerolemia (500 mg/dL). More recently a generic version of Lovaza has become available (Teva Pharmaceuticals USA, Inc.). Over-the-counter fish oil supplements, as well as formulations derived from vegetarian sources, containing similar EPA+DHA concentrations are also widely available. It is important to note, however, that no *n*-3 PUFA

formulation is currently approved by the FDA for the treatment of any psychiatric disorder, and reimbursement for off-label use is ultimately at the discretion of the insurance provider.

Regarding guidelines for dosing, the U.S. Food and Drug Administration (FDA) considers *n*-3 PUFA doses up to 3 g/d to be 'generally regarded as safe', and the European Food Safety Authority (EFSA) considers doses up to 5 g/d to be safe. The American Psychiatric Association has adopted the consensus recommendations of the American Heart Association for an EPA+DHA dose of 1 g/d in patients with MDD [259]. The American Heart Association also recommends 3 g/d EPA+DHA for reducing elevated triacylglycerol levels. Controlled dose-response studies suggest that daily EPA+DHA doses of 1–2 g are sufficient to increase erythrocyte EPA+DHA composition to levels 4% [79]. As with other psychotropic medications, upward dose titration may be required as clinically indicated (e.g., [151]) and lower initial starting doses may be appropriate for children.

Potential acute adverse events associated with *n*-3 PUFA supplementation include gastrointestinal disturbances, including nausea, diarrhea, gastroesophageal reflux, belching, and less commonly vomiting. To minimize these gastrointestinal adverse events patients should be instructed to take their pills with meals. Although taking fish oil at high doses (>3 g/d) has been associated in isolated cases with increased bleeding time in subjects also taking anticoagulant medications [260], controlled clinical trials have found that chronic high dose EPA+DHA alone or in combination with aspirin does not increase risk for clinically-significant increases in bleeding time [261]. Extant evidence further suggests that there is no relationship between *n*-3 PUFAs and prostate cancer risk [262]. Another safety consideration involves the potential threat of contamination of fish and seafood with methyl mercury and other environmental pollutants. However, most fish oil supplements are highly purified and do not exceed U.S. FDA limits for methyl mercury and other environmental contaminants. As with all medications, patients should be informed of potential risks associated with fish oil-based products.

8.0. Summary and conclusions

Emerging translational evidence over the past three decades suggests that habitual dietary *n*-3 PUFA insufficiency, particularly during perinatal development, may represent a modifiable risk factor for mood disorders. This is indirectly supported by cross-national as well as cross-sectional evidence for an inverse association between dietary *n*-3 PUFA intake and prevalence rates of mood disorders in the general population. Meta-analyses of cross-sectional fatty acid composition studies provide strong evidence that pediatric, adolescent, and adult patients with mood disorders exhibit blood *n*-3 PUFA deficits compared with healthy age-matched controls. While controversial, evidence also suggests that *n*-3 PUFA deficiency may decrease risk for suicide and cardiovascular disease, two primary causes of excess premature mortality in patients with mood disorders. Although the etiology of the *n*-3 PUFA deficits observed in patients with mood disorders may be multifactorial, extant evidence suggests that increasing dietary *n*-3 PUFA intake is sufficient to correct this deficit. Several independent meta-analyses of controlled trials suggest that acute *n*-3 PUFA supplementation may reduce mood symptom severity, and recent evidence further suggests

that increasing *n*-3 PUFA biostatus is protective against the initial development of mood symptoms in response to inflammation as well as cardiometabolic risk factors.

Neuroimaging and rodent studies are beginning to elucidate plausible biological mechanisms that may link low *n*-3 PUFA status and mood dysregulation. Evidence from rodent neurodevelopmental studies suggest that *n*-3 PUFA deficiency during perinatal development can recapitulate key neuropathological, neurochemical, and behavioral features associated with mood disorders including enduring impairments in dopamine and serotonin neurotransmission. Clinical neuroimaging evidence further suggests that low *n*-3 PUFA biostatus may contribute to abnormalities in cortical structure and function that are consistently observed in patients with mood disorders. Consistent with biochemical evidence that DHA and EPA, and their bioactive metabolites, have anti-inflammatory and inflammation resolving properties, one potential neuropathogenic mechanism linking *n*-3 PUFA deficiency and relevant neuropathological processes is neuroinflammation. Neuroinflammation may contribute to white matter pathology and associated deficits in regional network connectivity. As discussed, this mechanism is directly supported by the recent observation that fish oil supplementation increased white matter microstructural integrity in MDD patients in conjunction with reductions in depression symptom severity. Nevertheless, additional research is needed to better characterize the link between *n*-3 PUFA intake and biostatus, neuroinflammation, neurodevelopment, and risk of mood dysregulation.

When taken collectively, this body of evidence provides a strong empirical foundation in support of dietary *n*-3 PUFA deficiency being relevant to the pathophysiology and pathoetiology of mood disorders. Because *n*-3 PUFA deficiency can be corrected through dietary *n*-3 PUFA supplementation, it represents a 'modifiable' risk factor that is amenable to treatment and prevention. The reviewed translational evidence provides a compelling rationale to begin translating this knowledge into clinical practice in an effort to optimize treatment response and improve long-term health outcomes for patients and their offspring. As an initial step, screening for and treating *n*-3 PUFA deficiency in patients with mood disorders is currently feasible in routine psychiatric practice, as evidenced by our recent pilot program conducted in a mental health care center. Furthermore, because *n*-3 PUFA *monotherapy* is safe and well-tolerated it is ideally suited as a preemptive intervention for youth at increased risk for developing mood disorders. The latter approach is supported by the observation that fish oil supplementation prevented or delayed the onset of psychosis in ultra-high risk youth [263,264]. Within a 'clinical staging' framework, *n*-3 PUFA *monotherapy* would also represent a safe first-line intervention for the treatment of early moderate mood symptoms, particularly in those that may be at increased risk for adverse events associated with conventional pharmaceutical medications. While the notion of nutritional medicine has been slow to impact conventional psychiatric training and practice [265], dietary *n*-3 PUFA deficiency represents a primary therapeutic candidate that warrants incorporation into psychiatric practice.

Acknowledgments

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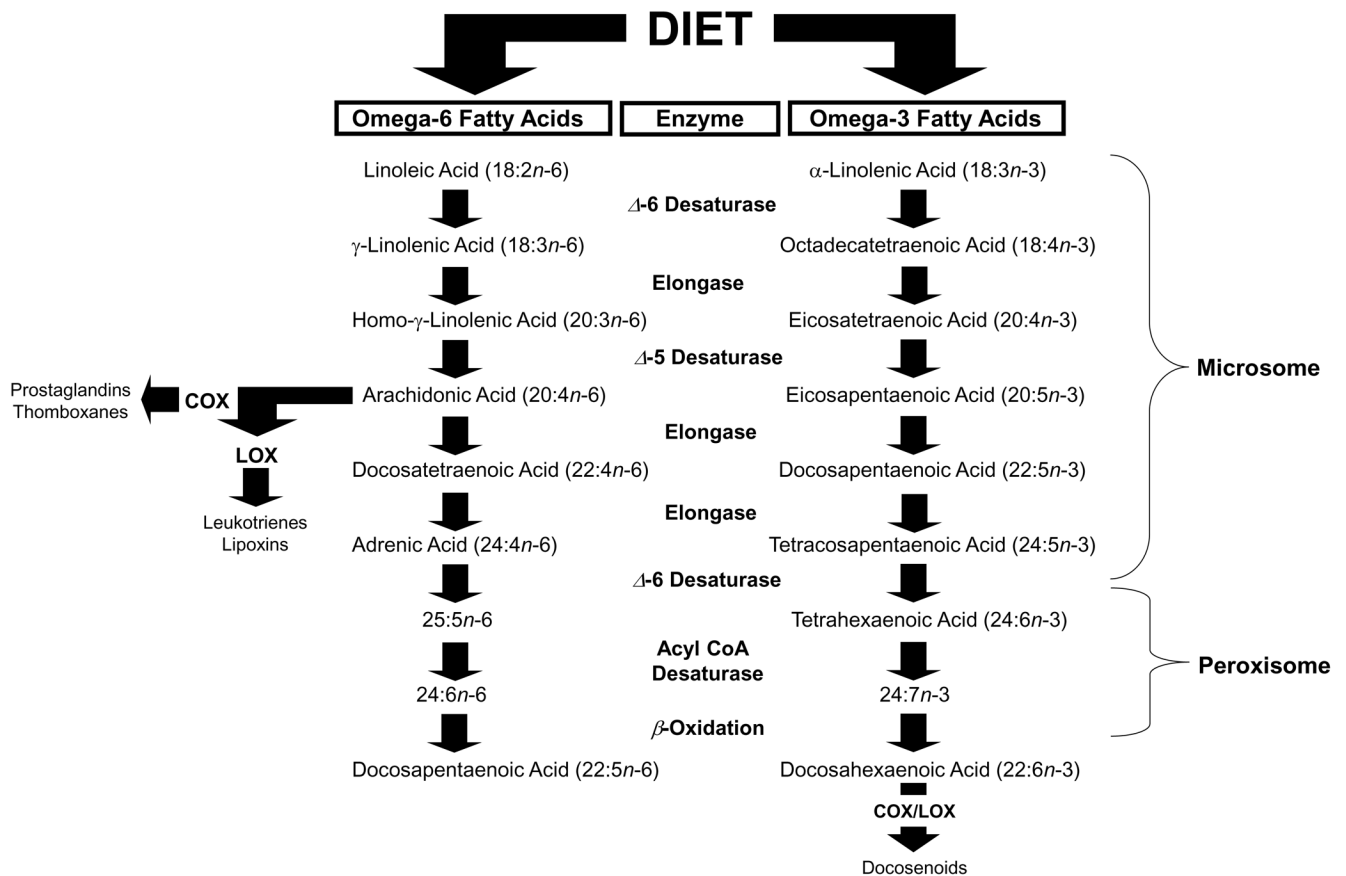
Figure 1.
Diagram illustrating the biosynthetic pathways of *n*-3 and *n*-6 PUFAs from plant-derived dietary precursors. The biosynthesis of docosahexaenoic acid (DHA, 22:6*n*-3) from α-linolenic acid (18:3*n*-3), and arachidonic acid (20:4*n*-6) from linolenic acid (18:2*n*-6), requires a series of common and competitive elongation and desaturation reactions mediated by microsomal enzymes. The final synthesis of DHA requires additional modifications including β-oxidation within peroxisomes. Unesterified arachidonic acid is a substrate for cyclooxygenase (COX)-mediated biosynthesis of prostaglandins and thromboxanes, as well as lipoxygenase (LOX)-mediated biosynthesis of leukotrienes and lipoxins. COX and LOX metabolites of unesterified DHA (i.e., docosanoids) as well as EPA have inflammation-resolving properties.
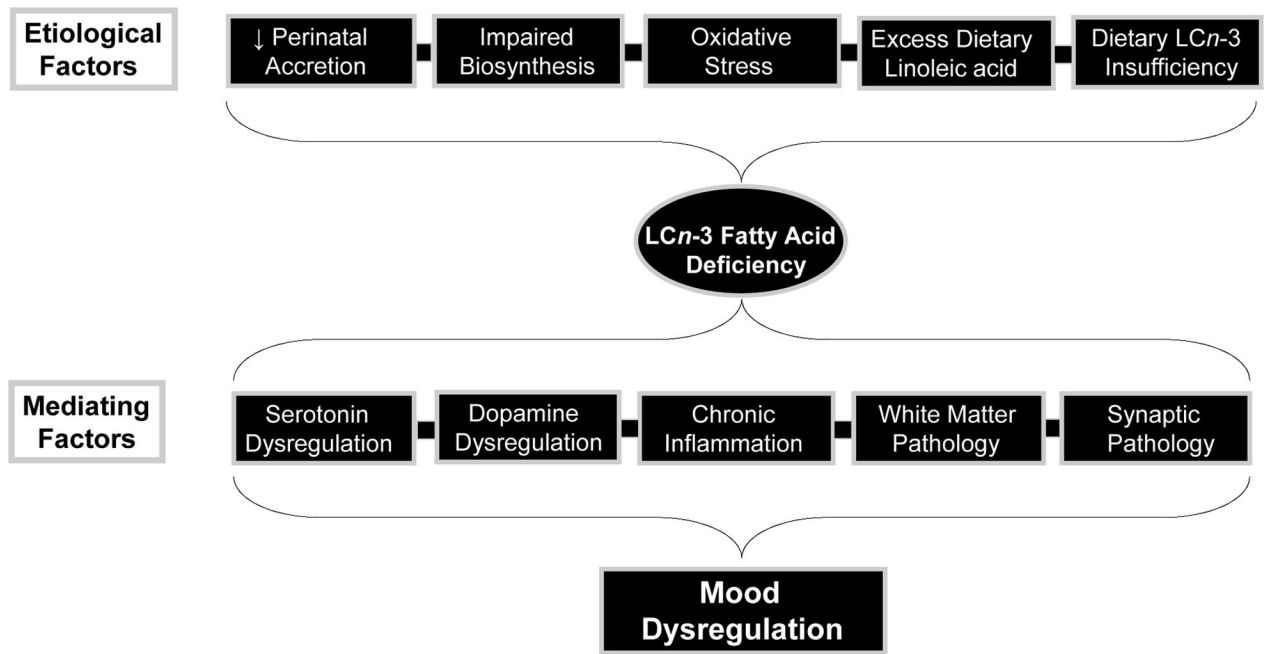
Figure 2.
Diagram illustrating candidate etiological factors that may contribute to *n*-3 PUFA deficiency in patients with mood disorders, and candidate pathogenic mechanisms that may mediate *n*-3 PUFA deficiency and mood dysregulation.