EXPERT REVIEWS

Therapeutic use of omega-3 fatty acids in bipolar disorder

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Bipolar disorder (BD) is a severe, chronic affective disorder, associated with significant disability, morbidity and premature mortality. Omega-3 polyunsaturated fatty acids (PUFAs) play several important roles in brain development and functioning. Evidence from animal models of dietary omega-3 (n-3) PUFA deficiency suggest that these fatty acids are relevant to promote brain development and to regulate behavioral and neurochemical aspects related to mood disorders, such as stress responses, depression and aggression, as well as dopaminergic content and function. Preclinical and clinical evidence suggests roles for PUFAs in BD. n-3 PUFAs seem to be an effective adjunctive treatment for unipolar and bipolar depression, but further large-scale, well-controlled trials are needed to examine its clinical utility in BD. The use of n-3 as a mood stabilizer among BD patients is discussed here. This article summarizes the molecular pathways related to the role of n-3 as a neuroprotective and neurogenic agent, with a specific focus on BDNF. It is proposed that the n-3–BDNF association is involved in the pathophysiology of BD and represents a promising target for developing a novel class of rationally devised therapies.

Keywords: BDNF • bipolar disorder • DHA • EPA • fish oil • lipids • neurogenesis • neuroprotection • neurotrophins • omega-3 fatty acids

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Bipolar disorder (BD) is a chronic, recurrent affective disorder characterized by cyclic episodes of mania/hypomania and depression, interspersed with periods of clinical remission or euthymia. BD is a complex syndrome characterized by the dysfunction of multiple neurobehavioral domains. Beyond the core dysfunction in mood regulation, the broad phenotypic expression of BD includes anxiety, psychosis, impulsivity, disturbances in cognition and circadian rhythm (e.g., sleep–wake cycle), as well as high rates of medical and psychiatric comorbidities [1,2].

Moreover, BD is a severe condition that is often associated with significant disability, morbidity and premature mortality [3,4]. All of this seems to be due to cognitive, as well as physical health, deterioration [2,5,6]. Persistent cognitive dysfunctions may predict a poorer long-term functional outcome among BD patients [7,8]. In addition, BD carries a higher risk for a wide range of medical conditions, including cardiovascular disease (CVD), cerebrovascular diseases and neurological disorders, such as migraine or epilepsy, as well as metabolic abnormalities, such as obesity/overweight and Type 2 diabetes mellitus [9–11]. These comorbidities frequently complicate the clinical presentation and management of BD and worsen treatment response, course, outcome and quality of life [12,13].

The omega-3 (n-3 or ω-3) and omega-6 (n-6 or ω-6) polyunsaturated fatty acids are either obtained from the diet or synthesized from the essential fatty acids α-linolenic acid (ALA) and linoleic acid (LA), respectively. Fatty acids play different physiological roles in the organism, are important in the structure of cellular membranes and are essential for brain functions and nerve impulse transmission [14]. The main n-3 long-chain polyunsaturated fatty acid (LC-PUFA or simply PUFA, hereafter) in the neural membrane is docosahexaenoic acid (DHA). DHA is necessary for the structure of brain cellular membranes and influences signaling events that are essential to neuron differentiation and survival [15,16]. n-3 PUFAs have been suggested as a treatment for clinical depression [17–19]. Recent evidence suggests an involvement of n-3 PUFAs with the BDNF/tyrosine kinase receptor B (TrkB) signaling pathway [20,21], which may in part explain some of the neuroprotective effects of n-3 in experimental models.

BDNF is a protein of the neurotrophin family, which is involved in neuroprotection, including neuronal survival, dendritic arborization, synaptic plasticity and neurodevelopment [22]. A growing body of evidence has suggested that BDNF is involved in the pathophysiology of BD [23]. Several agents that have positive effects in mood, including antidepressants and mood stabilizers, enhance BDNF levels [24–26], whereas acute episodes of BD have been associated with a decrease of its serum levels [27]. Therefore, it seems that drugs with a BDNF-enhancing capacity may have therapeutic effects on BD.

The BDNF/TrkB signaling pathway is one of the different neurobiological mechanisms of action that have been proposed to explain the mood-regulating effects of n-3 PUFAs in

BD [28–30], including the modulation of signal transduction pathways, the reduction of proinflammatory cytokines or the blockade of calcium channels [31].

In this article, we will examine the available evidence of the possible therapeutic use of n-3 in BD. A possible role via the BDNF neuroprotection/neurogenesis system is described.

Omega-3 long-chain, polyunsaturated fatty acids

Fatty acids play different physiological roles in the organism, are extremely important for the structure of cell membranes and metabolic processes, and are essential for brain functions and nerve impulse transmission [14].

Long-chain polyunsaturated fatty acids include omega-6 (n-6 or ω-6) and omega-3 (n-3 or ω-3) families of fatty acids, whose precursors are LA and ALA, respectively (Figure 1). Both of them have 18 carbon atoms, with a carboxylic group at one of the chain edges and a methylic group at the other, also known as omega (n) termination. LA presents two double bonds, and the first is located at the carbon 6 from the methylic group (n-6). ALA presents three double bonds, and the first is located at the third carbon from the methylic group (n-3).

The dietary precursors ALA and LA are rapidly absorbed and metabolized after their ingestion, mediated by a series of elongation and desaturation reactions. However, the conversion rates of n-3 and n-6 long-chain PUFAs from ALA and LA are very inefficient in humans and have been estimated to be approximately 1 and 3–6%, respectively [32–34]. The liver is the most active tissue in converting LA–arachidonic acid (AA) and ALA–DHA, and has a key role in providing PUFAs for less active tissues, such as the brain [34]. Elongases act by directing two carbon atoms into the initial part of the chain, whereas desaturases act by oxidizing two carbons of the chain and creating a double bond in a *cis* configuration [35]. After going through these processes, LA and ALA produce long-chain fatty acids. LA is precursor of AA, while eicosapentaenoic acid (EPA) and DHA are synthesized from ALA (Figure 1).

Arachidonic acid, through the action of cyclooxygenase (COX) enzymes, produces prostanoids of the family 2 (which include prostaglandins and thromboxanes), whereas through the action of lipoxygenase (LOX) enzymes AA forms leukotrienes of the family 4. These molecules have proinflammatory actions and influence multiple physiological and pathological mechanisms in the organism [36].

The EPA long-chain fatty acid goes under COX and LOX activities and forms prostanoids of the family 3 (including prostaglandins and thromboxanes) and leukotrienes of the series 5, both of which have anti-inflammatory properties [14]. The fatty acids AA and EPA compete for the same enzymes and a greater affinity of the AA fatty acid for COX and LOX results in an excessive production of proinflammatory molecules (Figure 1). Unbalanced dietary intake of n-6 relative to n-3 PUFA may exacerbate inflammatory states and is thought to account for the increasing incidence of lifestyle-associated, chronic conditions, such as CVD, metabolic syndrome (MetS), autoimmune/inflammatory conditions and mental health problems [37].

Docosahexaenoic acid is a long-chain fatty acid composed of 22 carbon atoms and 6 double bonds, the first being located at the carbon 3 from the methylic group. Most brain lipids are glycerophospholipids composed mainly of DHA and AA, and thus play important roles in the development and functioning of the CNS [38]. DHA is necessary for the structure of brain cell membranes and influences signaling events that are essential to neuron differentiation and survival [16,39].

Evidence suggests that PUFAs are capable of crossing the BBB [40]. In humans, the majority of DHA accumulation in the brain occurs during the perinatal period, from the beginning of the third trimester of pregnancy to the second year of life [41,42]. The ability to synthesize DHA from ALA is greater in the developing brain than in the mature brain, and therefore diet is considered to be the best way to maintain DHA levels in the adult brain [43,44].

Behavioral & neurochemical effects of PUFAs

Large amounts of n-3 PUFAs in the brain suggest a major role of these compounds in brain structure and function. The involvement of PUFAs in CNS function can be assessed with the use of dietary manipulation in animal models. Chronic dietary deficiency in ALA in rodents greatly affects the fatty acid composition of cerebral membrane phospholipids [45]. The balance between AA and DHA is a major determinant in the maturation of brain function [46]. It has been shown in rodents and nonhuman primates that inadequate supplies of n-3 PUFAs during the perinatal period result in impaired learning capacity, neurotransmission processes and visual function [47–50]. Therefore, the adequate ingestion of n-3 PUFAs is crucial for brain development, particularly at the time of neuronal migration, myelination, neurite growth and synaptogenesis [51].

Supplementation with n-3 PUFAs in rats improves parameters in different memory and learning tasks [52], while a restriction of these fatty acids in the diet leads to a worsening on these behavioral tests [53]. The supplementation with DHA in the diet also plays a synergic role with exercise, increasing synaptic plasticity, memory and learning through an increase of calcium–calmodulin protein kinase II (CaMKII) levels, cAMP response element-binding protein (CREB) and BDNF in the hippocampus of animals [54]. These proteins are essential to synaptic plasticity, memory consolidation and improvement of nerve impulse transmission [55].

In addition, n-3 fatty acids have a neuroprotective and antioxidant capacity. Studies have shown that rats that had suffered brain injury and were treated with n-3 supplementation demonstrate a decreased oxidative damage (e.g., diminished levels of nitric oxide and protein carbonyl formation), normalized BDNF levels and a better performance in memory tests compared with animals receiving a standard diet [20,56].

Studies using a single-generational n-3 PUFA-deprived rat model have reported that an n-3 PUFA-deficient diet induces long-lasting hyperactive locomotion independent of stress or exploratory behavior in rodents [53,57–60]. The development and expression of amphetamine-induced sensitization is significantly increased in DHA-deficient rodents [61]. n-3 PUFA-deprived rats

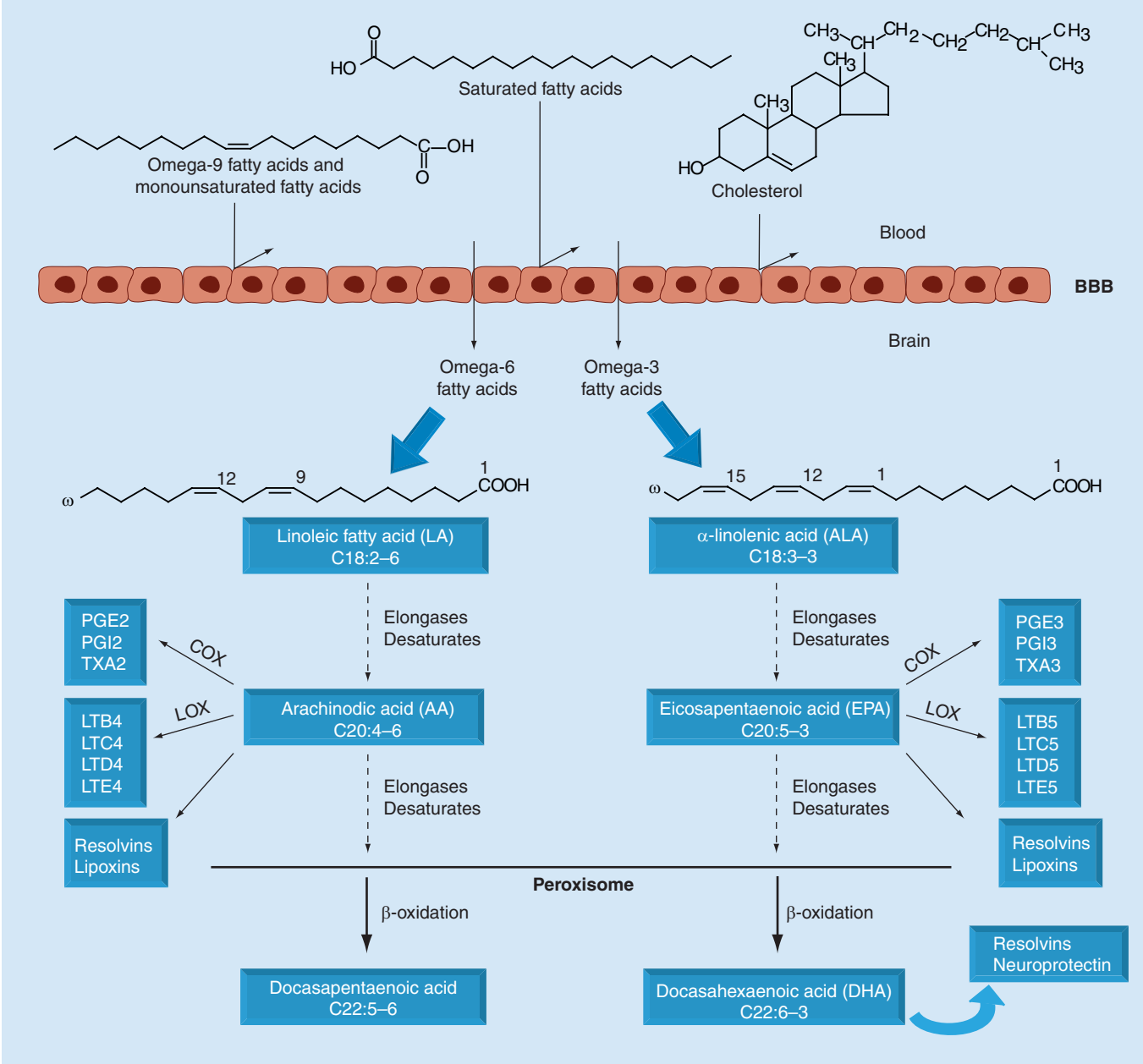

Figure 1. Metabolic pathways of omega-3 and omega-6 fatty acid synthesis. LA and ALA are converted to long-chain fatty acids through reactions of desaturation and elongation. The synthesis of DHA requires the passage of precursor fatty acids into the peroxisome, where they suffer one cycle of β-oxidation to produce DHA. The AA and EPA fatty acids synthesize prostanoids and leukotrienes by the enzymes COX and LOX, respectively. AA, EPA and DHA can also synthesize resolvins, proteins that have neuroprotective functions. These reactions occur primarily in the liver, but they can also take place in the brain, once omega-3 and omega-6 are transferred by the BBB.
AA: Arachinodic acid; ALA: α-linolenic acid; COX: Cyclooxygenase; DHA: Docasahexaenoic acid; EPA: Eicosapentaenoic acid; LA: Linoleic acid; LTB4: Leukotriene B4; LTB5: Leukotriene B5; LTC4: Leukotriene C4; LTC5: Leukotriene C5; LTD4: Leukotriene D4; LTD5: Leukotriene D5; LTE4: Leukotriene E4; LTE5: Leukotriene E5; LOX: Lipoxygenase; PGE2: Prostaglandin 2; PGE3: Prostaglandin 3; PGI2: Prostacyclin I2; PGI3: Prostacyclin I3; TXA2: Thromboxane A2; TXA3: Thromboxane A3.

also have an increased score on the Porsolt forced swim test for depression, and increased scores on the isolation-induced resident intruder test for aggression [62], suggesting that n-3 PUFAs may be involved in the development of behaviors commonly found in some psychiatric disorders, such as depression and aggression [63]. DHA supplementation completely reverses the anxiety-like behavior induced by an n-3 PUFA-deficient diet and attenuates the freezing behavior in conditioned-fear stress responses, which suggests that DHA is involved in the modulation of stress response in rats [64]. Fedorova *et al.* showed that n-3 PUFA deficiency differently affects anxiety levels in mice maintained under stressful conditions [16].

At a neurochemical level, long-term dietary deficiency in n-3 PUFAs induces a reduction in the amount of dopamine (DA) and DA D_2 receptors in the frontal cortex [65]. Following an amphetamine challenge, greater DA and DA metabolite concentrations were observed in the ventral striatum, but not in the prefrontal cortex in these animals [61]. In addition, using microdialysis, it was shown that there was a decrease in cortical DA release accompanied by an increase in metabolite release, suggesting modifications in DA turnover and metabolism in these rats [66,67]. Extracellular DA is increased in the nucleus accumbens of awakened n-3 PUFA-deficient rats [68]. These results suggest that the mesolimbic DA pathway is more active, whereas the mesocortical pathway is less active in n-3 PUFA-deficient rats than in control rats [69].

When offered during rodent gestation, n-3-deficient diets impact both the pregnant female and the fetus. Specific brain regions of the pregnant female rat are differentially depleted of DHA, namely the frontal cortex and the temporal lobe, regions involved in cognition and affect [70]. In addition, maternal dietary n-3 fatty acid deprivation impairs fetal brain DHA accretion and phosphatidylserine metabolism [71,72], which may change the release of lipid mediators and neurotransmitter precursors important to brain function [73,74]. In n-3-deficient animals, glucose utilization and glucose transporter $GLUT_1$ immunolabelling are significantly altered in cortical brain areas [75,76], suggesting an altered central energetic metabolism, which is essential to cognitive performance and neuronal activity.

These effects are not limited to the fetal period. Other systems implicated in certain psychiatric disorders seem to be persistently altered following a chronic deficiency in n-3 PUFAs from conception. For instance, immunohistochemical studies reveal an increase in the D_2 receptor in discrete regions of the mesolimbic and mesocortical pathways, as well as in a large number of brain areas from the n-3 PUFA-deficient pups at 2 weeks of age, possibly to compensate for low levels of DA in synaptic clefts during brain development [77]. In addition, a decrease of the DA-synthesizing enzyme tyrosine hydroxylase accompanied by a downregulation of the vesicular monoamine transporter (VMAT-2) and a depletion of VMAT-associated vesicles in the hippocampus were observed in deficient offspring compared with adequately fed controls [78]. In adulthood, rats raised from conception on diets containing low amounts of n-3 PUFAs have a decreased number of tyrosine hydroxylase-positive cells in the substantia nigra pars compacta and ventral tegmental area, with dendritic depletion and isolation of tyrosine hydroxylase-positive cells [79]. These findings support a role for n-3 PUFAs in the survival of DA neurons and suggest that altered DA cell number, as well as function, may play a role in the behavioral effects observed in rats raised on n-3 PUFA-deficient diets. Moreover, the n-3 PUFA-deficient diets can affect cholinergic neurotransmission, in which a higher basal acetylcholine release in the hippocampus and a reduction in muscarinic receptor binding was observed in deficient rats compared with controls [47].

Deficiency in n-3 PUFAs during fetal life is also associated with metabolic disturbances. The ingestive behavior in the maintenance of body fluid and metabolite homeostasis is affected by limiting the perinatal supply of dietary n-3 PUFA, with an exaggerated salt appetite caused by n-3 PUFA deficiency [80]. Blood pressure is elevated in n-3 PUFA-deficient animals [81,82]. It has been suggested that n-3 PUFA deficiency causes an enhanced activation of the renin–angiotensin system [83], a system involved in both the control of sodium appetite and blood pressure. Studies in rodents have shown that insulin resistance can be improved when fat-rich diets contain n-3 PUFAs [84–86]. These diets have been shown to promote changes in the fatty acid profile of membrane lipids of endothelial cells, as well as to modulate inflammatory cytokines, reducing the atherogenic lipid profile [87,88]. They also reduce the weight gain and improve postprandial lipemia in the obese JCR:LA-cp rat [89].

The chronic n-3 deficiency also seems to interact with early life stressors to predict vulnerability to behavioral alterations. For instance, the early maternal separation paradigm is a valid model for early life stress and development of a depression-like syndrome in rats [90]. Using this paradigm in chronically dietary n-3 PUFA-depleted dams, behavioral impulsivity and changes in the reward response were shown in the adult offspring [91]. The n-3 PUFA-deficient status and the maternal separation stress acted synergistically to increase sucrose consumption used as marker of reward sensitivity. Furthermore, n-3 PUFA-deficient rats showed increased reactivity to novelty in the open field test.

Researchers were able to demonstrate that a reversal diet with adequate n-6 and n-3 PUFAs given during the lactating period to rats originating from ALA-deficient dams is able to restore both the fatty acid composition of brain membranes and several parameters of dopaminergic neurotransmission. On the other hand, when given from weaning, there was only a partial recovery of biochemical parameters, such as fatty acid content, and no recovery of neurochemical factors, such as DA. Therefore, profound n-3 PUFA deficiency during the lactating period is suggested to be an environmental insult leading to irreversible damage to specific brain functions, mainly the ones related to the dopaminergic function. This could be linked to the emergence of critical neurodevelopmental processes during this period [92].

This evidence shows that n-3 PUFAs are relevant to the promotion of brain development and function, and are important to regulate behavioral and neurochemical aspects related to mood disorders, such as stress responses, depression and aggression, as well as dopaminergic content and function. In addition, these fatty acids also play important physiological roles as modulators of the metabolic status and physical health, decreasing CVD and other chronic diseases.

The role of n-3 PUFAs in BD

The role of n-3 PUFAs in mood disorders has been extensively reviewed (the interested reader can consult [17–19,93–96]). The focus here is on the potential role of n-3 PUFAs as therapeutic targets specifically in BD. First, we review the observational evidence on the relationship between BD and n-3 PUFA intake (epidemiological research) and n-3 PUFA status (biochemical studies). Second, human intervention studies that support the therapeutic efficacy of n-3 in BD are summarized.

An ecological study found that lower per capita fish/seafood consumption, a surrogate for n-3 dietary intake, was associated with higher prevalence rates of bipolar spectrum disorders, across ten countries [97]. In other cross-national epidemiological analyses, Hibbeln and colleagues found similar inverse correlations with prevalence rates of major depression [98] and postpartum depression [99]. Although this does not prove causality, these data suggest that a greater intake of seafood may account for a lower prevalence of mood disorders. However, most epidemiological research has been performed at the individual level, including cross-sectional studies of the association between depressive symptoms and fish/n-3 PUFA dietary intake. Most (e.g., [100,101]), although not all [102], studies have reported a negative association between fish or n-3 PUFA intake and self-reported major depressive disorder (MDD) or depressive symptoms, hence supporting a benefit of consumption of n-3 in affective disorders. For example, a large epidemiological study found that individuals who ate fish at least twice a week are less likely to report depressive symptoms [100].

Biomarkers of n-3 status are thought to reflect exposure better than estimates of dietary intake. Since the CNS is very difficult to examine *in vivo*, PUFA levels may be assessed in other cell types or peripheral tissues. Blood PUFA content is positively correlated with PUFA intake [103] and may be a suitable index of PUFA composition in brain cell membranes, although not identical [104]. The erythrocyte membrane phospholipid (fatty acid) content is the standard method to assess n-3 PUFA status in clinical practice. Several case–control, biochemical studies have found significantly decreased levels of DHA [105,106] or ALA and EPA [107] in erythrocytes of BD patients compared with healthy controls, although not all have [108]. In addition, healthy first-degree relatives of BD patients showed a tendency towards reduced n-3 fatty acids in blood phospholipids [109]. Still, blood PUFA levels have been negatively correlated with the severity of affective symptoms in some [108,110], although not all [106], studies. Patients with MDD also show lower levels of n-3 PUFAs, DHA and EPA, and higher ratios of n-6:n-3 PUFAs than controls (for a meta-analysis, see [111]), as well as a negative association between n-3 PUFA status and the severity of affective symptoms [96,112]. Moreover, DHA concentrations in the post-mortem orbitofrontal cortex of bipolar patients are significantly lower than those of healthy controls [113], whereas Schwarz and colleagues found lipid abnormalities in gray and white matter, and erythrocyte membranes of drug-naive BD patients [114].

The therapeutic effects of n-3 PUFAs have been tested in several neuropsychiatric disorders, mostly in MDD and Alzheimer's disease, but also in schizophrenia, attention-deficit/hyperactivity disorder and anxiety disorders (for reviews, see [94,95,115–117]). Few double-blind, placebo-controlled, randomized clinical trials (RCTs) to date have investigated the therapeutic role of n-3 PUFAs (fish oil, ethyl-EPA, EPA or DHA) in patients with BD.

In a pioneer prophylaxis trial, Stoll and colleagues showed that n-3 PUFAs improved the short-term course of BD [118]. During this 4-month study, patients randomized to adjunctive treatment with high doses of fish oil (9.6 g/day of DHA plus EPA; n = 14) had significantly longer remission and significantly greater improvements of depressive symptoms, bipolar symptoms and global functioning than the placebo group (n = 16). However, no positive effect on manic symptoms was observed.

In a subsequent 12-week RCT, Frangou *et al.* compared the efficacy of two doses of ethyl-EPA (1 g/day and 2 g/day) versus placebo as add-on treatment in 75 patients with bipolar depression [119]. Both doses of EPA significantly improved depressive symptoms, as well as global bipolar symptoms, compared with the placebo group, with no difference in manic symptoms. Moreover, a dose–response effect was not observed. By contrast, a multicenter collaborative trial of the Stanley Foundation did not find any evidence of efficacy over placebo of ethyl-EPA 6 g/day administered as adjunctive therapy for 4 months to outpatients with bipolar depression (n = 59) or rapid cycling BD (n = 62) [120]. The first RCT of pediatric BD has been published recently [121]. Augmentation with flax oil containing ALA did not confer better mood stabilization than placebo (olive oil). At study intake, 51 symptomatic children and adolescents were enrolled, but less than 50% completed this 16-week study.

Additional data from four small, open-label trials suggest that adjunctive n-3 fatty acids may reduce symptoms of bipolar depression [122], irritability associated with BD [123] and manic and depressive symptoms of children and adolescents with pediatric BD [124]. Moreover, monotherapy with EPA plus DHA was associated with modest improvements in manic symptoms in an 8-week study of juvenile BD [125].

Putative mechanisms of action

Several mechanistic pathways have been suggested to biologically explain the link between n-3 and BD, including: alterations in membrane function (membrane fluidity, receptor function, neurotransmission, membrane-related enzyme and ion channel activity, glucose transport and signal transduction) reviewed in [126]; mood stabilization by targeting the AA cascade [127]; BDNF enhancement [28] via several mechanisms (see below); inflammation; changes in the synthesis of eicosanoid (prostaglandins, leukotrienes and thromboxanes) and docosatriene (resolvins and neuroprotectins) families of lipid mediators [128,129]; and changes in the expression of many CNS genes [130]; EPA seems to increase oxygen and glucose supply to the brain [131]; and protection against oxidative stress [115]. The DHA fatty acid incorporation into neuron cell membranes increases its order, thereby leading to a better binding of neurotransmitters with their receptors [132]. Moreover, it eases signal transduction pathways [133,134]. DHA and EPA can also modulate brain function by changing the production and function of neurotransmitters, such as serotonin and DA [135,136].

Moreover, several neuroprotective effects of DHA have been reported in preclinical models of Alzheimer's disease, including anti-inflammatory activity, antioxidant effects, neuroprotective metabolites (neuroprotectin D1), enhanced glucose transport and improved synaptic and membrane fluidity [137]. These mechanisms result in reduced inflammation and oxidative stress, enhanced neuroprotective/neurogenic pathways, increased glucose utilization and neuron and synaptic function. PUFAs protect neurons directly by preventing neuronal apoptosis and

by suppressing production of proinflammatory cytokines [138]. Most of these neuroprotective mechanisms are relevant for BD. For example, n-3 supplementation increased cortical concentrations of *N*-acetyl-aspartate, a putative marker of neuronal density and integrity, in a small sample of female BD patients [139], thereby protecting against excitotoxic apoptosis. In addition, n-3 PUFAs also increased glutathione, the major endogenous antioxidant defence [140]. Altogether, n-3 and medications used to treat BD seem to share several mechanisms of action (see previously). It has been suggested that they both may work in a synergistic fashion and that n-3 may augment the therapeutic effects of standard antibipolar medications by means of those mechanisms [117,118,127,141]. This synergistic action could improve patients' mental health.

Discussion

This article shows the molecular pathways related to the role of n-3 as a neuroprotective and neurogenic agent. The relationship of n-3 with BDNF is the focus of this article. The use of n-3 as a mood stabilizer among BD patients is discussed.

A growing body of evidence has suggested that BDNF plays an important role in the pathophysiology of MDD and BD. BDNF is a member of the growth factor family, which is involved in synaptic efficacy, neuronal connectivity, dendritic arborization and neuroplasticity [22]. Different stimuli can induce BDNF synthesis in neuron cells. The human *BDNF* gene has an extremely complex structure composed of 11 exons and nine promoters, which can be differentially activated [142]. Such a complex set of genomic promoters and exons is thought to mediate an accurate control of the gene transcription. Evidence indicates that transcripts are differentially distributed across brain regions, in different cell types and even within different parts of the neuron [143]. *BDNF* transcription is regulated mainly by the transcription factor CREB [144]. CREB must be phosphorylated to pCREB in order to transcribe CREB-regulated genes, including *BDNF* [145]. Once synthesized and processed, the mRNA is translated into a precursor form of the protein named proBDNF. ProBDNF is either proteolytically cleaved intracellularly by enzymes and secreted as the mature BDNF, or secreted as proBDNF and then cleaved by extracellular proteases to mature BDNF (for a review, see [146]).

BDNF is highly expressed in the cerebral cortex and hippocampus, brain areas known to regulate complex brain functions, such as memory and emotion [147]. Furthermore, it has been consistently associated with cognitive function in different species. Several learning tasks are associated with increased BDNF mRNA levels in rats [148], and it seems that BDNF plays an important role in the late phase of long-term potentiation. Hippocampal BDNF is required for short-term memory formation of an aversively motivated learning task in one-trial inhibitory avoidance training in rats [149], and evidence suggests that there is a *BDNF*-dependent phase in memory persistence processes [150]. Furthermore, a significant positive association has been shown between serum BDNF levels and a test of verbal fluency in humans, once again suggesting the importance of BDNF in neurocognitive processes [151].

Such a cognitive impairment and functional decline has been shown in BD patients [152,153]. A single nucleotide polymorphism that leads to a valine-to-methionine substitution at the codon 66 in the *BDNF* gene is associated with impaired episodic memory in healthy subjects [154] and significantly worse performance in the Wisconsin Card Sorting Test (WCST) in Val/Met BD patients compared with patients with the Val/Val genotype [155]. In addition, a prospective study has demonstrated that BD patients that are carriers of the Met allele display greater temporal lobe reductions compared with Val/Val patients over a 4-year follow-up period [156]. Altogether, it seems that BDNF may be associated with the cognitive decline associated with the length and progression of BD.

Serum BDNF levels are decreased in BD patients during manic and depressive episodes compared with controls [27,157]. Moreover, Kauer-Sant'Anna and colleagues compared first-episode versus multi-episode BD patients, showing that BDNF levels are decreased after multiple episodes [158]. This has led to the hypothesis that episode-related changes in neurotrophins may explain some of the brain structural changes observed in BD patients. Serum BDNF levels have been negatively correlated with length of illness [158], and are thus suggested to play an important role in the pathophysiology of BD [23].

Accumulated data suggest that BDNF may be associated with the remission of symptoms in BD, thus emphasizing the potential therapeutic use of BDNF-enhancing drugs in their treatment. There is evidence for a normalization of BDNF levels after treatment and remission of acute manic symptoms in BD patients [159]. For instance, a twofold increase in the plasma levels of BDNF has been shown after 6 months of treatment in patients with a first episode of psychosis, including those with BD [160]. Such data have also been confirmed in a recent meta-analysis [161]. BDNF levels may be associated with improvement of acute symptoms in BD and may also offer a biological marker of clinical response to treatment in acute mania and psychosis.

Antibipolar medications, such as mood stabilizers and antidepressants, act in signaling pathways that enhance neurotrophic and neuroprotective effects [25,26,162,163]. Such enhancement has been partially explained by an increased activity of the transcription factor CREB via the adenylate cyclase pathway – that is, through increased PKA activity. n-3 PUFAs may play similar roles in BD, as previously mentioned [21,137,141,164]. Interestingly, lithium can increase 17-hydroxy-DHA, a metabolite of DHA with neuroprotective properties, in a rat model of neuroinflammation [165].

If both n-3 PUFAs and BDNF have been implicated in the pathophysiology of BD, one could ask whether any connection exists between n-3 PUFAs and BDNF, and ultimately whether such a connection, if it exists, is of any relevance for BD. The neuroprotective/neurotrophic effects of n-3 PUFAs have been reviewed elsewhere [166]. Here, the focus will be on neurogenesis and regulation of *BDNF* gene expression by n-3 PUFAs.

Mounting preclinical evidence suggests that n-3 PUFAs may promote hippocampal neurogenesis in adult animals [167–169]. Animals with n-3 PUFA supplementation showed an increase

of 5-bromo-2′-deoxyuridine (a timidine analogue) in neurons of the hippocampal dentate gyrus [167]. These positive effects of n-3 PUFA on neurogenesis may be explained by several mechanisms [168], including processes associated with the structural and functional roles of PUFAs in the neuronal membranes (i.e., membrane order), such as enhanced neurotransmission and cell signaling; and/or immunomodulatory effects via the inhibition of proinflammatory cytokines [170]. Apart from these indirect effects, n-3 PUFAs may enhance neurogenesis via directly controlling the transcription of key genes in the brain [130].

It is well-documented that n-3 PUFAs may regulate the transcription of many genes [171–173]. Specifically, microarray studies made it clear that n-3 PUFAs modulate the expression of genes involved not only in lipid metabolism, but also in the pathways of interest here, such as oxidative stress response and antioxidant capacity, cell proliferation, cell growth and apoptosis, and cell signaling [173]. Moreover, the effects of n-3 PUFAs on gene expression seem to show some tissue specificity and this would subserve the pleiotropic effects of these essential nutrients. Interestingly, PUFA-enriched diets lead to significant gene-expression changes in the rat brain [130] and this may help to better understand how n-3 PUFAs modulate the affective, neurocognitive and behavioral responses of the human brain.

BDNF expression can be enhanced by exercise, learning activities and dietary nutrients, such as vitamin E [174,175], whereas a diet high in saturated fat and sucrose inhibits its expression [174]. As previously discussed, medications used to treat BD are also associated with increased levels of BDNF [24,25,176]. Hence, a shift paradigm in the treatment of BD has been recently proposed [23]. Specifically, substances or interventions that increase BDNF levels/expression in the brain may exert mood-stabilizing effects and deserve further research.

In 2003, Logan proposed a novel mechanism of action "involving omega-3 modulation of CREB and BDNF" [28]. Recent evidence supports that n-3 PUFAs may modulate neurotrophins [20,21,30,177–179]. As a first confirmation of the original hypothesis [28], n-3 PUFAs normalized hippocampal BDNF levels and counteracted the learning disability after traumatic brain injury in rats [20]. Moreover, in a rat model of depression, a clinically relevant reduction in brain DHA content was associated with several neurobiological changes, including reduced hippocampal BDNF expression [30]. Consistent with this, n-3 PUFA deprivation led to decreased levels of DHA, BDNF, pCREB and p38 MAPK in the rat prefrontal cortex, whereas the addition of DHA induced BDNF protein expression in rat cortical astrocytes [21]. Hence, increasing *BDNF* gene expression would be a direct mechanism that may mediate at least in part the enhancing effects of n-3 PUFAs on neurogenesis [177]. In addition, it seems that not only do n-3 PUFAs increase BDNF levels, but they also increase neurotrophin signaling by activating one branch of classical neurotrophin signaling via the PI3K/Akt pathway (Figure 2) [166].

Collectively, these data suggest that reversing abnormal BDNF/CREB-related processes would be one of the potential mechanisms by which n-3 PUFAs may represent a particularly relevant molecular and therapeutic target in BD. However, other mechanisms, such as fatty acid composition of cellular membranes, modulation of the dopaminergic systems, and the role of n-3 PUFAs on neurodevelopment and oxidative stress [180], may also be essential to explain the potential beneficial effects of n-3 in BD.

Expert commentary

Epidemiological and biochemical research provides persuasive evidence for an association between BD and decreased n-3 PUFA intake/status. Overall, lower levels of n-3 PUFAs have been found in blood and post-mortem brain tissues of BD patients. The reason is not yet clear, but deficient intake/status has been invoked as a preventable risk factor for recurrent affective disorders [96]. Since observational research is useful to estimate the prevalence of this putative deficiency in BD, future studies need to use larger samples and better control for several confounders, such as socioeconomic status, which may be linked to more protective lifestyles and healthier diets [181].

So far, two studies found improvements in depressive and bipolar symptoms following supplementation with EPA plus DHA or ethyl-EPA, compared with placebo [118,119], although neither of the studies found similar improvements in mania. Conversely, two other studies found no benefit of supplementation with ethyl-EPA or flax oil [120,121] for depressive or manic symptoms. This evidence is also difficult to interpret owing to marked study differences in terms of dosage, composition and duration of interventions; inclusion criteria; comparators; and outcome measures, to name a few. Moreover, adequate, biologically inert placebos must be used in future RCTs. For example, olive oil may also have some neurotrophic/neuroprotective effects [182].

Overall, n-3 PUFAs seem to be more effective to improve depressive rather than manic symptoms [183]. Consistent with this, several independent meta-analyses concluded that n-3 PUFAs are an effective adjunctive treatment for unipolar and bipolar depression [17,18], and these antidepressant properties have been demonstrated in the forced swimming test in animal models [179,184]. Modest benefits on manic symptoms were found in juvenile BD patients following n-3 supplementation, and this suggests that the value of n-3 PUFAs on BD might vary according to the patients' age. However, this evidence stems from two small, open-label trials [124–125] and needs to be confirmed.

Several aspects of mania and depression can be replicated by pharmacological manipulations of dopaminergic neurotransmission in humans, such as elevation of mood, reduction in the need for sleep, increased impulsivity and impaired cognitive function [185]. There is evidence from structural [186] and functional [187] MRI studies that the brain areas innervated by DA may be abnormal in BD, although imaging studies still need to demonstrate consistent abnormalities. Analysis of the metabolites of DA indicates overactivity of DA in mania and decreased activity in depression [188,189]. Actions of n-3 PUFAs on dopaminergic content and function may explain why they are effective to treat negative, but not positive, psychotic symptoms [190] and this may also account for their higher efficacy in relatively

hypodopaminergic states, such as depression, versus the excessive dopaminergic neurotransmission in mania.

Supplementation with n-3 PUFAs is a potential treatment for BD, but far more work is needed to clarify this relationship. Future studies must be sufficiently powered and have an adequate length because duration of most existing studies may be too short to reverse a putative chronic deficit of n-3 PUFAs. If long-term supplementation seems to be necessary to observe benefits in cardiovascular health [191] and cognitive deterioration [192], it is likely that similar periods of months to years are also needed to obtain maximum benefits on mental health. The most suitable timing, dosage and duration of interventions must be established. These will probably differ according to the clinical staging [193,194], for example, primary prevention versus secondary prevention studies, early-stage versus late-stage BD patients. The prophylactic effects observed in the pioneer study of Stoll and colleagues [118] require replication.

Most of the studies regarding the neuroprotective effects of n-3 are *in vitro* studies with cell culture or *in vivo* studies with animal models, and there is an obvious difficulty in translating such findings to the clinic. For instance, as previously discussed, there are no studies showing an association between BDNF and n-3 PUFAs in BD patients, even though both of these molecules have already been assessed in this disorder, and seem to share common intracellular signaling pathways. Such studies may help to clarify and further support the beneficial effects of n-3 PUFAs on neuroprotective signaling in BD.

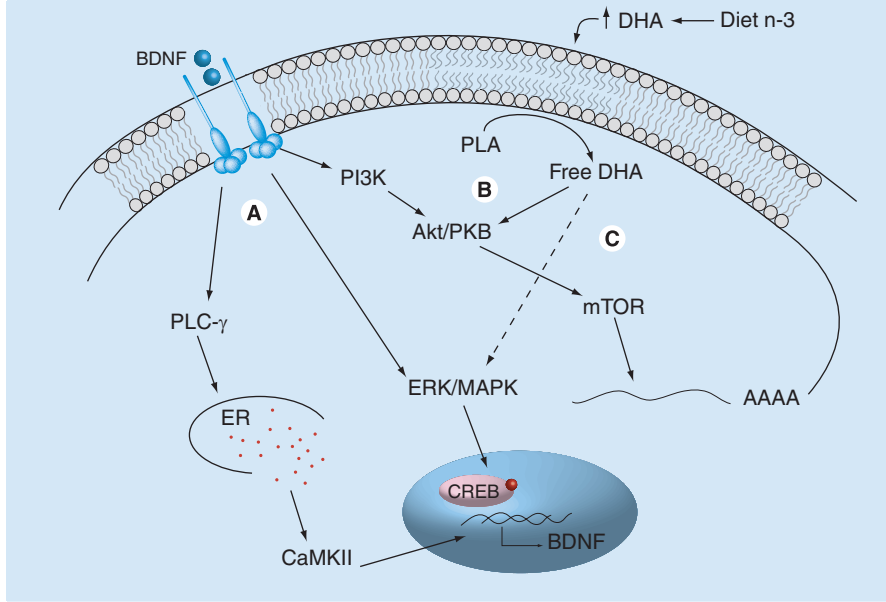

Figure 2. Omega-3 fatty acids increase BDNF synthesis and intracellular signaling in neurons. (A) Mature BDNF binds to the TrkB receptor and activates three main intracellular signaling pathways involving PLC-γ, ERK/MAPK and Akt/PKB. Activation of PLC-γ leads to the release of calcium from the ER and to the activation of CaMKII, leading to the phosphorilation of CREB and activation of gene transcription. Activation of the ERK/MAPK pathway can also regulate transcription through the phosphorylation of CREB, whereas PI3K phosphorylates and activates Akt/PKB and mTOR, regulating translation initiation. **(B)** DHA increases neurotrophic signaling by activating one branch of the classical BDNF signaling via PI3-K/Akt pathways. **(C)** DHA increases BDNF synthesis by activating MAPK signaling. Activated MAPK phosphorylates CREB, which translocates into the nucleus and activates *BDNF* gene transcription. BDNF: Brain-derived neurotrophic factor; CaMKII: Calcium–calmodulin kinase II; CREB: cAMP response element-binding protein; DHA: Docosahexaenoic acid; ER: Endoplasmic reticulum; n-3: Omega-3 fatty acids; PLA: Phospholipase A2; PLC-γ: Phospholipase C γ; TrkB: Tyrosine kinase receptor B.

Five-year view

Despite recent treatment progress, many BD patients still face several unmet needs, in terms of persistent affective and neurocognitive symptoms, and high rates of nonrecovery, as well as compromised quality of life and psychosocial functioning [7,153]. Given the limitations of the available antibipolar medications and the increasing awareness that BD is a systemic disease [5], interventions with pleiotropic effects are needed to obtain significant improvements in meaningful outcomes for BD patients. The similar actions of n-3 PUFAs and classical mood stabilizers modulating signal transduction systems, such as PKC, activity and phosphatidyl inositol, helped to unlock at least in part the pathophysiology of BD [118,141]. It is proposed that the n-3–BDNF association is a promising target for hypothesis-driven, rational drug development for this severe, prevalent disorder. Should this progress be confirmed, n-3 supplementation must be offered to BD patients.

Individual differences in genetic background or baseline n-3 status, among other factors, may explain why not all patients respond to PUFA supplementation. On the one hand, intervention trials in the field of cognitive deterioration reveal that DHA only benefits those patients lacking the ApoE4 allele [137]. Similarly, polymorphisms in genes regulating key enzymes of PUFA metabolism might modulate the effects of n-3 on mental health outcomes [195]. Indeed, polymorphisms in genes coding for fatty acid desaturases may influence DHA status [196] and treatment response [197]. In this regard, pharmacogenomic studies will help to target BD patients most likely to benefit from adjuvant intervention. The fatty acid composition of serum phospholipids is genetically controlled by the *FADS1 FADS2* gene cluster [197] located in the chromosomal region 11q12–13.1, which in turn is a susceptibility locus for BD [198]. Moreover, polymorphisms or mutations in the desaturase genes may account for PUFA dysregulation in BD [199] and impaired fatty acid and phospholipid metabolism has been involved in the etiology of BD [200]. On the other hand, it has been suggested that therapeutic effects from supplementation may be found only in PUFA-deficient patients [201]. Conversely, subjects without baseline deficits are less likely to obtain benefits from additional supplementation [51].

If that is the case, future intervention trials should use suboptimal baseline n-3 status as an inclusion criterion to select more homogenous samples of likely 'responsive' patients [202].

Biochemical measures of PUFA levels are necessary to detect PUFA-deficient subjects and may represent clinically useful biomarkers. The n-3 index (EPA plus DHA% in erythrocyte membrane) has been suggested as a biomarker to flag coronary heart disease risk. An n-3 index of 8% or higher would confer maximum protection, whereas an index of 4% or less has been associated with the least cardioprotection [203]. This represents a significant step ahead of psychiatry, but by the same token, a new avenue to be explored in mental health [202]. Indexes of n-3 content may be useful for different purposes in clinical and research settings, such as monitoring patients' adherence during intervention trials, stratifying patients according to risk levels or devising interventions aimed to optimize values of these indexes.

Currently, the erythrocyte membrane fatty acid content is the standard method to assess n-3 PUFA status in clinical practice. This process is time consuming [204] and sometimes blood extraction may be uncomfortable or difficult to perform in certain patients. Measuring PUFA levels in cells of the oral mucosa is an easy, noninvasive assessment that may be useful for patients reluctant to consent because of blood sampling or for special populations, such as pediatric BD. In infants, this has been shown to reflect blood PUFA levels and dietary intake [205], but not long-term exposure [206]. In addition, desaturase expression in leukocytes has been suggested as a new diagnostic method to detect nutritional PUFA deficits at an early stage [207], although this needs replication.

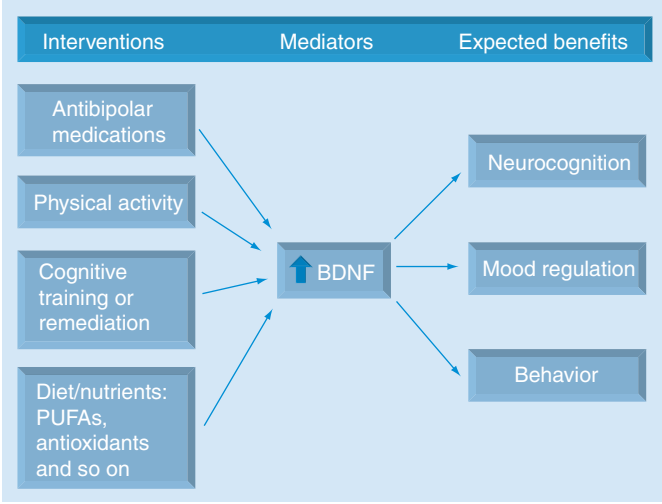

Figure 3. BDNF as a common mediator of the potential benefits that may be obtained with multimodal interventions in bipolar disorder. Several pharmacological agents used to treat bipolar disorders, such as mood stabilizers, antidepressants and atypical antipsychotics, increase BDNF levels. Interventions on lifestyle-related factors, such as regular physical exercise and diet/nutrition, also increase neurotrophins. In addition, the neurocognitive benefits derived from psychosocial interventions, such as cognitive training or remediation, are thought to be mediated by neurotrophins. These strategies may have synergistic effects. Multitargeted interventions that increase BDNF and other neutrophins may maximize neurogenesis/neuroprotection, and as a result potentially improve mood, neurocognitive functioning and mental health. The expected benefits from each intervention may be different, but in all instances BDNF would be a putative key mediator.
BDNF: Brain-derived neurotrophic factor; PUFA: Polyunsaturated fatty acid.

In parallel with RCTs, experimental studies (cell culture and animal models) must be prioritized to identify the mechanistic pathways that could explain some or all of the reported benefits of n-3 PUFAs on mood, cognition and behavior. It is likely that the benefits of n-3 PUFAs for physical health might be mediated mostly by their anti-inflammatory effects, whereas mental health benefits might result from additional mechanisms, such as enhancing BDNF [28] or regulating key signal transduction pathways (the 'arachidonic acid cascade' [127]). Future research should also monitor specific biomarkers to examine the putative effects of n-3 PUFAs on the pathophysiological processes of BD, such as decreased neurogenesis and increased apoptosis, oxidative stress, excitotoxicity or neuroinflammation [180]. The interaction of n-3 PUFA status and life-course events, such as chronic stress, may affect the vulnerability to CNS abnormalities and therefore to psychiatric disorders.

Potential benefits of n-3 PUFAs have been described for CVD, MetS and related conditions, autoimmune and inflammatory conditions and cancer [208–211], all of which are frequently associated with BD. It has been hypothesized that n-3 may represent a biological link between affective disorders and CVDs [212]. These comorbidities might be even explained by a common impairment in fatty acid and phospholipid metabolism, which would be corrected by PUFA [201]. Predictably, supplementation with n-3 PUFAs will improve BD patients' physical health and decrease allostatic load (see later), and this clearly represents an emerging area of research. Here we propose that future studies examine the effects of PUFA supplementation above and beyond measures of clinical outcomes, by also using intermediate variables. The inclusion of biomarkers of allostatic load (e.g., interleukins, TNF-α, C-reactive protein, glucocorticoids, oxidative stress, Systemic Toxicity Index [213]) and neurogenesis/neuroprotection (the BDNF–TrkB signaling pathway and other neurotrophins) represents a significant opportunity for future studies and merits further development. To our knowledge, these issues have not been explored previously.

Similarly, family studies may help to reveal whether the putative n-3 PUFA deficiency and/or abnormal metabolism show a familial association or even fulfill endophenotype criteria [214]. If that is the case, this endophenotype might be used for early detection and treatment of at-risk individuals, genetic studies or the development of animal models of BD. Potential benefits of n-3 PUFAs have been recently demonstrated among subjects at ultra-high-risk for psychosis [215].

Finally, we suggest undertaking multimodal, structured intervention programs in BD. n-3 PUFAs may have a synergistic effect not only with standard medications used to treat BD, but probably also with other lifestyle interventions that enhance neurogenesis or the BDNF–TrkB signaling pathway, such as physical exercise. There is preliminary, preclinical evidence supporting this (Figure 3) [216].

Conclusion

Epidemiological, biochemical, experimental and intervention evidence is still limited, but support the hypotheses that low PUFA status is involved in the pathogenesis of BD and that n-3 supplementation is useful for BD, especially to treat depressive symptoms. Longer-term, well-controlled RCTs are justified to confirm this efficacy and establish the minimum dose and length of supplementation required to significantly improve intermediate and clinical outcomes in BD. It is proposed that the n-3–BDNF connection is involved in the pathophysiology of BD and represents a promising target for developing a novel class of rationally devised therapies.

Bipolar disorder is a severe disorder, which is frequently associated with chronic conditions, such as CVD and MetS. Benefits of n-3 fatty acids have been shown for these disorders [217]. n-3 PUFAs are safe and well-tolerated nutrients [218] and only mild, transient adverse events, such as nausea, are likely to occur [116,183]. Moreover, they represent an appealing option for patients, their relatives and clinicians because they are relatively cheap and perceived as a 'natural remedy'. Altogether, it is predicted that supplementation with n-3 PUFAs will benefit the physical health of BD patients. To our knowledge, this hypothesis has not been tested to date.

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Key issues

- The omega-3 (n-3) and omega-6 long-chain, polyunsaturated fatty acids (LC-PUFAs or PUFAs) are important for many functions in the organism, including the structures of cellular membranes, metabolic processes, inflammation and brain function.
- PUFA incorporation into neuron cell membranes increases its fluidity, thereby enhancing neurotransmission and facilitating signal transduction pathways.
- Evidence from animal models of dietary n-3 deficiency suggest that these fatty acids play important roles modulating neurochemical pathways controlling behavioral aspects such as locomotor activity, depressive-like states and responses to reward, domains classically linked to BD models.
- Blood n-3 PUFA content is positively correlated with n-3 PUFA intake and may be a suitable index of PUFA composition in brain cell membranes. Lower levels of n-3 PUFAs have been found in blood and post-mortem brain tissues of BD patients.
- n-3 PUFAs seem to be an effective adjunctive treatment for unipolar and bipolar depression, but further large-scale, well-controlled trials are needed to examine its utility in BD.
- BDNF, a protein involved in neurogenesis and neuroplasticity, has been consistently associated with the pathophysiology of BD. Changes in neurotrophins in BD and the effects of antibipolar medications on neurotrophin levels are well-documented.
- BDNF levels could be a marker of clinical response to treatment in BD and emphasizes the potential therapeutic use of BDNF-enhancing drugs in their treatments.
- n-3 PUFAs have been shown to induce BDNF expression, which may be responsible for their neuroprotective effects.
- The BDNF–TrkB signaling pathway is one of the neurobiological mechanisms of action that have been proposed to explain the mood-regulating effects of n-3 PUFAs in BD. Moreover, the potential antiapoptotic effects of n-3 PUFAs deserve more attention.

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Therapeutic use of omega-3 fatty acids in bipolar disorder

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Based on the above review by Dr. Balanzá-Martínez and colleagues, which of the following statements about the role of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in brain development and functioning is **most likely** correct?

- ☐ **A** Animal models of n-3 PUFA deficiency suggest that the neurotransmitter most affected is acetylcholine
- ☐ **B** The site of action of n-3 PUFAs within the neuron is the nucleus
- ☐ **C** n-3 PUFAs modulate neurochemical pathways controlling locomotor activity, depressive-like states, and responses to reward
- ☐ **D** n-3 PUFA intake is not associated with blood n-3 PUFA content

2. Your patient is a 34-year-old white female with bipolar disorder. Based on the above review, which of the following statements are you **most likely** to tell her about the role of n-3 PUFAs in managing her condition?

- ☐ **A** n-3 PUFAs are most effective to treat manic symptoms
- ☐ **B** Adverse effects of n-3 PUFAs preclude their routine use
- ☐ **C** Long-term, well-designed, randomized, controlled trials (RCTs) have proven that a specific dose regimen and duration of n-3 PUFA supplementation is an effective stand-alone treatment for bipolar depression
- ☐ **D** Preclinical and clinical evidence suggests a role for n-3 PUFAs as adjunctive treatment for bipolar depression

3. Based on the above review, which of the following statements about the role of brain-derived neurotrophic factor (BDNF) in bipolar disorder is **most likely** correct?

- ☐ **A** BDNF is a neurotrophic factor involved in neurogenesis and neuroplasticity
- ☐ **B** Antibipolar medications have not been shown to affect neurotrophin levels
- ☐ **C** Many studies have shown an association between BDNF and n-3 PUFAs in bipolar patients
- ☐ **D** Dietary nutrients have not been shown to affect BDNF