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Reconsidering Dietary Polyunsaturated Fatty Acids in Bipolar Disorder:
A Translational Picture

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ABSTRACT

Inflammation is an important mediator of pathophysiology in bipolar disorder. The omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acid (PUFA) metabolic pathways participate in several inflammatory processes and have been linked through epidemiologic and clinical studies to bipolar disorder and its response to treatment. We review the proposed role of PUFA metabolism in neuroinflammation, modulation of brain PUFA metabolism by antimanic medications in rodent models, and anti-inflammatory pharmacotherapy in bipolar disorder and in major depressive disorder (MDD). Although the convergence of findings between preclinical and postmortem clinical data is compelling, we investigate why human trials of PUFA as treatment are mixed. We view the biomarker and treatment study findings in light of the evidence for the hypothesis that arachidonic acid hypermetabolism contributes to bipolar disorder pathophysiology and propose that a combined high n-3 plus low n-6 diet should be tested as an adjunct to current medication in future trials.

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Bipolar disorder affects 1%–4.4% of the population and has an episodic, recurrent course that causes significant disability and has a complex, incompletely understood etiology.[1] Effective pharmacotherapies for acute episodes and prevention of relapse include lithium salts, certain antiepileptic agents (eg, valproic acid, carbamazepine, and lamotrigine), and antipsychotic agents.[2]

Although mood-stabilizing medications come from several pharmaceutical classes with differing primary mechanisms of action, downregulation of brain metabolism of arachidonic acid (AA, 20:4n-6), a long-chain omega-6 (n-6) polyunsaturated fatty acid (PUFA), has been suggested from preclinical studies as one common effect of mood-stabilizing medications.[3–5] Linoleic acid (18:2n-6) is the dietary-essential shorter-chain n-6 PUFA precursor of AA, which is also consumed in the diet. Alterations of turnover of PUFAs in membrane lipids, including AA, and resultant alterations in cell-signaling pathways in brain cell membranes have long been hypothesized to be central to perturbations of neurotransmitter systems in mood disorders.[6,7]

Both studies of biological concentrations of PUFAs, circulating in the plasma or incorporated into red blood cell membranes, and treatment trials using omega-3 (n-3) PUFAs as dietary supplements have had mixed results in bipolar disorder. While heterogeneity in methods and treatment intervention are confounding factors, one additional reason may be that trials did not also involve alterations in dietary n-6 as well as n-3 PUFA intake. Preclinical studies suggest that neurotransmission and other brain functions depend on a balance between n-6 and n-3 PUFAs and their downstream metabolites, such as proinflammatory prostaglandins, lipoxins, and thromboxanes and anti-inflammatory resolvins and neuroprotectins, respectively. We present the biological underpinnings of PUFA-related interventions in a physiological, biochemical, and molecular context. To do this, we drew upon literature from preclinical animal work, postmortem brain studies, and parallel investigations in major depressive disorder (MDD).

We will review evidence for the proposed role of PUFA metabolism in neuroinflammation, modulation of brain PUFA metabolism by antimanic medications in rodent models, and anti-inflammatory pharmacotherapy in bipolar disorder and in MDD. On the basis of the reviewed evidence, we propose that dietary manipulation combining high n-3 PUFA with low n-6 PUFA should be tested as an adjunct to traditional mood-stabilizing medications in future clinical trials, rather than using a simple high n-3 PUFA–containing diet.

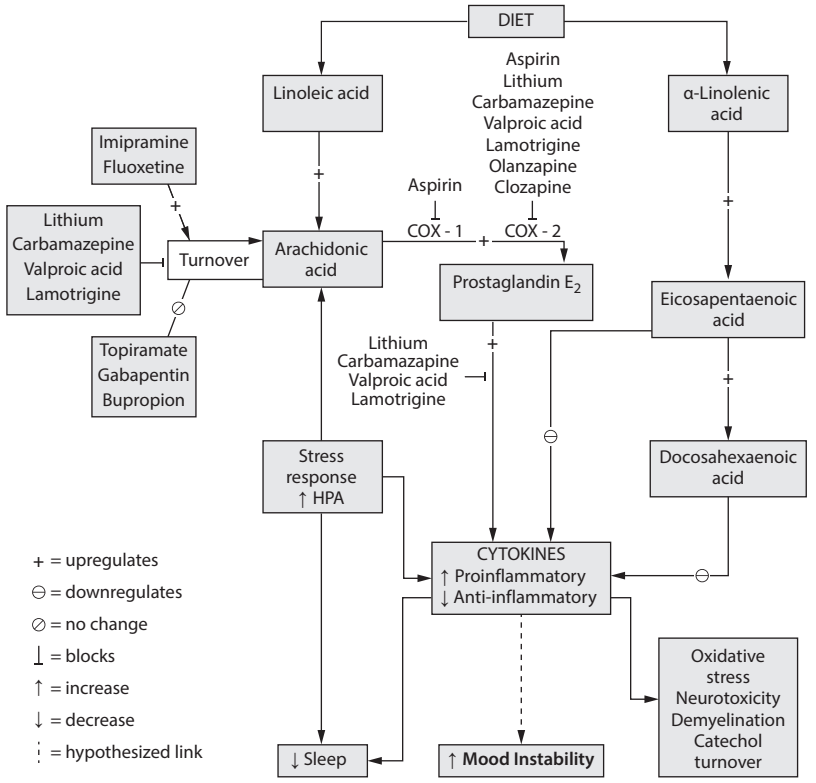
PUFAs and Neuroinflammation

The long-chain PUFAs AA and docosahexaenoic acid (DHA, 22:6n-3) comprise over 90% of PUFAs in the mammalian brain.[8] Arachidonic acid and DHA can be either derived from the diet or synthesized in the liver from their respective nutritionally essential shorter-chain PUFAs, linoleic

Clinical Points

- Omega-3 and omega-6 fatty acids are important for brain function and are part of inflammatory processes.
- Alteration of fatty acid intake with diet may be an additional way to investigate clinical benefits of changes in the omega-3 and omega-6 pathways.

Figure 1. Impact of Psychotropic Medication on Metabolic Pathways of the Polyunsaturated Fatty Acids



Abbreviations: COX = cyclooxygenase, HPA = hypothalamic pituitary adrenal.

acid and α-linolenic acid (18:3n-3). AA, DHA, and their metabolites function as intracellular second messengers and as modulators of neuroinflammation, neurotransmission, gene transcription, and other important brain process.[6] Proinflammatory cytokines can stimulate release of AA from membrane phospholipids, which then is available for metabolism by cyclooxygenase (COX)-1 or COX-2 to proinflammatory prostaglandins (eg, prostaglandin E_2), by lipoxygenases to cytotoxic leukotrienes, or by cytochrome p450 epoxygenases to cytoprotective epoxyeicosatrienoic acids with the AA metabolic cascade (Figure 1).[9] Prostaglandin E_2 affects sleep, and may mediate pain pathways and interleukin-1–induced "sickness behavior," which includes suppressed appetite, social withdrawal, psychomotor retardation, and poor concentration, symptoms that overlap with depression.[10–12] Prostaglandins also regulate the hypothalamic pituitary adrenal axis by inducing corticotropin-releasing hormone release.[13,14] Acetylsalicylic acid, a COX-1 inhibitor and COX-2 inhibitor and acetylator,[15] reduces the cortisol response,[16] and in a rat neuroinflammation model, chronic low-equivalent dose aspirin reduced brain levels of prostaglandin E_2 and 8-isoprostane.[17]

Arachidonic acid is hydrolyzed from membrane phospholipids by cytosolic or secretory phospholipase A_2 (PLA_2). While early genetic linkage studies[18,19] of the chromosomal region coding for secretory PLA_2 were promising, subsequent studies[20–23] failed to find significant association between *PLA_2* genes and bipolar disorder. Serum PLA_2 levels were reported to be elevated in schizophrenia, bipolar disorder, MDD, posttraumatic stress disorder, and substance abuse.[24] While a subsequent study[25] showed no difference between bipolar disorder and control in enzyme activity of PLA_2, calcium-independent PLA_2 was elevated in patients with bipolar disorder and a history of psychosis compared to those without psychosis. A recent study,[26] however, showed lower enzyme activity of 3 PLA_2 species in platelet membranes of drug-naive bipolar disorder subjects compared to controls. Increased AA metabolism in bipolar disorder has been suggested by postmortem brain studies (eg, Kim et al[27]). Compared to controls, the frontal cortex of bipolar disorder patients had increased expression of some AA metabolism enzymes, including AA-selective cytosolic PLA_2-IVA, secretory PLA_2-IIA, COX-2, and membrane prostaglandin E synthase (PGES), while expression of others (COX-1 and cytosolic PGES) was reduced and of others (calcium-independent PLA_2-VIA; 5-, 12-, and 15-lipoxigenase; thromboxane synthase; and cytochrome p450 epoxygenase) was unchanged,[27] suggesting an increase in activity in the AA cascade.[18,21,22] In this regard, a rat model of excitotoxicity using chronic administration of *N*-methyl-D-aspartate, a glutamate receptor agonist, showed increased cytosolic PLA_2 and increased AA signaling in the frontal cortex.[28,29]

Data from postmortem human brain and animal models are consistent with the proposition that neuroinflammatory processes could contribute to disease progression in bipolar disorder. Upregulated markers of the proinflammatory AA cascade, which activate pathways leading to cell dysfunction and death, have been reported in postmortem human brain.[27,30,31] Excitotoxic and proapoptotic factors were elevated and antiapoptotic and synaptic markers were decreased in the frontal cortex of those with bipolar disorder

compared to controls.[30,32] Studies[33–40] of peripheral PUFA markers in bipolar disorder show converging findings that abnormalities in the n-6 and n-3 metabolism pathways are present in bipolar disorder.

Neuroinflammation associated with excitotoxicity and apoptosis in bipolar disorder may promote future episodes and disease worsening. Although bipolar disorder is an episodic illness, progressive changes in cognitive function and brain structure occur and correlate with severity and chronicity of illness. Neuroinflammation and excitotoxicity, leading to neuronal apoptosis and synaptic loss, have been hypothesized to underlie progression of bipolar disorder (reviewed in Berk et al[41]). Subtle cognitive changes are reported during and between episodes and are related to number and amount of time in manic episodes.[42–44] Peripheral markers of inflammation are elevated in bipolar disorder.[45,46] Neuroimaging studies[47–49] have also reported brain atrophy and gray matter deficits in emotion regulation circuits linked to length of illness. In vivo imaging studies using functional magnetic resonance imaging have shown hemodynamic changes in the right amygdala and ventromedial prefrontal cortex and left hippocampus in euthymic bipolar disorder in response to an emotion task, and activation correlated with gene expression in inflammatory pathways.[50] In another study,[51] peripheral markers of inflammation in the kynurenine pathway were correlated with hippocampal volume. Additionally, a study[52] using positron emission tomography has shown elevated markers of microglial activation in bipolar disorder in the hippocampus.

Upregulation of the AA cascade in bipolar disorder also could modulate signal transduction and interfere with synaptic function[53] to promote worsening of illness and cognitive changes associated with duration of illness. Changes in the balance between the n-3 and n-6 PUFAs and their bioactive lipid autacoid derivatives (Figure 1) most likely influence the inflammatory response.[36]

Antimanic Medications Alter AA Metabolism

If upregulation of the AA cascade and subsequent neuroinflammation are associated with the pathophysiology and progression of bipolar disorder, effective treatments for bipolar disorder might act by downregulating the brain AA cascade.[3–5] A study supporting this proposition found that chronic administration to rats of a therapeutically relevant dose of lithium reduced AA turnover in brain phospholipids, expression of important AA-metabolizing enzymes, and generation of prostaglandin E_2,[5] while not affecting DHA and/or palmitic acid (16:0) turnover.[54] Other antiepileptic drugs with clinically proven antimanic efficacy (carbamazepine, valproate, lamotrigine) also downregulated the rat brain AA metabolic cascade,[55–57] while topiramate or gabapentin, antiepileptic medications that have failed phase 3 trials, did not.[4,58–60] Synthesizing these data has led to the hypothesis that therapeutic downregulation of the AA cascade can be tied specifically to effective treatment of bipolar disorder. Intervention could involve drugs (as discussed in this paragraph) as well and a change in the PUFA content of the diet (see The Way Forward).

Pharmacotherapy in Bipolar Disorder: Anti-Inflammatory and n-3 PUFA Agents

In addition to the proven effective mood stabilizers, other pharmaceutical agents that interfere with brain AA metabolism would be of interest to investigate clinically in bipolar disorder. They might include acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, nonselective COX inhibitors) or selective COX-2 or COX-1 inhibitors. Stolk et al[61] retrospectively used a Netherlands database to investigate effects of some of these agents in subjects on lithium. Long-term low-dose aspirin was associated with reduced risk for worse outcomes, while short-term use of a nonselective NSAID, or of more than 1 inhibitor, increased risk. Nery et al[62] found that celecoxib, a selective COX-2 inhibitor for treatment of depression or mixed episode in bipolar disorder, reduced severity of depression at 1 week, but did not have a sustained effect in a 6-week, double-blind, randomized controlled trial as an adjunct to usual treatment. The effect of anti-inflammatory treatments on mood outcome in bipolar disorder needs further consideration.

Studies in rodents report differing actions of antidepressants compared with mood-stabilizer medication on the brain AA and cytokine-based inflammatory systems. In unanesthetized rats, chronic imipramine and fluoxetine (a selective serotonin reuptake inhibitor [SSRI]), antidepressants that can increase risk for switching from depression to mania in bipolar disorder patients,[63] upregulated brain AA turnover and metabolism (opposite to direction of changes with mood stabilizers), but bupropion, an antidepressant causing lower switch rates, did not.[64,65] These comparisons suggest that increased brain AA metabolism may be associated with the manic phase of bipolar disorder and that stimulating AA metabolism may be associated with a switch of depression to mania with certain antidepressants. Indeed, coadministration of lithium, which depresses AA metabolism in rats, is recommended when fluoxetine is administered[66]; it might dampen the untoward AA upregulation of the SSRI. In mice, SSRIs increased inflammatory markers tumor necrosis factor-α, interferon (IFN)-γ, and p11 in the frontal cortex.[67] Because of the complex interactions between AA metabolism and inflammation, the clinical implications of these findings remain to be elucidated. Interestingly, a study of n-3 to prevent IFN-α–induced depression in 162 patients treated for hepatitis C showed lower rates of IFN-α–induced depression in EPA- but not DHA-treated patients, and both n-3 treatments delayed the onset of depression.[68]

Studies of treatment of bipolar disorder with supplementation of n-3 preparations, either EPA or DHA or both, have been mixed, and several recent reviews[33,69] have discussed these studies in detail. Briefly, open-label and nonrandomized trials[70–74] have been largely positive, while in 5 of 7 individual randomized clinical trials (RCTs),[75–81] the intervention group did not separate from placebo for

treatment of depression or mania. A meta-analysis[69] of RCTs in bipolar disorder showed a signal for treatment of bipolar disorder depression, but not mania. Interpretation of the responses seen in RCTs is confounded by factors including differing design of trials, compliance to study drug, composition and dose of supplements, and potential publication bias.

The Way Forward: Lessons From Migraine

We have described several ways in which altered brain AA metabolism may be important in the pathophysiology and pharmacologic or dietary treatment of bipolar disorder and have highlighted the mixed results of n-3 PUFA supplementation trials. If the brain PUFA metabolism system is important in bipolar disorder, what might account for the lack of consistent effects of dietary n-3 PUFA supplementation? One possibility is that n-3 PUFA supplementation without concurrent dietary reduction of n-6 PUFAs may not produce therapeutically relevant alterations in the interactive brain n-6 and n-3 PUFA pathways.[82,83] In this regard, consumption of the n-6 PUFA precursor linoleic acid has increased in the past 100 years in the average US diet—the predictable effect of this is increasing tissue concentrations of linoleic acid and decreasing tissue concentrations of n-3 EPA and DHA, and thus an imbalance of n-6 over n-3 PUFAs and their metabolites.[84] Simple addition of an n-3 PUFA supplement without concurrent reduction in dietary n-6 linoleic acid may not alter brain PUFA metabolism to the extent required to produce clinically meaningful benefit. To gain some insight into this issue and its relevance to bipolar disorder, we will describe a recent dietary intervention trial[85] in migraine headache.

Migraine headache has a clinical comorbidity with bipolar disorder of around 30% for both genders when studied together,[86–92] and in a recent study that investigated comorbidity by gender, 39% of women and 16% of men had migraine headache.[93] The pain associated with migraine headache has been hypothesized to be caused by prostaglandin E_2,[94] and thus related to increased AA metabolism[95] as well as increased neuroinflammation in general.[96–98] Both bipolar disorder and migraine headache respond to several of the same medications, including valproic acid[99,100] and lamotrigine,[101] indicating a potential shared pathology.

A recent 12-week, randomized clinical trial by Ramsden et al[85] compared clinical efficacy and biochemical effects of a high n-3 EPA + DHA plus low n-6 linoleic acid (H3-L6) diet to effects of only a low n-6 PUFA diet (L6) in 67 patients with chronic headache. Both the H3-L6 and L6 groups experienced statistically significant clinical improvement compared to the preintervention run-in phase, but the H3-L6 group experienced a significantly greater reduction in headache hours per day, headache days per month, headache-related quality-of-life, and psychological distress. Clinical improvements in the H3-L6 group were accompanied by reductions in erythrocyte linoleic acid and AA, as well as bioactive oxidized linoleic acid and AA metabolites that have been linked to pain.[102] The H3-L6 intervention also increased n-3 EPA, DHA, and the n-3 index, as well as pathway precursors for biosynthesis of anti-inflammatory and proresolving EPA and DHA metabolites.[96] Thus, the Ramsden et al trial[85] suggests that lowering dietary n-6 linoleic acid may be a key component to efficacy of n-3 PUFA supplementation in migraine treatment. On the basis of the clinical and neuroinflammatory links between bipolar disorder and migraine, concurrent dietary n-6 lowering in bipolar disorder may also be necessary for effective treatment of bipolar disorder with n-3 PUFA supplementation.[103]

Summary and Future Directions

An extensive body of human postmortem and animal studies implicates excessive brain AA metabolism and inadequate DHA metabolism in bipolar disorder pathogenesis and progression. However, the specific molecular mechanisms linking dysfunctional AA and DHA metabolism to bipolar disorder are incompletely understood. Future studies should be directed toward identifying specific signaling pathways and lipid mediators linking AA and DHA to bipolar disorder pathophysiology. This line of inquiry could lead to development of novel, targeted strategies for affecting PUFA metabolism through modulation of dietary AA and DHA intake that can be tested for improvement of mood stabilization in randomized controlled trials.

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