Nutrition, psychoneuroimmunology and depression: the therapeutic implications of omega-3 fatty acids in interferon-α-induced depression

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1. Introduction

Major depressive disorder (MDD) is a serious psychiatric illness with a high lifetime prevalence rate of up to one-tenth or possibly even one fifth [1]. Nevertheless, available treatments fail to meet the clinical needs of patients adequately, making this illness difficult to treat and burdensome to a patient’s life, family, and career. The growing burden of major depressive disorder (MDD) is evidenced by the projection that depression will become a leading cause of disease or injury worldwide by 2020 [2].

Clinical features, biological markers, and treatment outcomes for MDD are heterogeneous. Therefore, using our current diagnostic schemas undoubtedly contributes to the difficulty in finding any reliable biological markers for the disease [3]. According to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), individuals within the same diagnostic categories of MDD may have distinct clinical manifestations. Furthermore, the diagnostic classification does not provide reliable or predictive effects in treatment efficacy and/or the ability to predict the occurrence of adverse effects associated with specific antidepressants. Accordingly, with unsatisfactory outcomes for all the antidepressant treatments and the small-to-moderate effect sizes from all the biomarker studies and clinical trials, it is impossible to explain the whole picture of the aetiology of MDD with any single hypothesis.

The heterogeneity of depression could also be reflected by the current classification system with monoamine reuptake mechanisms for antidepressant agents (Figure 1). For example, the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which inhibit serotonin reuptakes, have been found to be associated with the development and treatment for depression in human and animal models. Here I review recent epidemiological studies, cross-sectional and longitudinal case-controlled studies, interventional clinical trials, as well as basic animal and cellular studies to prove the linkage among omega-3 PUFAs, inflammation, and depression.
The heterogeneity of depression could be reflected by the limits of pharmacotherapy and pharmacological classification based on serotonin, norepinephrine, and dopamine. Controversially, the agents that inhibit (i.e., SSRI & SNRI), enhance (i.e., SSRE), or even neglect (i.e., NDRI & SGAs) the serotonin reuptake action could all be approved to be antidepressant treatments, yet all of them seem to share the common mechanism of anti-inflammation. Interestingly, this common mechanism is applicable not only for antidepressant agents from different categories but also for omega-3 PUFAs, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (TMS).

is also approved as an antidepressant treatment. Furthermore, we have antidepressant agents that have nothing to do with serotonin reuptakes, such as norepinephrine-dopamine reuptake inhibitors (NDRIs) and second-generation antipsychotics (SDA). Indeed, the limits of pharmacotherapy and pharmacological classification based on serotonin, norepinephrine, and dopamine imply that the ‘monoamine hypothesis’ is woefully insufficient in approaching the aetiology of depression. Interestingly, all the antidepressant treatments seem to share the common mechanism of anti-inflammation.

Inflammation theory lights a promising path to resolve the dilemma of depression. Administration of therapeutic cytokine interferon-α (IFN-α) can lead to clinical depression [4-6]. In fact, looking for antidepressant therapies from anti-inflammatory pathways has become a hot topic in current medical research [7]. Chronic inflammation is linked with early childhood trauma, major psychiatric disorders, and several physical diseases [8, 9]; inflammation theory thus provides a clear window to investigate mind-body interface.

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs or n-3 PUFAs) are anti-inflammatory and have been proposed to be associated with the neurobiology of depression. The human body holds two main serial types of PUFAs: omega-6 (n-6) derived from cis-linoleic acid (LA, 18:2) and omega-3 (n-3) derived from α-linolenic acid (ALA, 18:3). Omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and omega-6 PUFAs, arachidonic acid (AA), are important constituents of all cell membranes, essential for the survival of humans and other mammals [6, 10]. PUFAs appear active in biological functions; some of their functions require conversion to eicosanoids and products like prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs). A deficit of omega-3 PUFAs is reported to be associated with neurological, cardiovascular, cerebrovascular, autoimmune, and metabolic diseases, as well as bipolar disorder and depression [10]. This review summarizes current evidence about omega-3 PUFA biological mechanisms of and—inflammation in—depression.

2. Omega-3 fatty acids in depression

Societies with high consumption of fish in their diets appear to have a lower prevalence of MDD, mood disorders, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality, and all-cause mortality [11], which implies a possible protective effect of omega-3 PUFAs in physical and psychiatric disorders. Consistent with epidemiological findings, patients with MDD show lower levels of omega-3 PUFAs in tissues of blood [12] and brain [13]. Deficits in omega-3 PUFA levels are reported in other populations with mood disorders: e.g., lower DHA and total omega-3 PUFAs in postpartum depression [14], lower DHA and EPA in social anxiety disorder [15], and lower DHA and AA in bipolar disorders [16].

Consistent with case-control studies of PUFA levels in human tissues, omega-3 PUFAs have been reported to be effective in treatment of MDD. Six meta-analytic reviews from four independent groups have reported on the antidepressant effect of PUFAs [17-22], yet three previous meta-analyses from the two of the four groups did not support these effects in heterogeneous populations (such as subclinical subjects in community samples) [23-26]. Negative findings must be interpreted with caution due to limitations: e.g., differing mood assessments, pooling heterogeneous populations, and implementing different intervention methods. For example, in a recent meta-analysis showing no benefits [24], their meta-analysis included clinical trials of enrolled individuals according to self-rating scales in settings like general practice surgery, a shopping mall and a university freshmen’s fair [27]. It found no beneficial effects of omega-3 PUFAs and was weighted 31.7% of a pooled estimate among a total of 13 clinical trials. Similar results emerged from the meta-analytic review by Appleton et al. [26]. Take one clinical trial [28] included in Appleton’s meta-analysis for example: Ness’s study enrolled a relatively large number of patients, 452, yet it did not focus on treating depression or using appropriate tools for the diagnosis of—as well as the severity rating of—depression. Intervention with omega-3 PUFAs was defined as “advising” subjects with anxiety to “eat more fish.” Treatment outcomes of omega-3 PUFAs in Ness’s study were negative and contributed greatly to the pooled estimate in Appleton’s meta-analysis.

Despite the uneven quality of published studies, recent meta-analytic evidence strongly supports the adjunctive use of omega-3 to treat bipolar depression [29]. However, studies regarding the effectiveness of omega-3 PUFAs in the acute manic phase of bipolar disorder are still lacking. To date, only one small double-blind placebo-controlled trial has been published, and it does not support omega-3 PUFAs’ anti-manic effects [30, 31]. Omega-3 PUFAs offer promise in treating special populations with depression [32, 33]. Our 8-week double-blind, placebo-controlled study showed monotherapy with omega-3 PUFAs was associated with a significant improvement in depressive symptoms and a higher response rate in pregnant women with depression [34]. Most importantly, omega-3 PUFAs are safe for and well tolerated by depressed women during pregnancy and postpartum [35]. In addition, omega-3 PUFAs are proven effective and safe for children with depression [36], and supplementation with omega-3 PUFAs lowers the risk of suicide [37], alleviates MDD depressive symp-
toms associated with menopausal transition [38], and diminishes aggression in women with borderline personality disorder [39].

2.1. Safety and tolerability

Numerous clinical studies have shown omega-3 PUFAs are tolerated well by patients with chronic medical illnesses and mental disorders [6, 40-42]. Adverse reactions are rare; and if they occur at all, they usually involve belching, eructation or perhaps a fishy taste [43]. It is theorized that a potential anti-thrombotic effect of omega-3 PUFAs may increase the risk of bleeding. Clinical trials have shown that a high-dose consumption of omega-3 PUFAs is safe, even when concurrently administered with other agents that increase bleeding, such as aspirin and warfarin [40]. According to Harris’s systematic review on 19 available clinical trials with n-3 PUFAs supplementation for patients with an already high risk of bleeding (n = 4397) [44], the risk of clinically significant bleeding was virtually nonexistent. Another potential safety concern is the susceptibility of omega-3 fatty acids to undergo oxidation, which may contribute to patient intolerance and potential toxicity. Yet it must be said that conclusions on this issue are quite inconsistent [42]. Adding an antioxidant like vitamin E to omega-3 PUFAs is a common way to reduce oxidation and rancidity, maintain freshness, and increase shelf life. The concurrent use of vitamin E with omega-3 PUFAs may also overcome the potential risk of oxidative stress, yet most published studies show either unchanged or decreased oxidation [42]. Given omega-3 PUFAs’ antidepressant effects, another possible adverse effect is drug-induced mania. Yet until now, only one case report shows omega-3 PUFAs inducing hypomania [45]. A comprehensive assessment of manic symptoms in patients receiving omega-3 PUFAs is recommended for future clinical trials.

As depression is heterogeneous, any currently available antidepressant treatment only has modest effects. For example, the effect sizes of n-3 PUFAs in MDD treatment are only 0.17~0.23 [20, 22], which are similar to antidepressant drug treatments of 0.11 for mild to moderate, 0.17 for severe, and 0.47 for very severe MDD [46]. Therefore, it is of clinical interest to identify specific populations who might benefit from specific treatments.

3. Inflammation in depression

Accumulating evidence suggests that depression might be associated with activated inflammatory processes: e.g., depressed patients with elevated c-reactive protein (CRP), acute phase proteins, and pro-inflammatory cytokines [4, 7]. Depression is highly comorbid with chronic physical diseases [47]. In fact, children exposed to early-life adverse experiences display enduring low-grade systemic inflammation upon reaching adulthood [8], which is not only a risk factor for depression but also a feature of chronic physical diseases. Inflammation theory thus explains the high comorbidity of physical illness in depression and the potential “interface between mind and body [48].”

Systemic inflammatory challenges like lipopolysaccharide (LPS) or pro-inflammatory cytokine in experiments on animals cause behavioural changes induced by neuroinflammation that include anorexia, sleep abnormalities, reduction of locomotor activity and exploration, anhedonia, and cognitive disturbances, which share a strong similarity with the somatic symptoms of depression [4]. Sick individuals are often somewhat depressed and lethargic. The idea of a sickness’s behaviour emanates from a series of observed symptoms related to infection and cytokine/prostaglandins administration in humans and animals. It offers a good model to study the effects of cytokine on the brain and behaviour [10, 49]. Excessive secretion of pro-inflammatory cytokines has been proposed to cause depression [50]. Microglia are the resident macrophages of the brain, and they act as the chief immune defense in the central nervous system (CNS) [51]. Upon activation, microglia up-regulate the expression of detrimental factors of reactive oxygen species such as nitric oxide via inducible nitric oxide synthase (iNOS) and induce oxidative stress, contributing to neuropsychiatric pathogenesis [52]. On the other hand, the expression of anti-oxidative enzymes like heme oxygenase-1 (HO-1) can reduce oxidative stress and may characterize antidepressant mechanisms [53, 54]. In addition, neuroinflammation reduces the survival of serotonergic neurons [55] and decreases neurogenesis [56], while antidepressants exert neuroprotection against microglia-mediated neurotoxicity [57].

3.1. IFN-α-induced depression

Substantiating evidence for the inflammation theory of depression is that interferon-alpha (IFN-α) induces clinical depression [5]. IFN-α is a standard cytokine therapy for chronic HCV infection, yet it associates with common and severe neuropsychiatric adverse effects. MDE during IFN-α therapy (IFN-α-induced depression) in patients with HCV is common, with incidence ranging from 23% to 45% [58]. Several biological mechanisms potentially play a role in this clinical phenomenon. For example, IFN-α-induced increases in IL-6 have been reported to predict development of depressive symptoms [59]. Cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA), but with no inflammatory markers, are associated with depressive symptoms induced by IFN-α [60]. Other studies are also mechanistically insightful by examining biomarkers such as plasma adrenocorticotropic hormone (ACTH), cortisol [61], serum tryptophan concentrations [62], and even brain function changes revealed in functional imagings [63]. Recent studies have identified genetic markers on serotonin transporters and interleukin-6 genes that seem to predict the development of IFN-α-induced depression [64].

4. Omega-3 fatty acids in interferon-α-induced depression

Chronic HCV infection is a major public health issue, and has a high rate of progression to liver cirrhosis and hepatocellular carcinoma [65, 66]. IFN-α is the standard therapy for chronic HCV infection, and will remain a cornerstone of therapy even with new combinations with ribavirin and protease inhibitors [67]. Because of the high rate of neuropsychiatric adverse effect like sickness behaviour and depression during IFN-α therapy, some clinicians consider adding prophylactic antidepressant use [68]. In patients with HCV infection, the prophylactic effects with SSRIs have been demonstrated by some [69-71], but not all [72-74] studies. Moreover, it has been associated with adverse events, including gastric discomfort, headache, dizziness, and an increased risk of rare but severe adverse effects, such as retinal haemorrhaging and cotton-wool spots [75, 76], bone marrow suppression, hepatotoxicity [74, 77], and manic episodes [78]. In addition, symptoms of IFN-α-induced sickness behaviour, once they develop, are only partially responsive to SSRIs [79]. As most patients receiving
IFN-α do not develop clinically significant depression with IFN-α therapy, the routine pre-treatment with antidepressant drugs might expose patients to unnecessary medications. It is thus important to find alternative strategies for the prevention of IFN-α-induced depression.

One advantage of nutritional medicine is its application in early intervention that can avoid unnecessary exposure to medication. Omega-3 PUFAs have been shown in numerous clinical studies to be tolerated well by patients with chronic medical illnesses, including liver diseases (Mori, 2004; Bays, 2006; Mozafar and Rimm, 2006; Bays, 2007; Lee et al., 2007). One of the hypothesized mechanisms underlying PUFAs’ antidepressant effects is their anti-inflammatory action (10). Moreover, omega-3 PUFAs have been found to have beneficial effects in cytokine-induced behavioural changes in animal models of depression [80, 81]. Of particular relevance, our previous study demonstrated that lower omega-3 PUFA levels in the peripheral blood are associated with an increased risk of developing IFN-α-induced depression over the following weeks [5]. Based on this and the other evidence discussed above, we further conducted a 2-week, double-blind, placebo-controlled trial, to test the differential effects of the omega-3 PUFAs, EPA and DHA, against a placebo, in the prevention of IFN-α-induced depression. We have specifically prescribed a short (2 weeks) intervention before IFN-α therapy, in order to potentially correct the lower omega-3 fatty acid levels that we had previously identified as a risk factor for the development of IFN-α-induced depression [5]. According to most studies, the active antidepressant component from omega-3 PUFAs is EPA (20, 22), but we also wanted to test DHA because, as mentioned above, we have found that lower levels of this omega-3 PUFA predispose patients to IFN-α-induced depression [5].

The results of that newly published clinical trial [41] support our previous findings, showing that omega-3 PUFAs play a role in the risk of IFN-α-induced depression. To summarize, the incident rates of IFN-α-induced depression were significantly lower in EPA-, but not in DHA-treated patients (rates: 10% and 28%, respectively, vs. 30% for placebo, \( P = 0.037 \)), as compared with the placebo. Both EPA and DHA pre-treatment significantly delayed the onset of IFN-α-induced depression (average weeks of onset: 12.0 and 11.7, respectively, vs. 5.3 for placebo, \( P = 0.002 \)). Previous clinical trials and meta-analyses have shown that the efficacy of omega-3 fatty acids as antidepressants might be dependent on the selection of the subject populations as well as the ratio of EPA and DHA, and have further suggested that EPA, rather than DHA, might be the most active component of omega-3 PUFAs’ antidepressant effects [20, 22]. However, Mischoulon et al. found a dose-response effect supporting 1 g/day as superior to 2 g/day or 4 g/day, though the latter study was limited by the lack of a placebo arm [82]. A recent meta-analysis has suggested that both EPA and DHA contribute to antidepressant effects, but that the effects of EPA are stronger [17]. Our current study, showing that EPA reduces the incidence of depression while DHA only delays the onset of depression, further supports this notion.

The anti-inflammatory action of omega-3 PUFAs is likely to be particularly important in the biological explanation for the antagonism of depressogenic effects of IFN-α. The model for IFN-α-induced depression reveals the increases of pro-inflammatory cytokines both in the periphery and in the brain of patients, with subsequent activation of the indoleamine 2,3-dioxygenase (IDO) pathway and the production of potentially depressogenic tryptophan metabolites, such as quinolinic acid [83]. EPA has numerous anti-inflammatory properties. Therefore, depressogenic mechanisms induced by proinflammatory cytokines and the IDO cascades are less likely to respond to standard antidepressants and more likely to respond to anti-inflammatory drugs [84-87]. In addition to this anti-inflammatory action, EPA and DHA may both exert their preventive effects also through neuroplasticity effects [88-90], which is a relevant molecular mechanism for antidepressant actions [91, 92].

5. Conclusions

The inflammation theory of depression draws support from several lines of evidence: e.g., increasing inflammatory biomarkers in clinical depression, and observed behavioral changes related to inflammatory activation. Interferon-α-induced depression in chronic HCV cases is the most notable clinical observation to support the inflammation theory of depression and an excellent model to probe the etiology of depression in a prospective way. Anti-inflammatory omega-3 PUFAs prove beneficial in depression and several inflammation-related physical diseases. In addition, omega-3 PUFAs have been shown to have prophylactic effects in bipolar disorder [31, 42, 93, 94], psychotic transition in ultra-high risk individuals [95], and the development of post-traumatic stress disorder (PTSD) following accidental injury [96]. Furthermore, omega-3 PUFAs may particularly benefit children, pregnant women, and/or patients with comorbid cardiovascular or metabolic disorder, who all face greater risks of adverse effects from antidepressants, antipsychotics, and mood stabilizers. Therefore, our findings confirm and extend the notion that this nutritional intervention can have preventive effects in mental health populations, and they also corroborate the existing evidence that anti-inflammatory strategies may have antidepressant effects, especially in the context of depression associated with inflammation.

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REFERENCES

[1] Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008; 358: 55-68.
[2] Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997; 349: 1498-504.
[3] Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004; 29: 1765-81.

[4] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006; 27: 24-31.

[5] Su KP, Huang SY, Peng CY, Lai HC, Huang CL, Chen YC, et al. Phospholipase A2 and Cyclooxygenase 2 Genes Influence the Risk of Interferon-alpha-Induced Depression by Regulating Polyunsaturated Fatty Acids Levels. Biol Psychiatry 2010; 67: 550-7.

[6] Su KP. Inflammation in psychopathology of depression: Clinical, biological, and therapeutic implications. BioMedicine 2012; 2: 68-74.

[7] Maes M, Leonard B, Fernandez A, Kubera M, Nowak G, Veerhuis R, et al. (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to kinase inhibitors. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35: 659-63.

[8] Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry 2008; 65: 409-15.

[9] Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA 2007; 104: 1319-24.

[10] Su KP. Biological Mechanism of Antidepressant Effect of Omega-3 Fatty Acids: How Does Fish Oil Act as a ‘Mind-Body Interface’? Neurosignals 2009; 17: 144-52.

[11] Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. Am J Clin Nutr 2006; 83: 1483S-93S.

[12] Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry 2010; 67: 550-7.

[13] McNamara RK, Hahn CG, Jandacek R, Rider T, Tso P, Stanford KE, et al. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. Biol Psychiatry 2007; 62: 17-24.

[14] De Vriese SR, Christophe AB, Maes M. Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-PUFAs are related to major depression. Life Sci 2003; 73: 3181-7.

[15] Green P, Hermesh H, Monselise A, Belski AG, Weizman A. Red cell membrane omega-3 fatty acids are decreased in nondepressed patients with social anxiety disorder. Eur Neuropsychopharmacol 2006; 16: 107-13.

[16] Chiu CC, Huang SY, Su KP, Lu ML, Huang MC, Chen CC, et al. Polyunsaturated fatty acid deficit in patients with bipolar mania. Eur Neuropsychopharmacol 2003; 13: 99-103.

[17] Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry 2011; 72: 1577-84.

[18] Freeman MP, Mischoulon D, Teleschini E, Goodness T, Cohen LS, Fava M, et al. Complementary and alternative medicine for major depressive disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. J Clin Psychiatry 2010; 71: 682-8.

[19] Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry 2006; 67: 1954-67.

[20] Lin PY, Mischoulon D, Freeman MP, Matsuoka Y, Hibbeln J, Belmaker RH, et al. Are omega-3 fatty acids antidepressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression. Mol Psychiatry 2012; 17: 1161-3.

[21] Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry 2007; 68: 1056-61.

[22] Martins JG, Bentzen H, Puri BK. Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. Mol Psychiatry 2012; 17: 1144-9.

[23] Appleton KM, Hayward RC, Gunnell D, Peters TJ, Rogers PJ, Kessler D, et al. Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. Am J Clin Nutr 2006; 84: 1308-16.

[24] Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry 2012; 17: 1272-82.

[25] Appleton KM, Rogers PJ, Ness AR. Is there a role for n-3 long-chain polyunsaturated fatty acids in the regulation of mood and behaviour? A review of the evidence to date from epidemiological studies, clinical studies and intervention trials. Nutr Res Rev 2008; 21: 13-41.

[26] Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr 2010; 91: 757-70.

[27] Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, et al. No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. Br J Nutr 2008; 99: 421-31.

[28] Ness AR, Gallacher JE, Bennett PD, Gunnell DJ, Rogers PJ, Kessler D, et al. Advice to eat fish and mood: a randomised controlled trial in men with angina. Nutr Neurosci 2003; 6: 63-5.

[29] Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 2012; 73: 81-6.

[30] Chiu CC, Huang SY, Chen CC, Su KP. Omega-3 fatty acids are more beneficial in the depressive phase than in the manic phase in patients with bipolar I disorder. J Clin Psychiatry 2005; 66: 1613-4.

[31] Su KP, Shen WW, Huang SY. Are omega-3 fatty acids beneficial in depression but not mania? Arch Gen Psychiatry 2000; 57: 716-7.

[32] Su KP, Shen WW, Huang SY. The use of omega-3 fatty acids for the management of depression and psychosis during pregnancy and breast-feeding. In: Peet M, Glen I, Horrobin DF, editors. Phospholipid spectrum disorder in psychiatry and neurology. 2 ed. Carnforth: Marius Press; 2003. pp. 391-9.

[33] Chiu CC, Huang SY, Chen CC, Su KP. Omega-3 fatty acids for depression in pregnancy. Am J Psychiatry 2003; 160: 385.

[34] Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2008; 69: 644-51.

[35] Freeman MP. Omega-3 fatty acids and perinatal depression: a review of the literature and recommendations for future research.
[36] Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. Am J Psychiatry 2006; 163: 1098-100.

[37] Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-center double-blind randomised controlled trial. Br J Psychiatry 2007; 190: 118-22.

[38] Freeman MP, Hibbeln JR, Silver M, Hirschberg AM, Wang B, Yule AM, et al. Omega-3 fatty acids for major depressive disorder associated with the menopausal transition: a preliminary open trial. Menopause 2011; 18: 279-84.

[39] Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry 2003; 160: 167-9.

[40] Bays HE. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol 2007; 99: 35C-43C.

[41] Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. Biol Psychiatry 2014; 76: 559-66.

[42] Su KP, Wang SM, Pae CU. Omega-3 polyunsaturated fatty acids for major depressive disorder. Expert Opin Investig Drugs 2013; 22: 1519-34.

[43] Bays H. Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. Am J Cardiol 2006; 98: 71i-6i.

[44] Harris WS. Expert opinion: omega-3 fatty acids and bleeding causation of concern? Am J Cardiol 2007; 99: 44C-6C.

[45] Kinrys G. Hypomania associated with omega-3 fatty acids. Arch Gen Psychiatry 2000; 57: 715-6.

[46] Fournier JC, DeRubeis RJ, Hollon SD, Fava M, Golay X, Bini E, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010; 303: 47-53.

[47] Zanarini MC, Frankenburg FR. Omega-3 Fatty acid treatment of borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry 2003; 160: 167-9.

[48] Bays HE. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol 2007; 99: 35C-43C.

[49] Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. Biol Psychiatry 2014; 76: 559-66.

[50] Harris WS. Expert opinion: omega-3 fatty acids and bleeding causation of concern? Am J Cardiol 2007; 99: 44C-6C.

[51] Kinrys G. Hypomania associated with omega-3 fatty acids. Arch Gen Psychiatry 2000; 57: 715-6.

[52] Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam LD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010; 303: 47-53.

[53] Katon W, Sullivan MD. Depression and chronic medical illness. J Clin Psychiatry 1990; 51 Suppl: 3-11.

[54] Lu DY, Leung YM, Su KP. Interferon-alpha induces nitric oxide synthase expression and haem oxygenase-1 down-regulation in microglia: implications of cellular mechanism of IFN-alpha-induced depression. Int J Neuropsychopharmacol 2013; 16: 433-44.

[55] Lu DY, Tsao YY, Leung YM, Su KP. Docosahexaenoic acid suppresses neuroinflammatory responses and induces heme oxygenase-1 expression in BV-2 microglia: implications of antidepressive effects for omega-3 fatty acids. Neuropsychopharmacology 2010; 35: 2238-48.

[56] Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, Woolwine BJ, et al. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. Biol Psychiatry 2009; 65: 296-303.

[57] Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. Am J Psychiatry 2003; 160: 1342-5.

[58] Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. Biol Psychiatry 2003; 54: 906-14.

[59] Capuron L, Pagnoni G, Demetrashvili M, Woolwine BJ, Nemeroff CB, Berns GS, et al. Anterior cingulate activation and error processing during interferon-alpha treatment. Biol Psychiatry 2005; 58: 190-6.

[60] Bull SJ, Huez-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, et al. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. Mol Psychiatry 2009; 14: 1145.

[61] Lauer GM, Walker BD. Hepatitis C virus infection. Nat Rev Immunol 2001; 1: 109-17.

[62] Schaefer M, Capuron L, Friebe A, cruz-Quevedo C, Robaey G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol 2012; 57: 1379-90.

[63] Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C. Psychosomatics 2003; 44: 104-12.

[64] Raison CL, Woolwine BJ, Demetrashvili MF, Borisov AS, Weinreb R, Staab JP, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. Aliment Pharmacol Ther 2007; 25: 1163-74.
Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami Wu PL, Liao KF, Peng CY, Pariante CM, Su KP. Manic episode as-

Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna Hejny C, Sternberg P, Lawson DH, Greiner K, Aaberg TM, Jr.

Morasco BJ, Loftis JM, Indest DW, Ruimy S, Davison JW, Felker B, Diez-Quevedo C, Masnou H, Planas R, Castellvi P, Gimenez D,

Schaefer M, Sarkar R, Knop V, Effenberger S, Friebe A, Heinze L, de Knegt RJ, Bezemer G, Van Gool AR, Drenth JP, Hansen BE,

Droogleever Fortuyn HA, et al. Randomised clinical trial: escitalo-

pharmacol 2008; 18: 639-45.

Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, et al. CSF concentrations of brain tryptophan and kynureni

during immune stimulation with IFN-alpha: relationship to CNS im-
mune responses and depression. Mol Psychiatry 2010; 15: 393-403.

Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. Candidate genes expression profile associated with anti-
depressants response in the GENDEP study: differentiating between baseline ‘predictors’ and longitudinal ‘targets’. Neuropsychophar-
camology 2013; 38: 377-85.

Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Jurusena MF, Markopoulou K, et al. Lack of clinical therapeutic benefit of antide-
pressants is associated overall activation of the inflammatory system. J Affect Disord 2013; 148: 136-40.

Zamszain PA, Anaeker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM, et al. Interleukin-1beta: a new regulator of the kynure-
nine pathway affecting human hippocampal neurogenesis. Neur-
sychopharmacology 2012; 37: 959-49.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013; 70: 31-

Bazinet RP, Laye S. Polysaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci 2014; 15: 771-85.

Rao JS, Ertley RN, Lee HJ, DeMar JC, Jr., Arnold JT, Rapoport SI, Perez DJ, Sano M. 15-hydroxyprostaglandin dehydrogenase defi-
cypharmacol 2008; 18: 639-45.

Felicisko A, Nemeroff CB, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine respon-
siveness of symptom dimensions. Neuropsychopharmacology 2002; 26: 643-52.

Song C, Phillips AG, Leonard BE, Horrobin DF. Ethyl-eicosapen-
e tic acid ingestion prevents corticosterone-mediated memory impair-
ment induced by central administration of interleukin-1beta in rats. Mol Psychiatry 2004; 9: 630-8.

Song C, Leonard BE, Horrobin DF. Dietary ethyl-eicosapentaenoid acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. Stress 2004; 7: 43-54.

Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu SL, et al. A double-blind dose-finding pilot study of docosa-
hexaenoic acid (DHA) for major depressive disorder. Eur Neuropsy-
chopharmacol 2008; 18: 639-45.

Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, et al. CSF concentrations of brain tryptophan and kynureni

during immune stimulation with IFN-alpha: relationship to CNS im-
mune responses and depression. Mol Psychiatry 2010; 15: 393-403.

Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. Candidate genes expression profile associated with anti-
depressants response in the GENDEP study: differentiating between baseline ‘predictors’ and longitudinal ‘targets’. Neuropsychophar-
camology 2013; 38: 377-85.

Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Jurusena MF, Markopoulou K, et al. Lack of clinical therapeutic benefit of antide-
pressants is associated overall activation of the inflammatory system. J Affect Disord 2013; 148: 136-40.

Zamszain PA, Anaeker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM, et al. Interleukin-1beta: a new regulator of the kynure-
nine pathway affecting human hippocampal neurogenesis. Neur-
sychopharmacology 2012; 37: 959-49.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013; 70: 31-

Bazinet RP, Laye S. Polysaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci 2014; 15: 771-85.

Rao JS, Ertley RN, Lee HJ, DeMar JC, Jr., Arnold JT, Rapoport SI, Perez DJ, Sano M. 15-hydroxyprostaglandin dehydrogenase defi-
cypharmacol 2008; 18: 639-45.

Felicisko A, Nemeroff CB, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine respon-
siveness of symptom dimensions. Neuropsychopharmacology 2002; 26: 643-52.

Song C, Phillips AG, Leonard BE, Horrobin DF. Ethyl-eicosapen-
e tic acid ingestion prevents corticosterone-mediated memory impair-
ment induced by central administration of interleukin-1beta in rats. Mol Psychiatry 2004; 9: 630-8.

Song C, Leonard BE, Horrobin DF. Dietary ethyl-eicosapentaenoid acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. Stress 2004; 7: 43-54.

Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu SL, et al. A double-blind dose-finding pilot study of docosa-
hexaenoic acid (DHA) for major depressive disorder. Eur Neuropsy-
chopharmacol 2008; 18: 639-45.