

Review Article

Mind-body interface: the role of n-3 fatty acids in psychoneuroimmunology, somatic presentation, and medical illness comorbidity of depression

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With the unsatisfaction of monoamine-based pharmacotherapy and the high comorbidity of other medical illness in depression, the serotonin hypothesis seems to fail in approaching the aetiology of depression. Based upon the evidence from epidemiological data, case-control studies of phospholipid polyunsaturated fatty acids (PUFAs) levels in human tissues, and antidepressant effect in clinical trials, PUFAs have shed a light to discover the unsolved of depression and connect the mind and body. Briefly, the deficit of n-3 PUFAs has been reported to be associated with neurological, cardiovascular, cerebrovascular, autoimmune, metabolic diseases and cancers. Recent studies revealed that the deficit of n-3 PUFAs is also associated with depression. For example, societies that consume a small amount of omega-3 PUFAs appear to have a higher prevalence of major depressive disorder. In addition, depressive patients had showed a lower level of omega-3 PUFAs; and the antidepressant effect of PUFAs had been reported in a number of clinical trials. The PUFAs are classified into n-3 (or omega-3) and n-6 (or omega-6) groups. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the major bioactive components of n-3 PUFAs, are not synthesized in human body and can only be obtained directly from the diet, particularly by consuming fish. DHA deficit is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, which might connect to the aetiology of mood and cognitive dysfunction of depression. On the other hand, EPA is important in balancing the immune function and physical healthy by reducing arachidonic acid (AA, an n-6 PUFA) level on cell membrane and prostaglandin E2 (PGE2) synthesis. Interestingly, animals fed with high AA diet or treated with PGE2 were observed to present sickness behaviours of anorexia, low activity, change in sleep pattern and attention, which are similar to somatic symptoms of depression in human. Therefore, the deficit of EPA and DHA in depression might be associated with mood disturbance, cognitive dysfunction, medical comorbidity and somatic symptoms in depression. Indeed, the role of n-3 PUFAs in immunity and mood function supports the promising psychoneuroimmunologic hypothesis of depression and provides an excellent interface shared by body and mind.

Key Words: major depressive disorder, depression, polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), Phospholipase A2 (PLA2), cyclo-oxygenase 2 (COX2)

INTRODUCTION

The growing burden of depression is evident by the projection that depression will be the second leading cause of disease or injury in the world by 2020.¹ Less than 50% of patients achieve full remission with optimized medication treatment,² despite the good availability of antidepressants on the market, among which are more than 40 drugs developed with the mechanisms related to serotonin, norepinephrine and/or dopamine. Depression frequently presents with medical comorbidity. The prevalence of major depression increases from 3%–5%, 5%–10%, to 10%–14% when the studied subjects moved from community settings, primary-care settings, to inpatient medical settings, respectively.³ The unsatisfactory outcome of pharmacotherapy and high comorbidity with physical illness imply that the monoamine hypothesis is insufficient to approach the aetiology of depression.^{2,4}

The phospholipid polyunsaturated fatty acids (PUFAs) hypothesis of depression is shedding a light to discover the unsolved of depression.⁵⁻⁷ There are two main types of PUFAs in human body, the omega-6 (n-6) series derived from cis-linoleic acid (LA, 18:2) and the omega-3 (n-3) series derived from α -linolenic acid (ALA, 18:3). N-3 and N-6 PUFAs are important components of all cell membranes, essential for humans and other mammals, and they cannot be synthesized in the body; hence, they have

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to be obtained in our diet and, thus, are called essential fatty acids (EFAs).⁸ The PUFAs themselves appear to be active in biological function, while some of their functions require their conversion to eicosanoids and other products. ALA can be converted to eicosapentaenoic acid (EPA, 20:5, n-3) and docosahexaenoic acid (DHA). EPA forms the precursor of the 3 series of PGs and the 5 series of LTs. LA can be converted to γ -linolenic acid (GLA, 18:3, n-6) and GLA can be elongated to form dihomo-GLA (DGLA, 20:3, n-6), which is the precursor of the 1 series of prostaglandins (PGs). DGLA can be further converted to arachidonic acid (AA, 20:4, n-6), which is the precursor of 2 series of PGs, thromboxanes (TXs) and the 4 series of leukotrienes (LTs). Both PGs and LTs are highly biologically active, have anti- or pro-inflammatory actions, and are known to be involved in various pathological processes, such as atherosclerosis, asthma, metabolic syndrome X, inflammatory bowel disease, neurological, cardiovascular, cerebrovascular, autoimmune, and several other inflammatory conditions.⁸⁻¹⁰ DHA deficit is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, which might connect to aetiology of mood and cognitive dysfunction of depression. On the other hand, EPA is important in balancing the immune function and physical healthy by reducing membrane arachidonic acid (AA, an n-6 PUFA) and prostaglandin E2 (PGE2) synthesis, and might be associated with medical comorbidity and somatic symptoms in depression.

The role of omega-3 polyunsaturated fatty acids (PUFAs) on depression

Major depressive disorder (MDD) is a serious affective illness with a high prevalence rate.¹¹ The occurrence of depression is commonly comorbid with other medical illnesses. While 6% of primary care patients experience depression, the prevalence is higher (12%) among medical inpatients.¹² Furthermore, the annual prevalence of major depressive disorder shows nearly a 60-fold variation across countries.¹³ It is similar to the cross-national differences in coronary artery disease mortality, which suggests that similar dietary risk factors might be important.^{14,15} Specifically, societies with a high consumption of fish, in which contains more n-3 PUFAs, appear to have a lower prevalence of major depressive disorder, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality and all cause mortality.¹⁵⁻¹⁷

Interestingly, n-3 PUFAs have been reported recently to be effective in treatment of depressive disorders. A mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in high dosage was effective in a case report of a pregnant depressive woman.¹⁸ EPA alone¹⁹⁻²¹ or a combination of EPA and DHA²² had positive effects for patients with major depressive disorder; however, two studies of DHA treatment showed no effect.^{23,24} Moreover, omega-3 PUFAs might be effective in treatment of bipolar depression,^{25,26} but the result was inconsistent.²⁷ In the preliminary trial, Stoll et al. found that n-3 PUFAs could improve the 4-month course of illness in patients with bipolar disorder.²⁸ Along with further analysis with Stoll's data,²⁹ and our clinical trial,³⁰ n-3 PUFAs were found a preventive effect on depression but not "anti-

mania" among the patients with bipolar disorder. However, the active component of the antidepressant effect in n-3 PUFAs is still unknown, although it has been argued that EPA might be more effective than DHA.³¹

The mechanism of the antidepressant effect of n-3 PUFAs is not yet elucidated. One of the explanations is the biological regulation of neurotransmitters and signal transduction by PUFAs.^{5,32,33} The change of PUFAs concentration in the brain could alter serotonergic and dopaminergic neurotransmission and then led to an increase in 5-HT₂ and decrease in D₂ frontal cortex receptor density.³⁴ The upregulation of 5-HT_{2A/C} is thought to play a role in the pathophysiology of depression.³⁵ The other explanation is that omega-3 PUFAs play an important role on mood stabilization by targeting on parts of the "arachidonic acid cascade", which has been identified as one of the mechanisms of mood stabilization.³⁶ The "arachidonic acid cascade" hypothesis in mood disorders has been supported by a number of evidences, including the higher ratio of AA³⁷⁻³⁹ and hyperactivity of its major metabolic enzyme phospholipase A2 (PLA2) in patients with mood disorders,⁴⁰ the inhibitory effect on PLA2 activity of mood stabilizers,⁴¹⁻⁴⁴ and the therapeutic effect of n-3 PUFAs in mood disorders.^{18-22,28}

EPA and DHA, the major bioactive components of omega-3 PUFAs, can not be synthesized in human body and can only be obtained directly from the diet, particularly in by consuming fish.⁴⁵ DHA, the main omega-3 fatty acid in brain, comprises 10–20% of total fatty acids composition, whereas the other omega-3 fatty acids like α -linolenic acid (ALA), EPA, and docosapentaenoic acid (DPA) comprise only 0.1% of total brain composition.⁴⁶ DHA is associated with neuronal membrane stability and functions of serotonin and dopamine transmission, which might connect to depression.^{5,22,34} On the other hand, EPA is important in balancing the immune and neuronal functions by antagonizing membrane arachidonic acid (AA, an n-6 PUFA) and reducing prostaglandin E2 (PGE2) synthesis.⁴⁷ Interestingly, animals fed with high AA diet or treated with PGE2 were found to demonstrate sickness behaviours like anorexia, low activity, change in sleep pattern and attention,^{48,49} which are similar to somatic symptoms of depression in human.⁵⁰ In addition to immune modulation, EPA might have a beneficial effect on improving the hypothalamic-pituitary-adrenal axis dysfunction and treatment-resistant depression through the action of p-glycoprotein (p-gp) and multi-drug resistance receptors.^{51,52}

Consistently, with the findings from epidemiological data and recent clinical trials, the abnormal fatty acid compositions on cell membrane in patients with mood disorders have been reported extensively.^{37-39,53-61} In 1996, Maes and colleagues reported that depressive patients had significantly higher levels of AA in phospholipids, AA/EPA ratio in both serum cholesteryl esters and phospholipids and n6/n3 ratio in cholesteryl esters; and lower levels of EPA in both serum cholesteryl esters and phospholipids and total n-3 fatty acid in cholesteryl esters.³⁹ Adams et al reported that there was a significant correlation between the ratio of erythrocyte AA/EPA and severity of depression.⁵⁶ However, Peet and colleagues reported that the only abnormal erythrocyte PUFA's level

was lower DHA, but not EPA or AA.⁶⁰ In contradiction to their previous report,³⁹ the level of AA was reported to be significantly lower in depressive patients in Maes's later report.³⁸ Depressed elderly patients had lower levels of DHA and higher levels of AA, higher ratio of n-6/n-3, AA/EPA and AA/DHA, than healthy volunteers.⁶¹ In a sample of patients with acute coronary syndromes, the depressive patients had lower DHA, EPA and total n-3 PUFAs; and higher AA, higher ratio of n-6/n-3, AA/EPA and AA/DHA than those without depression.⁵³ In the subjects with suicide risk, a lower DHA and a higher n-6/n-3 ratio had been reported to predict more future suicide attempts.⁵⁴ The similar finding of lower DHA, EPA and total n-3 PUFAs and higher n-6/n-3 ratio had been reported in the case-control study of Chinese patients who had suicide attempt.⁵⁹ The deficit in PUFA levels and abnormal compositions had been reported in other mood disorders, including lower DHA and total omega-3 PUFAs in postpartum depression;⁵⁷ lower DHA and EPA in social anxiety disorder;⁵⁵ and lower DHA and AA in bipolar disorder.³⁷

As mentioned previously, DHA, EPA and n-6 PUFA AA, are different in their biological functions. Since depression is heterogeneous in terms of aetiology and symptom presentation, the differentiation of depressive symptom clusters could be due to the various patterns of PUFAs deficits. However, the association between depressive symptom clusters and the variation of individual PUFAs level has not been determined yet.

Somatic symptoms in depression: Role of AA and EPA on sickness behaviour and somatic symptoms

Depressive disorders with predominantly somatic presentation are the most common form of depression. In a clinical study, somatic symptoms, particularly somatic anxiety and fatigue, were accounted for up to 80% of major depression.⁶² Two out of the three most common symptoms (low mood: 76%, fatigue: 73% and sleep disturbances: 63%) reported during a current depressive episode could be determined as somatic ones, as shown in the European Study Society study (DEPRES II).⁶³ Somatic symptoms were the main reason for the initial visit to the primary care physician.⁶⁴ In a US study, two thirds (69%) of depressed patients complained about general aches and pains, implying the close relationship between painful somatic symptoms and depression.⁶⁵

Typical symptoms of sickness include weakness, malaise, fatigue, muscle and joint aches, loss of interest in their surroundings, loss of appetite, and inability to concentrate, which are similar to somatic symptoms of depression.^{66,67} The idea of sickness behaviour⁶⁸ is from a series of observed symptoms related to infection and cytokine/prostaglandins administration in human and animals. Sick individuals are somewhat depressed and lethargic. Symptoms of sickness behaviour are not specific to identify the underlying pathological process, therefore most physicians do not pay much attention to them.⁶⁹ However, since cytokine-induced sickness behaviours provide a good model to study the effect of cytokine in the brain and behaviours, more neuroscientists show a greater interest on it (see reviews^{67,69-72}).

Symptoms of cytokine-induced sickness behaviour are mediated by prostaglandins (PGs).^{67,73-75} The endogenous metabolism of PGs can be modulated by dietary supplementation with PUFAs.⁴⁵ N-6 PUFA, AA is the major substrate for PGE2. An AA-enriched diet can increase glucocorticoid and PGE2 secretion, as well as anxiety behaviour.⁷⁶ In contrast, EPA can suppress proinflammatory effects of AA, thereby reducing PGE2 synthesis⁷⁷ and attenuating IL-1 β 's effect to activate PGE2.⁴⁸ Food enriched with ethyl-EPA (n-3 PUFA), but not soybean oil (n-6 PUFA), significantly attenuated most of the IL-1 β and thus induced sickness, stress and anxiety-like behaviours.⁴⁹ According to the evidence of EPA effect on antagonizing sickness behaviour in animals, we form the hypothesis that EPA might be specifically impair in depressed patients with prominent somatic symptoms and will respond well to EPA treatment in this proposal.

The role of n-3 polyunsaturated fatty acids (PUFAs) on medical conditions

Chronic low-grade systemic inflammation is a feature of chronic diseases, such as metabolic syndrome, type 2 diabetes,⁷⁸ cardiovascular disease,⁷⁹ coronary artery disease, erectile dysfunction,⁸⁰ cancers,⁸¹ dementia,⁸² which are highly comorbid in depression.^{3,12} It is evident that PUFAs and their products participate in the pathobiology of inflammation. The proinflammatory eicosanoids PGE2 and LTB4 are derived from the n-6 PUFAs AA, whereas anti-inflammatory LTs, PGD2, PGE1, PGIs, are derived from n-3 PUFAs EPA and DHA.⁷⁷ Proinflammatory cytokines induce oxidant stress, which enhances the production of free radicals by monocytes, macrophages, and leukocytes. Increased production of proinflammatory cytokines, such as IL-1, IL-2, IL-6, and TNF- α , and free radicals occurs due to systemic inflammation as seen in type 2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X. EPA/DHA and high-density lipoprotein (HDL) inhibit free radical generation and, thus, prevent oxidant stress.⁸

The amount and type of PUFAs released in response to inflammation depends on the phospholipid fatty acid composition on cell membrane, which is determined by the dietary intake and the regulatory enzymes. The beneficial effect of fish consumption with high contents of EPA and DHA might be attributed to the displacement of AA from the cell membrane phospholipid and to a preferential formation of less proinflammatory PGs (such as PGE3, PGF3 α , TXA3), and LTs (such as LTB5, LTC5, and LTD5).⁸ In summary, the role of n-3 PUFAs on medical conditions might be mediated with the inflammatory function related to themselves or their active bio-products.

The regulatory enzymes for PUFAs have effects on inflammatory process and pathogenesis of several medical conditions. Phospholipase A2 (PLA2) is the key enzyme of the phospholipids metabolism. The superfamily of PLA2 enzymes currently consists of 15 Groups and many subgroups includes five distinct types of enzymes, namely the secreted PLA2s (sPLA2), the cytosolic PLA2s (cPLA2), the Ca²⁺ independent PLA2s (iPLA2), the platelet-activating factor acetylhydrolases (PAF-AH), and the lysosomal PLA2s.⁸³ The main subtype of PLA2

enzymes is the cPLA2, which has a 50-fold preference for catalyzing the release of AA from membrane phospholipids.⁸⁴ The cPLA2 is involved in inflammation, intestinal ulceration, acute lung injury, polyposis, brain injury through ischemia/reperfusion, anaphylaxis, parturition and pain reaction.^{85,86} PAF-AH, or lipoprotein-associated phospholipase A2 (LP-PLA2), is an important inflammatory marker that is used to assess the risk for cardiovascular disease (CVD) and associated conditions.⁸⁷ Cyclooxygenase 2 (COX2) converts AA into PGE2, which is participant in many cellular responses and pathophysiologic processes including modulation of the inflammatory reaction, erosion of cartilage and juxtaarticular bone, gastrointestinal cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics, and progression of kidney disease,⁸⁸ as well as mood disorders.³⁶

Genetic regulation of PUFAs and PGE2 metabolism in depression and somatization

The gene for cPLA2, *PLA2G4A*, has been cloned and localized to chromosome 1q25.^{89,90} Interestingly, the gene coding for COX2 (also known as prostaglandin-endoperoxidase synthase 2, hence the name, *PTGS2*) is immediately centromeric of the *cPLA2* locus. These two gene loci are arranged in a head-to-head configuration, and hence potentially share a common regulatory region. Six single nucleotide polymorphisms (SNPs) present in the *PTGS2/PLA2* locus have been detected among 118 British family trios of schizophrenia patients, and a SNP termed by the authors as SNP4 (located in the 5'-flanking region in the first intron of the gene which creates a *BanI* polymorphic site) was associated with schizophrenia.⁹¹ Some studies have repeated the findings of association between this *BanI* polymorphism of the *PLA2* gene and schizophrenia,⁹¹⁻⁹³ but the other studies failed to demonstrate the association.⁹⁴⁻⁹⁷ Recently, Pae and colleagues found an association between this *BanI* polymorphism of the cPLA2 gene and depression in a Korean population, which showed a significant excess of A2/A2 (G/G genotype precisely) homozygotes.⁹⁸

The hypothesis here is that this *BanI* polymorphism, and other variations of genes involved in PUFAs and PGE2 metabolism, might have an effect on PUFAs' levels and somatic/anxiety symptom clusters rather than depressive disorder as a whole. For example, Tao et al. found that *BanI* polymorphism is likely to contribute to the development of negative symptoms of schizophrenia.⁹⁹ When examining the association of *BanI* polymorphism with every symptom cluster in 82 patients with major depressive disorder, we found that *BanI* is associated with only somatic anxiety symptom cluster (Chen et al, *submitted*). With chronic hepatitis C patients receiving interferon- α (IFN- α) treatment as a model of somatic symptoms in depression, we found that there are significant effects of cPLA2 *BanI* and COX-2 rs4648308 polymorphisms on IFN-induced depression and somatic symptoms. Specifically, the allelic association of *BanI* polymorphism of cPLA2 gene revealed that G allele had a significant effect on the development of IFN-induced depression. Subjects with the genotype G/G of *BanI* polymorphism had an increased risk of IFN-induced depres-

sion. In addition, subjects with the A/G of COX-2 rs4648308 polymorphism also had an increased risk than those with G/G (Su et al, *submitted*). In the future, the studies would need to focus on the associations among *PLA2G4A*, *PTGS2* genes, levels of PUFAs, and the somatic symptoms in depression.

SUMMARY

The phospholipid hypothesis of depression seems to be promising and has been supported by numerous evidences of omega-3 PUFAs effects on immunomodulation, signal transduction, neurotransmission and neuroprotection. Indeed, omega-3 PUFAs are safe, health promoted, and have several advantages for pregnant mothers, newborns, children, and patients with cardiovascular, cerebrovascular, immunological, or oncologic diseases. This review, with anticipation, can provide an insight of better understanding of depression and the interface between body and mind.

AUTHOR DISCLOSURES

Kuan-Pin Su, no conflicts of interest.

REFERENCES

- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498-1504.
- Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nat Rev Neurosci*. 2006;7:137-51.
- Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*. 2003;54:216-26.
- Skolnick P. Beyond monoamine-based therapies: clues to new approaches. *J Clin Psychiatry*. 2002;63(Suppl 2):19-23.
- Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. Possible candidate genes. *Prostaglandins Leukot Essent Fatty Acids*. 1999;60:217-34.
- Horrobin DF. Phospholipid metabolism and depression: the possible roles of phospholipase A2 and coenzyme A-independent transacylase. *Hum Psychopharmacol*. 2001;16:45-52.
- Su KP, Shen WW, Huang SY. Effects of polyunsaturated fatty acids on psychiatric disorders. *Am J Clin Nutr*. 2000;72:1241.
- Das UN. Essential fatty acids: biochemistry, physiology and pathology. *Biotechnol J*. 2006;1:420-39.
- Torpy JM, Lynn C, Glass RM. JAMA patient page. Eating fish: health benefits and risks. *JAMA*. 2006;296:1926.
- Connor WE. Importance of n-3 fatty acids in health and disease. *Am J Clin Nutr*. 2000;71:171S-5S.
- The World Health Report. *Mental health: new understanding, new hope*. Geneva: WHO; 2001.
- Katon W, Sullivan MD. Depression and chronic medical illness. *J Clin Psychiatry*. 1990;51(Suppl):3-11.
- Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276:293-99.

14. 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.
15. Hibbeln JR. Fish consumption and major depression. *Lancet.* 1998;351:1213.
16. Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukka A, Viinamaki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001;52:529-31.
17. Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry.* 2001;58:512-3.
18. Chiu CC, Huang SY, Shen WW, Su KP. Omega-3 fatty acids for depression in pregnancy. *Am J Psychiatry.* 2003;160:385.
19. 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.
20. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry.* 2002;159:477-9.
21. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry.* 2002;59:913-9.
22. Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol.* 2003;13:267-71.
23. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry.* 2003;160:996-8.
24. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids.* 2005;72:211-8.
25. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry.* 2006;188:46-50.
26. Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry.* 2005;66:726-9.
27. Keck PE, Jr., Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS, Denicoff KD, Grunze H, Duan N, Post RM. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry.* 2006;60:1020-2.
28. Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry.* 1999;56:407-12.
29. Su KP, Shen WW, Huang SY. Are omega3 fatty acids beneficial in depression but not mania? *Arch Gen Psychiatry.* 2000;57:716-7.
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. 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;68:1056-1061.
32. Hibbeln JR, Salem N, Jr. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr.* 1995;62:1-9.
33. Smith RS. The macrophage theory of depression. *Med Hypotheses.* 1991;35:298-306.
34. Chalon S. Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot Essent Fatty Acids.* 2006;75:259-69.
35. Maes M, Meltzer HY. The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology, the Fourth Generation of Progress.* New York: Raven Press; 1995:933-41.
36. Rapoport SI, Bosetti F. Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder? *Arch Gen Psychiatry.* 2002;59:592-6.
37. Chiu CC, Huang SY, Su KP, Lu ML, Huang MC, Chen CC, Shen WW. Polyunsaturated fatty acid deficit in patients with bipolar mania. *Eur Neuropsychopharmacol.* 2003;13:99-103.
38. Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res.* 1999;85:275-91.
39. Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord.* 1996;38:35-46.
40. Noponen M, Sanfilippo M, Samanich K, Ryer H, Ko G, Angrist B, Wolkin A, Duncan E, Rotrosen J. Elevated PLA2 activity in schizophrenics and other psychiatric patients. *Biol Psychiatry.* 1993;34:641-9.
41. Chang MC, Contreras MA, Rosenberger TA, Rintala JJ, Bell JM, Rapoport SI. Chronic valproate treatment decreases the in vivo turnover of arachidonic acid in brain phospholipids: a possible common effect of mood stabilizers. *J Neurochem.* 2001;77:796-803.
42. Rintala J, Seemann R, Chandrasekaran K, Rosenberger TA, Chang L, Contreras MA, Contreras MA, Rapoport SI, Chang MC. 85 kDa cytosolic phospholipase A2 is a target for chronic lithium in rat brain. *Neuroreport.* 1999;10:3887-90.
43. Chang MC, Jones CR. Chronic lithium treatment decreases brain phospholipase A2 activity. *Neurochem Res.* 1998;23:887-92.
44. Ghelardoni S, Tomita YA, Bell JM, Rapoport SI, Bosetti F. Chronic carbamazepine selectively downregulates cytosolic phospholipase A2 expression and cyclooxygenase activity in rat brain. *Biol Psychiatry.* 2004;56:248-54.
45. Lands WE. Biochemistry and physiology of n-3 fatty acids. *FASEB J.* 1992;6:2530-6.
46. McNamara RK, Carlson SE. Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukot Essent Fatty Acids.* 2006;75:329-49.
47. Farooqui AA, Ong WY, Horrocks LA. Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders. *Pharmacol Rev.* 2006;58:591-620.
48. Song C, Phillips AG, Leonard BE, Horrobin DF. Ethyl-eicosapentaenoic acid ingestion prevents corticosterone-mediated memory impairment induced by central administration of interleukin-1beta in rats. *Mol Psychiatry.* 2004;9:630-8.
49. Song C, Leonard BE, Horrobin DF. Dietary ethyl-eicosapentaenoic acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. *Stress.* 2004;7:43-54.

50. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition ed. Washington, DC: American Psychiatric Association; 1994.
51. Murck H, Song C, Horrobin DF, Uhr M. Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression. *Int J Neuropsychopharmacol*. 2004;7:341-9.
52. Huang SY, Yang HT, Chiu CC, Pariante CM, Su KP. Omega-3 fatty acids on the forced-swimming test. *J Psychiatr Res*. 2008;42:58-63.
53. Frasurre-Smith N, Lesperance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry*. 2004;55:891-6.
54. Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am J Psychiatry*. 2006;163:1100-2.
55. Green P, Hermesh H, Monselise A, Marom S, Presburger G, Weizman A. Red cell membrane omega-3 fatty acids are decreased in nondepressed patients with social anxiety disorder. *Eur Neuropsychopharmacol*. 2006;16:107-13.
56. Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids*. 1996;31 Suppl:S157-61.
57. 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.
58. Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord*. 1998;48:149-55.
59. Huan M, Hamazaki K, Sun Y, Itomura M, Liu H, Kang W, Watanabe S, Terasawa K, Hamazaki T. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. *Biol Psychiatry*. 2004;56:490-6.
60. Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry*. 1998;43:315-9.
61. Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MM. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am J Clin Nutr*. 2003;78:40-6.
62. Hamilton M. Frequency of symptoms in melancholia (depressive illness). *Br J Psychiatry*. 1989;154:201-6.
63. Tylee A, Gastpar M, Lepine JP, Mendlewicz J. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. DEPRES Steering Committee. *Int Clin Psychopharmacol*. 1999;14:139-51.
64. Kirmayer LJ, Robbins JM, Dworkin M, Yaffe MJ. Somatization and the recognition of depression and anxiety in primary care. *Am J Psychiatry*. 1993;150:734-41.
65. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163:2433-45.
66. Kent S, Bluth RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. *Trends Pharmacol Sci*. 1992;13:24-8.
67. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. *Trends Neurosci*. 2002;25:154-9.
68. Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev*. 1988;12:123-37.
69. Dantzer R. Cytokine-induced sickness behaviour: a neuro-immune response to activation of innate immunity. *Eur J Pharmacol*. 2004;500:399-411.
70. Dantzer R. Innate immunity at the forefront of psychoneuro-immunology. *Brain Behav Immun*. 2004;18:1-6.
71. Kelley KW, Bluth RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. *Brain Behav Immun*. 2003;17(S1):S112-8.
72. Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun*. 2001;15:7-24.
73. Milton AS. Thermoregulatory actions of eicosanoids in the central nervous system with particular regard to the pathogenesis of fever. *Ann N Y Acad Sci*. 1989;559:392-410.
74. Mahony SM, Tisdale MJ. Role of prostaglandins in tumour necrosis factor induced weight loss. *Br J Cancer*. 1989;60:51-5.
75. Uehara A, Ishikawa Y, Okumura T, Okamura K, Sekiya C, Takasugi Y, Namiki M. Indomethacin blocks the anorexic action of interleukin-1. *Eur J Pharmacol*. 1989;170:257-60.
76. Song C, Li X, Leonard BE, Horrobin DF. Effects of dietary n-3 or n-6 fatty acids on interleukin-1beta-induced anxiety, stress, and inflammatory responses in rats. *J Lipid Res*. 2003;44:1984-91.
77. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000;71:343S-8.
78. Kempf K, Rose B, Herder C, Kleophas U, Martin S, Kolb H. Inflammation in metabolic syndrome and type 2 diabetes: Impact of dietary glucose. *Ann N Y Acad Sci*. 2006;1084:30-48.
79. Daryani A, Basu S, Becker W, Larsson A, Riserus U. Antioxidant intake, oxidative stress and inflammation among immigrant women from the Middle East living in Sweden: Associations with cardiovascular risk factors. *Nutr Metab Cardiovasc Dis*. 2007;17:748-56.
80. Vlachopoulos C, Rokkas K, Ioakeimidis N, Stefanadis C. Inflammation, Metabolic Syndrome, Erectile Dysfunction, and Coronary Artery Disease: Common Links. *Eur Urol*. 2007;52:1590-600.
81. Petersen AM, Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. *J Physiol Pharmacol*. 2006;57(S10):43-51.
82. Zuliani G, Ranzini M, Guerra G, Rossi L, Munari MR, Zurlo A, Volpato S, Atti AR, Ble A, Fellin R. Plasma cytokines profile in older subjects with late onset Alzheimer's disease or vascular dementia. *J Psychiatr Res*. 2007; 41:686-93.
83. Schaloske RH, Dennis EA. The phospholipase A2 superfamily and its group numbering system. *Biochim Biophys Acta*. 2006;1761:1246-59.
84. Law MH, Cotton RG, Berger GE. The role of phospholipases A2 in schizophrenia. *Mol Psychiatry*. 2006;11:547-56.
85. Lucas KK, Svensson CI, Hua XY, Yaksh TL, Dennis EA. Spinal phospholipase A2 in inflammatory hyperalgesia: role of group IVA cPLA2. *Br J Pharmacol*. 2005;144:940-52.
86. Uozumi N, Shimizu T. Roles for cytosolic phospholipase A2alpha as revealed by gene-targeted mice. *Prostaglandins Other Lipid Mediat*. 2002;68-69:59-69.
87. Sudhir K. Clinical review: Lipoprotein-associated phospholipase A2, a novel inflammatory biomarker and independent risk predictor for cardiovascular disease. *J Clin Endocrinol Metab*. 2005;90:3100-5.
88. Patrignani P, Tacconelli S, Sciuilli MG, Capone ML. New insights into COX-2 biology and inhibition. *Brain Res Brain Res Rev*. 2005;48:352-9.

89. Miyashita A, Crystal RG, Hay JG. Identification of a 27 bp 5'-flanking region element responsible for the low level constitutive expression of the human cytosolic phospholipase A2 gene. *Nucleic Acids Res.* 1995;23:293-301.
90. Tay A, Simon JS, Squire J, Hamel K, Jacob HJ, Skorecki K. Cytosolic phospholipase A2 gene in human and rat: chromosomal localization and polymorphic markers. *Genomics.* 1995;26:138-41.
91. Wei J, Hemmings GP. A study of a genetic association between the PTGS2/PLA2G4A locus and schizophrenia. *Prostaglandins Leukot Essent Fatty Acids.* 2004;70:413-5.
92. Peet M, Ramchand CN, Lee J, Telang SD, Vankar GK, Shah S, Wei J. Association of the Ban I dimorphic site at the human cytosolic phospholipase A2 gene with schizophrenia. *Psychiatr Genet.* 1998;8:191-2.
93. Pae CU, Yu HS, Lee KU, Kim JJ, Lee CU, Lee SJ, Jun TY, Lee C, Paik IH. BanI polymorphism of the cytosolic phospholipase A2 gene may confer susceptibility to the development of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;28:739-41.
94. Meira-Lima I, Jardim D, Junqueira R, Ikenaga E, Vallada H. Allelic association study between phospholipase A2 genes and bipolar affective disorder. *Bipolar Disord.* 2003;5:295-9.
95. Frieboes RM, Moises HW, Gattaz WF, Yang L, Li T, Liu X, Vetter P, Macciardi F, Hwu HG, Henn F. Lack of association between schizophrenia and the phospholipase-A(2) genes cPLA2 and sPLA2. *Am J Med Genet.* 2001;105:246-9.
96. Chowdari KV, Brandstaetter B, Semwal P, Bhatia T, Deshpande S, Reddy R, Wood J, Weinberg CR, Thelma BK, Nimgaonkar VL. Association studies of cytosolic phospholipase A2 polymorphisms and schizophrenia among two independent family-based samples. *Psychiatr Genet.* 2001;11:207-12.
97. Wei J, Lee KH, Hemmings GP. Is the cPLA2 gene associated with schizophrenia? *Mol Psychiatry.* 1998;3:480-1.
98. Pae CU, Yu HS, Kim JJ, Lee CU, Lee SJ, Lee KU, Jun TY, Paik IH, Serretti A, Lee C. BanI polymorphism of the cytosolic phospholipase A2 gene and mood disorders in the Korean population. *Neuropsychobiology.* 2004;49:185-8.
99. Tao R, Wei J, Guo Y, Yu Y, Xu Q, Shi J, Liu S, Ju G, Li Y, Shen Y. The PLA2G4A gene and negative symptoms in a Chinese population. *Schizophr Res.* 2006;86:326-8.

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