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Omega-3 fatty acids in mood disorders: an overview

Omega-3 em transtornos do humor: revisão

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Abstract This review addresses the potential role of omega-3 fatty acids in mood disorders, from the biochemical rationale for their use to the growing body of data supporting their clinical efficacy.

Keywords Omega-3. Mood disorders. Treatment.

Resumo Essa revisão aborda o papel potencial que o ácido graxo Omega-3 tem no tratamento dos transtornos do humor. Parte da fundamentação bioquímica para o corpo de evidências que tem sustentado a eficácia clínica desse procedimento.

Descritores Omega-3. Transtornos do humor. Tratamento.

Background: mood disorders and the need for novel therapies

Major depression and bipolar disorder are serious illnesses that combined may afflict as many as 10 to 15% of the population. These disorders are associated with substantial costs to individuals, their families and society through suicide, lost productivity, and elevated rates of service utilization. Depression and bipolar disorder have been ranked first and sixth as worldwide causes of disability adjusted life years (DALYs) among people ages 15 to 44.[1] Despite advances in psychotherapies, pharmacotherapy and other biological approaches, the treatments for these elusive illnesses continue to hit multiple stumbling blocks. With limited efficacy, frequent side effects, and poor adherence affecting many patients, the need for novel pharmacological approaches to the treatment of these debilitating illnesses is a priority area for research.

Present medication regiments for depression have limited efficacy. As a class, the Serotonin Selective Reuptake Inhibitors (SSRI's) are the most widely prescribed, yet reduce depressives symptoms by 50% in less than half of patients who start them, and by less than 60% of those who complete a full course.[2] Other antidepressants, such as the tricyclic antidepressants and norepinephrine reuptake inhibitors have similar overall efficacy. It has also been demonstrated that in clinical trials, close to 30% of patients will stop treatment, due to limited efficacy, troublesome side effects, or a combination of both.

Similarly, standard treatments of bipolar disorder have limited efficacy and are fraught with potential adverse events. Lithium, a major break through treatment, has been associated with a 20-40% rate of treatment failure. For rapid cycling and mixed episodes, a presentation more common in youth, the failure rates may be even higher. A high incidence of tremor, thyroid dysfunction, polyuria, weight gain and acne can lead to low rates of adherence. Valproate has also demonstrated efficacy in the acute treatment and management of bipolar disorder, with one study showing as many as 48% of individuals experiencing marked improvement in bipolar symptoms. The agent is likely more effective than lithium for the treatment of mixed and rapid cycling states, yet like all other mood stabilizers, it is associated with potentially serious side effects. Tremor, gastrointestinal distress, hair thinning, hepatitis, pancreatitis and weight gain are some of the potential side effects that effect patient compliance. Additionally, these mood stabilizers require monitoring of blood levels and specific tests to track liver, thyroid and renal function. With refractory forms of both major depression and bipolar disorder often requiring augmentation strategies and polypharmacy, there is a clear need for novel, safe and effective treatment alternatives.

The development of new antidepressants and mood stabilizers, the implementation of more rigorous psychotherapy trials,

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and the exploration of newer biological treatments such as transcranial magnetic stimulation, vagal nerve stimulation and bright light therapy continues. The focus of this article will be to review the potential contribution of an essential dietary substance, omega-3 fatty acids, in the armamentarium of potential treatments for the mood disorders.

Something fishy: a dietary connection?

Lipids, which comprise roughly 60% of the solid mass of the brain, are essential for normal brain structure and function. The majority of lipids are phospholipids made up of an unsaturated fatty acid attached to a 3-carbon glycerol structure. Within this configuration, the two most common types of unsaturated fatty acids are omega-3 and omega-6. The main omega-3 fatty acid is docosahexaenoic acid, and the main omega-6 fatty acid is arachidonic acid, respectively touted in the lay press as 'good' and 'bad' fats. Both of these fatty acids are essential substances, meaning that they can not be manufactured in the body and so must be ingested through food sources. The omega-3's typically come from fish such as salmon, cod, and tuna, as well as from flax seed oil and some nuts. By comparsion, omega-6's are primarily found in vegetable oils, like those derived from corn or sunflower seed.

It has been suggested that changes in the refining processes of foods, as well as the process of cultural dietary selection, particularly in industrialized nations, has led to a decrease in the consumption of omega-3 fatty acids, with a corresponding relative increase in the consumption of omega-6 fatty acids. The ensuing elevated ratio of omega-6 to omega-3 fatty acids is thought to be linked to increased production of inflammatory cytokines, changes in turn associated to medical and psychiatric disorders at least partly mediated through chronic inflammatory changes. Taken together, these dietary changes as etiologically relevant factors have been referred to as the phospholipid deficiency hypothesis.

Within the central nervous system, phospholipids that are composed of omega-3 and omega-6 fatty acids have important functions in neuronal signal transduction, as in nerve cell membrane integrity and fluidity. These roles allow for the positioning and function of proteins such as neurotransmitter receptors and protein kinases, both of which are vital for cell signaling systems. The correct balance of omega-3 and omega-6 fatty acids within phospholipids is ultimately essential for normal neuronal function. Research has indicated that a disrupted balance of these fatty acids within the phospholipid structures may be linked to depression.

The annual prevalence of major depression is reported to vary as much as 60-fold across nations. Some investigators have noted a similar cross-national pattern in mortality rates by coronary artery disease (CAD). Citing the established relationship of CAD to dietary factors, similar cross-national patterns of CAD and depression have led to the suggestion that dietary risk factors may be of significance in depression.[3]

Epidemiological studies examining the dietary habits of several countries have noted that places with higher rates of omega-3 consumption, where fish is a core part of the diet, have lower rates of depressive disorders.[4] Indirect evidence from dietary research has further demonstrated a lowering of omega-3 fatty acids in Western diets over the past century in comparison to the prior, or to other countries.[5] In countries such as Japan, where annual fish consumption rates are close to 150lbs per person, prevalence rates of depression are 0.12%, compared to Germany, where annual fish consumption is less than 30lbs per person and the prevalence rate of depression is 5% (Figure).

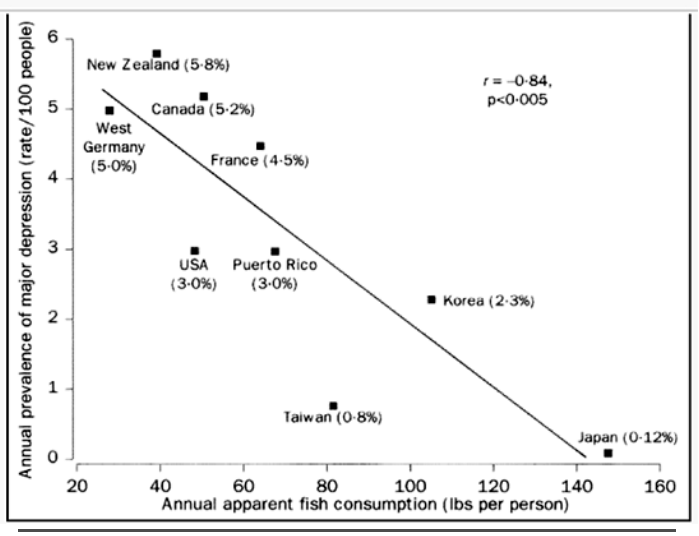

Figure - Taken from: Hibbeln J. (1998).

A rationale for use: omega-3 mechanisms of action

Depression and suicide have repeatedly been associated with low levels of cerebrospinal fluid 5-hydroxyindolacetic acid (CSF 5-HIAA), a marker of brain serotonin, evidence that partially led to the development of the SSRIs. It has also been suggested that abnormal cell membrane fatty acid composition may be associated with depression. For example, low concentrations of the omega-3 fatty acid docosahexaenoic acid predict low concentrations of CSF 5-HIAA.[6]

Further studies have looked at omega-3 fatty acids, a crucial component of synaptic cell membranes, by measuring red blood cell membrane fatty acids in a group of depressed patients compared to matched healthy control group.[7] A negative correlation between depressive severity and RBC membrane omega-3 levels has been described.[8] Peet et al[9] similarly reported on depleted omega-3 fatty acid levels in the red blood cell membranes of depressed patients. Among others, Maes et al[8] have put forth the theoretical grounds for a connection between fatty acid intake and existing receptor and neurotransmitter theories of depression. This is largely based on changes seen in serotonin receptor and function associated with changes in polyunsaturated fatty acids.

In bipolar disorder, successful treatment strategies that have been studied have focused primarily on pharmacologic interventions. The primary mechanism that has been suggested through which many mood stabilizers work is the inhibition of neuronal signal transduction processes.[10] Other properties that mood stabilizing medications appear to have besides their ef-

fects on neuronal signal transduction are through antikindling activity as well as inhibition of the phosphatidylinositol system.[11,12] Kindling, initially proposed as a mechanism in epilepsy, refers to a series of minimum stimuli eventually leading to an 'afterdischarge' which may then lead in vulnerable brain regions to a seizure.[13] Post[14] further advanced the theory of kindling to bipolar disorder highlighting similar features between the two disease states, suggesting potential similarities in pathophysiology and pharmacology. Omega-3 fatty acids, much like lithium and valproate, have antikindling properties that have been demonstrated in animal models.[10,15] Similarly, the standard mood stabilizers lithium and valproate have been found to reduce the overactive signaling of the phosphatidylinositol system that has been linked to rapid Ca2+ release and activation of multiple cellular processes associated with mania.[16] Finally, in animal models, omega-3 fatty acids have shown modulation and suppression of voltage-gated Ca2+ channels.[17,18] The initial idea of using omega-3 fatty acids as mood stabilizers was developed with the knowledge of those biochemical mechanisms.[5]

From theory to clinical application

Bipolar disorder

In a preliminary double-blind, placebo-controlled trial, Stoll et al[19] compared omega-3 fatty acids (9.6 g/d) to placebo in addition to usual treatment over a 4-month study period. In survival analysis of the cohort, the patient group treated with additional omega-3 fatty acids had a significantly longer period of remission than the placebo group. Additionally, the omega-3 treated group performed better on secondary outcome measures. The findings were in fact so robust that the trial was prematurely terminated as it was deemed unethical to withhold treatment from the placebo group.

Open label experience has been reported as well for a plant-based oil. Flaxseed oil contains *a*-linolenic acid, a shorter-chain omega-3 fatty acid, and is more palatable than standard commercial fish oil.[20] Stoll et al[19] have reported on the benefits to 18 of 22 bipolar patients treated with flaxseed oil. Many patients have described mood elevation on flaxseed oil and elected to remain on it as a long term adjunct to their mood stabilizer regimens.

Major depression

A recent, randomized, double-blind, dose-ranging study of the effects of ethyl-eicosapentanoate in 70 patients with ongoing depression despite apparently adequate treatment with standard drugs found significant improvements over placebo across three depression scales for the low dose group[21] (1 g/d; in a maintenance study Nemets et al[22]) found significant benefits from augmentation with omega-3's in patients with depression already receiving antidepressants. The trial was a four weeks, parallel groups design, where twenty patients participated in the double-blind addition of either placebo or ethyl ester of eicosapentaenoic acid (E-EPA) to ongoing antidepressant therapy. Six of 10 patients receiving E-EPA had a greater than 50% drop in Hamilton depression score, while only one of 10 receiving placebo achieved a significant reduction in Hamilton scores. Few side effects were reported in either of these studies, nor in another of omega-3 use in patients with behavioral disorders.[23]

In a letter to the editor, Puri et al[24] report one of the first cases of omega-3 fatty acids in the successful treatment of unipolar depression. In their account, a 21 year old male with a 7-year history of unremitting depressive symptoms without response to antidepressants and augmenting strategies had a positive response to the omega-3 fatty acid eicosapentaenoic acid, as evidenced by a significant Montgomery-Asberg Depression Rating Scale (MADRS) drop from 32 to 0 over one month.

Dosing and monitoring

Dosing has varied over the few studies that have been reported. In the placebo-controlled bipolar trial, 9.6 g/d of omega-3 fatty acids were used, while in the Nemets trial augmenting maintenance medications, omega-3's were dosed at a much lower 2 g/d. Nemets' group based their decision on anecdotal reports of successful clinical uses at lower doses. In Stoll's study few people reported side effects, with the most common one being mild gastrointestinal distress characterized by loose stools. In the depression study no relevant side effects were reported, including fishy tastes or sensations. Because of the relatively low potency of the available preparations, a relatively large number of capsules are required daily, a consideration that may affect compliance and provide to be limiting among certain patients – particularly very young or elderly ones.

Comment

In recent years there has been a significant increase in the use of complimentary medical services, including natural treatments, which has outpaced the limited number of rigorous trials to support their safety and efficacy.[25] With the increasing need for new treatments, the omega-3 fatty acids may prove promising as additional agents in the armamentarium of treatments for mood disorders. Several factors have come to light in the early stages of their study. Omega-3's may show benefit for both unipolar depression and bipolar disorder. There also appears to be evidence that their mechanism of action may be similar to some other mood stabilizers and anticonvulsant agents that are being studied for efficacy in bipolar disorder.

Omega-3's additionally show little evidence of adverse effects, toxicity or drug interactions. This is increasingly important as the side effects of newer mood stabilizers come to light and the growing evidence that multiple mood stabilizers are required for long-term stabilization. Other important areas of study relate to the increasing phenomenon of the diagnosis of mood disorders, in particular of bipolar disorder among children and adolescents. There is a need for new treatments that are more tolerable in children who are vulnerable to the adverse effects of traditional treatments, especially when considering the chronicity and at times lifelong impairment associated with these illnesses.

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