Introduction and Background on Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA's) derived from plants and marine organisms. The parent omega-3 fatty acid, alpha linoleic acid, which is converted by the liver to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is found in many plants. PUFA's are important constituents of the cell membrane of a majority of cerebral neurons. One in every three fatty acids in the central nervous system is a PUFA and 20% of the dry weight of the brain is made up of these fatty acids (**1**). While the exact ratio of the various PUFA's in the brain is unknown, it is known that EPA and DHA are two PUFA's that are important in neuronal function. Marine organisms are a good source for EPA and DHA and there is accumulating evidence that reduced fish consumption is associated with increased prevalence of mood disorders. While it is very difficult to measure the levels of polyunsaturated fatty acids in the brain, it is possible to determine their levels in other cell types. In major depression there are significant decreases in the levels of omega-3 fatty acids, especially DHA and EPA in the membrane of erythrocytes (**2**). The goal of this paper is to outline and discuss some of the major epidemiological and clinical data examining the association and possible role of omega-3 fatty acids in mood disorders, particularly depression and bipolar disease.

Epidemiological Data

There is both epidemiological and clinical evidence that there is a connection between omega-3 fatty acids and depression and bipolar disease. We will examine the epidemiological data first. In these studies the prevalence rates of depression and bipolar disease were obtained from published epidemiological data and from the Cross-National Collaborative Group epidemiological study of ten countries **(3).** Several studies have examined the prevalence of bipolar disorder and major depression in various countries and compared them to levels of fish consumption, wit the rationale that fish is a rich source of EPA and DHA. Fish consumption was a measure of disappearance of fish and is calculated as total catch plus imports minus exports (**4**). Most of these studies have found a lower prevalence of bipolar disease and major depression in countries with higher national fish consumption. Specifically, Noaghiul et al. found a lower lifetime prevalence of bipolar I, bipolar II, and bipolar spectrum disorder in countries like Iceland, Korea and Taiwan where fish consumption neared or exceeded 100 lb/person/year, and a higher lifetime prevalence of these disorders in countries like the United States, Germany, and Switzerland, where national fish consumption was less than 50 lb/person/year (**4**). In another study Peet determined a negative correlation between the rates of fish consumption and the prevalence of depression in multiple countries (**5).** Another study examined the amount of fish consumption in 23 countries and found lower incidences of postpartum depression among those countries with higher fish consumption. Additionally, the same study found an inverse correlation between the levels of EPA and DHA in mother's milk and postpartum depression (**6)**

In further support of the notion that omega-3 fatty acids may be associated with better mental health, a study in Finland has shown that increased fish consumption is associated with lower incidences of depression and less suicidal thought (**7**). Another study in New Zealand has also determined that people who consume more fish generally report better mental health status. The study from New Zealand and Finland are of unique value, because they examined differences

within the same country where there may be less confounding variables. Even though there is a strong growing body of epidemiological data demonstrating an inverse correlation between the consumption of fish and the prevalence of mood disorders, there is a small body of conflicting evidence demonstrating no correlation or positive correlation between fish consumption and depression. The most prominent of these is a population-based study of Finnish men. In this study, those men who consumed high levels of fish were more likely to have depressed mood or anxiety (**8)**. One drawback of this report is that it was conducted in smokers who generally tend to be more depressed and anxious.

These data demonstrate an association between fish consumption and these mental health disorders but many confounding variables may be involved. For example, generally fish is more expensive than beef and poultry and as a result people from higher economic backgrounds would be more likely to eat fish. These individuals are under less financial stress, and therefore may be less depressed. In addition, people who eat fish may generally be more likely to watch their health and participate in other activities that reduce stress and improve mood, such as exercise.

Clinical Data

Within the clinical literature, the general consensus is that administration of EPA and DHA alone or in addition to antidepressants helped improve depressive symptoms in studied populations. Interestingly these studies primarily looked at the effects of omega-3 fatty acids over the course of months. The major limitation with most of these studies is that the sample sizes are small. One randomized double blind study in Taiwan examined 22 individuals over an eight week period and found that at the end of eight weeks, patients who were given 440 mg of EPA and 220 mg of DHA per day were less depressed as measured by the Hamilton Depression Scale, than those who were given a placebo. All 22 participants in this study were on anti-depressants (**9)**. Another double-blind placebo-controlled study examined depression in 70 patients who were treated with 1, 2, or 4 g of ethyl EPA over a course of twelve weeks and found that treatment with 1 g of ethyl EPA helped reduce symptoms of depression more than Placebo (**10**). The sample size was small, therefore it was difficult to draw conclusions about the 2 or 4 gram sample size. However, preliminary results suggested that the 4 gram treatment may actually be even more efficacious in treating these symptoms of depression. In this study the Hamilton Depression Scale, Montgomery-Asberg Depression Scale, and the Beck Depression Inventory were used. The participants were mostly women, and since the sample size was quite small, it is difficult to draw conclusions about men. In a separate study, thirty individuals with a history of major depression who were treated for four months with a combination dosage of 6.2 g of EPA and 3.4 g of DHA per day stayed in remission for significantly longer periods of time and reported less symptoms of depression (**11**). In another double blind, placebo controlled study, adding 2 grams of EPA to antidepressants showed an enhanced effect of the antidepressants as measured by the Hamilton depression scale **(12).** There is no conflicting data in which EPA alone was used, but in one double-blind placebo-controlled study where 2 g of DHA alone per day were administered in 36 patients for six weeks, the treatment group did not show statistically significant differences on the Montgomery-Asberg scale as compared to placebo (**13**). There are two other studies in which DHA alone or DHA with EPA did not improve depressive symptoms in the treatment group as compared to placebo. However, both of these studies examined postpartum depression in very small sample sizes.

Concluding Remarks

Mechanisms by which omega 3 fatty acids influence mental health are not well understood. However, it is postulated that one of the major effects of these compounds is their anti-inflammatory capability. This finding is consistent with the notion that omega-3 fatty acid consumption is also associated with lower incidences of cardiovascular disease, cerebrovascular disease, and cancer (**14**). Like many inflammatory diseases, major depression and possibly bipolar disorder are associated with increases in inflammatory modulators including interleukins1 beta, 2, and 6, interferon gamma, and tumor necrosis factor alpha (**15**). Exactly how these inflammatory agents can affect the central nervous system is not well understood, however, it is thought that they reduce the metabolic synthesis of certain neurotransmitters, alter expression of genes that are involved in neurotransmitter synthesis, and activate the hypothalamic-hypophyseal axis. It is postulated that omega-3 fatty acids inhibit the production of these inflammatory modulators. Another possible mechanism by which omega-3 fatty acids may alter mental health is through alteration of nerve cell membrane composition. Deficiencies in the composition of nerve cell membrane omega 3 fatty acids are thought to be associated with depressed mood (**16**). These fatty acids allow for appropriate signaling to take place within the nerve cells and help to maintain appropriate neurotransmitter vesicle fusion. Omega-3 fatty acids may also be involved in proper nervous tissue development (**17**) and this may explain why countries that have higher fish consumption have a lower prevalence of mood disorders.

There are several drawbacks to the studies that have so far been conducted. There are large-scale epidemiological data and very small clinical trials. The epidemiological data mostly compare nations and look at the LONG TERM association between omega-3 fatty acid consumption and depression or bipolar disorder. The clinical trials all examine the effects that these fats may have over the course of months. The fact that these agents have shown some efficacy in the short term is of clinical value in the more immediate management of depressive and bipolar disorders. However, clinical studies that would examine the long-term effects of these agents may augment the epidemiological data and be valuable in prevention or long-term reduction of the incidence of depression and bipolar disease. Additionally, more clinical trials with larger sample sizes are needed to be able to draw more stern conclusions about the connection between fatty acids and mood disorders. The epidemiological data mostly compare various countries in which many variables other than fish consumption may have confounding effects. Thus, it would be of value to conduct more epidemiological studies in which fish consumption within a more homogeneous group such as the members of one country are studied and the prevalence of mood disorders are determined.

Omega 3 fatty acids are inexpensive and they are free of major adverse side effects. It is yet to be determined whether these nutrients in combination with other agents can have a synergistic effect. For example folic acid has been shown to help improve the effects of selective serotonin reuptake inhibitors by increasing their absorption (**18**). In one aforementioned study it was shown that omega-3 fatty acids in combination with antidepressants were more effective in treating depression than antidepressants alone. Therefore, it is of value to examine the effects of omega 3 fatty acids in combination with agents such as folic acid.

Even though there is some conflicting evidence in the role of omega-3 fatty acids in depression and bipolar disease, there is a substantially greater amount of data present suggesting a link between fatty acid consumption and reductions in the prevalence of mood disorders. Additionally, there is solid evidence that omega-3 fatty acids can help improve the symptoms of mood disorders alone or in the presence of antidepressants. Despite the limitations of these studies, one cannot deny this growing body of evidence in favor of these agents. With further research into the role of these agents, they may become an effective treatment for mood disorders and provide additional relief for those who are resistant to antidepressants, those whose symptoms are not fully alleviated by antidepressants, or those who refuse to take antidepressants because of social or cultural stigmas.

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