As the scientific research unfolds, it is becoming increasingly clear that nutritional influences on neurological and psychiatric disorders are currently underappreciated. The human brain requires a broad range of nutrients, including polyunsaturated omega-3 fatty acids, for its structure, function and protection. One area of nutritional research supported by a growing body of literature is that related to the relationship between omega-3 fatty acids and human depressive disorders. Since 20% of the dry weight of the brain is made of fat, and one out of every three fatty acids in the central nervous system are of the polyunsaturated variety, such a relationship between fats and mood should not be entirely surprising.

Depression

Major depressive disorder is a recurrent, potentially life-threatening disorder associated with significant disability, family burden and healthcare costs. Up to 20% of those residing in the United Kingdom and North America will experience depression in the course of their lifetime. Typical depressive symptoms include lowered mood, reduced energy, alterations in sleep and appetite, cognitive difficulties, suicidal thoughts and loss of interest in previously pleasurable activities. Episodes of depression are associated with an increased risk of chronic disease states later in life, such as heart disease. In turn, depressive symptoms are common to many chronic medical conditions.

Rates of depression in the UK and North America have risen through the latter half of the 20th Century. The age of onset of depressive symptoms has dipped down steadily, and overall, the rates of depression are now up to 20-fold higher post-1945. While it may be tempting to dismiss the rise in depression as merely a result of changes in attitudes of health professionals, diagnostic criteria, reporting bias, institutional or other artifacts, the research suggests that stress and environmental factors are involved.

The first-line treatment options include new classes of prescription medications and sophisticated cognitive behavioural interventions. Despite success in some patients, a significant number of those with major depression remain treatment resistant. Recent research has questioned the effectiveness of traditional anti-depressant medications beyond that provided by the placebo (sugar pill). Selective serotonin reuptake inhibitor (SSRI) medication produces a 50% improvement in only about half of those who stay on the medication, while some 30% of depressed patients discontinue medications before a six-week trial is complete. The largest study on depression in the United States, involving over 4,000 patients, showed that one of the most commonly prescribed medications was ineffective in 67% of those with major depression. Clearly, there is room for improved treatment outcomes and other avenues of research, including nutrition.

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids of plant and marine origin that are considered essential, because they cannot be synthesized by the human body. Plant sources rich in the parent omega-3 fatty acid, alpha-linolenic acid (ALA), include flaxseeds, walnuts, hemp and canola oil. Dark green
leafy vegetables also contribute to our dietary ALA intake. Fish and seafood, particularly ocean fish such as sardines, anchovies, salmon and mackerel, provide significant quantities of two key pre-formed omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary ALA is metabolized into EPA and DHA in the liver; this conversion is limited in human beings as only five percent to 15% of ALA is ultimately converted into DHA. Various factors such as chronic illness, stress, ageing, nutritional deficiencies and excess dietary oils rich in linoleic acid (corn, sunflower, safflower, cottonseed, soybean) can interfere with the conversion process.

While the overall intake of omega-3 fatty acids has decreased over the last century, there has been a sharp rise in the supply of the aforementioned vegetable oils which supply omega-6 linoleic acid. The omega-6 intake of Western nations is now outnumbering omega-3 intake by a ratio as high as 20:1. This ratio is a far stretch from the ideal ratio of 2:1 (omega-6 to omega-3) recommended by an international panel of lipid experts in the Journal of the American College of Nutrition. The average daily intake of combined EPA/DHA in the United States is only 130mg, which is over 500mg short of published recommendations and close to 900mg short of the 1000mg recommended by the American Heart Association in cases of heart disease. While reliable estimates of dietary EPA and DHA are lacking in the UK, research from chemical analysis of diet, blood and adipose (fat) cells in U.K. residents show similar deficits to that of the US. The epidemiological, experimental and clinical research which follows suggests that these dramatic dietary fatty acid alterations, and the indiscriminate message that all fats are harmful, are not without neuro-behavioural consequence.

**Fish Consumption and Depression**

If omega-3 fatty acids are involved in human behavioural disorders, one would expect that greater consumption of dietary fish and seafood might be protective against conditions such as depression. There have been a number of studies that have examined national and international fish consumption data and compared them to rates of depressive disorders. Researchers from the United States National Institutes of Health have consistently shown that greater fish and seafood consumption within nations is associated with lower rates of depressive disorders, including major depressive disorder, bipolar (manic) depression, post-partum depression and seasonal affective disorder.

The same connections between fish and mood have been shown in population studies within nations. Frequent fish consumption and depression rates are inversely correlated. These findings have been corroborated by clinical research showing the positive effects of omega-3 fatty acids on depression. For example, a study by researchers from the University of California, San Diego, found that patients with major depression who were treated with omega-3 fatty acid supplements showed a 50% improvement in their symptoms.

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Recent studies have shown that patients with depression have worse states of clinical depression. In addition, three of these chemicals, known as cytokines, are elevated in depression. In fact, higher levels of TNFα and IL-1β are associated with severity of depression. When these inflammatory cytokines are experimentally elevated in healthy adults, three major complaints are observed—depressive symptoms, anxiety, and lack of mental sharpness.

Finally, EPA has been hypothesized to increase brain-derived neurotrophic factor (BDNF), which is known to be lower in depressed patients. Lower levels of BDNF are associated with more severe depression. BDNF protects nerve cells, enhances neurotransmission, has anti-depressant activity and supports...
normal brain structure even throughout adulthood. Pharmaceutical companies are spending millions to research medications which may influence BDNF, as it appears to prevent the death of nerve cells in depression and neurodegenerative diseases. In 2004, researchers from the University of California, Los Angeles, showed that omega-3 fatty acids can positively influence BDNF levels in animals, while diets high in sugar and saturated fats inhibit BDNF production. Omega-3 fatty acids may also help to regulate the release of stress hormones. It is well known that the stress hormone cortisol is elevated in many cases of depression (up to 60%). Fish oil containing EPA and DHA has been shown to prevent sharp rises in adrenal stress hormones including cortisol. The influence of fish oil on adrenal stress hormones appears to result from activity in the brain and central nervous system.

Clinical Studies

The background evidence related to epidemiology, experiments, lab tests, etc., have led to a greater understanding of how omega-3 fatty acids might influence mental functioning and behaviour. Ultimately, however, clinical trials are required to truly determine if omega-3 fatty acids might have a place in mental health care. Some sporadic case reports using omega-3 fatty acids as an intervention have been published over the years. In particular, one series of reports suggested that various doses of flaxseed oil may be helpful in cases of bipolar depression and the anxiety disorder agoraphobia. A separate report indicated that 4g of EPA and 2g of DHA was helpful in alleviating treatment resistant depression during pregnancy. A small open-label study also showed the value of EPA (1.5-2g daily) in eight of ten patients with bipolar depression when taken for six months. A non-placebo-controlled study has also shown that various doses of an EPA/DHA combination (0.5g, 1.4g, 2.8g) significantly improve depressive symptoms in women with post-natal depression. Perhaps the most useful case report is one which corroborated the improvement in depressive symptoms with sophisticated brain imaging (MRI) technology. In this case 4g of pure EPA improved the symptoms of depression and social phobia which were previously unaltered by various anti-depressant medications. The brain imaging showed that over the nine-month course of treatment with EPA there was an increase in brain tissue, due likely to the increase in the manufacture of the lipids which help make up the nerve cell walls, and a decrease in breakdown of those same phospholipids. Studies have shown that depressed patients can have a notable decrease in the volume of various areas of the brain. EPA appeared to reverse that situation, possibly by way of influencing BDNF.

The first well-designed clinical trial with placebo intervention and fish oil was published in the Archives of General Psychiatry in 1999. Although small, with just 30 subjects, the results indicating that omega-3 fatty acids may be of benefit in depression was highly significant. In this case, 9.6 g of EPA/DHA versus placebo led to longer periods of remission and improvement in depressive symptoms in those with bipolar depression. Recently, investigators from the Institute of Psychiatry in London backed up this initial report by showing that either 1g or 2g of pure EPA leads to improvement (versus placebo) in the depressive symptoms of bipolar disorder. Some researchers, including Dr David Horrobin, the founding father of this area of research, suggested that such high doses of EPA/DHA may not be necessary and that, due to the effect on cytokines and intra-cellular communication, lower levels of pure EPA may be of benefit. Research so far has supported this position. In a double-blind, placebo-controlled study, researchers showed that just 2g of pure EPA could improve the symptoms of treatment-resistant depression. They found that 2g of pure EPA, when added to an ineffective anti-depressant for one month, significantly improved depressive symptoms. There were improvements in depressed mood, insomnia, feelings of guilt and worthlessness, and there were no side-effects. A larger study, again published in Archives of General Psychiatry, replicated these findings, however, this time various doses of EPA were examined. Those on ineffective anti-depressants were given 1g, 2g or 4g of pure EPA or a placebo, in addition to the medication, for 12 weeks. Interestingly, the 1g daily dose of EPA led to the most significant improvements, with 53% achieving a 50% reduction in depression scores; it appeared that 'less was more'. There were significant improvements in depressive symptoms, sleep, anxiety, lassitude, libido and thoughts of suicide. Researchers from Taiwan Medical University published a recent study in which they found that a mixture of 4.4g EPA and 2.2g DHA alleviated depression (versus placebo) in those with treatment-resistant depression. This was a two-month study involving patients who were on anti-depressants that were not working. As with the other omega-3 studies discussed, the fish oil was well-tolerated and no adverse events were reported.

There is also a growing body of research which indicates that omega-3 oils may be of value in treating depressive symptoms associated with other medical conditions. Researchers from Montreal, Canada, showed that Antarctic krill oil (400mg EPA, 240mg DHA) could improve the depressive symptoms associated with pre-menstrual syndrome when taken over three months (versus placebo). In addition, Harvard University of California, Los Angeles, researchers have also shown that just 1g of pure EPA is beneficial in the treatment of borderline personality disorder. This personality disorder, which is particularly difficult to treat, is characterized by both depressive and aggressive symptoms. In this two-month placebo-controlled study, the researchers showed that EPA has a mood-regulating effect, improving both depression and aggression without clinically relevant side-effects. Finally, researchers from Italy recently showed that 1.6g of EPA and 0.8g of DHA taken daily for 35 days improved overall mood state (anger, anxiety, fatigue, depression, confusion) and cognitive function in healthy adults (average age 33) vs placebo oil. The clinical trials conducted on omega-3 fatty acids and mood have, to date, been mostly positive in their

With adequate omega-3 supply, the nerve cell becomes more flexible, or 'fluid', and this allows for proper chemical communication, transport and reception of mood regulating chemicals. When omega-3 intake is inadequate, the nerve cell becomes stiff as cholesterol and omega-6 fatty acids are substituted for omega-3. When a nerve cell becomes rigid due to omega-3 deficiency, proper neurotransmission from cell to cell and within cells will be compromised, regardless of which anti-depressant medication is used.
outcomes. There have been some negative reports, particularly related to pure DHA (i.e. no EPA) or mostly DHA and little EPA in patients with depression. The first negative study showed that DHA alone (2g daily) was no better than placebo in alleviating depressive symptoms when taken for six weeks. A pure DHA supplement (just 200mg daily, taken for four months) also failed to influence the symptoms of post-natal depression among a group of women who were healthy at delivery. An additional clinical trial showed that DHA-rich tuna oil (2.4g DHA and 0.6g EPA) was no better than olive oil in improving depressive symptoms when taken for twelve weeks when added to existing therapy. The use of olive oil, which has potential mood-regulating affects, has been criticized as a choice of ‘placebo’ oil. Both groups showed significant improvement in depressive symptoms. Based on both the positive and negative clinical intervention studies, the preponderance of the evidence so far supports the theory that EPA is the mood-regulating omega-3 fatty acid.

Nutritional Co-factors
Omega-3 fatty acids tend to be viewed in nutritional isolation. Of course from a research perspective it is appropriate to isolate the effects and functions of omega-3 fatty acids to determine effective interventions. However, from a practical and clinically relevant standpoint, it is important to consider the nutrients which assist in the metabolism of omega-3 fatty acids. Low blood levels of zinc, selenium and folic acid have all been shown (individually) to be related to human depression. The common thread is that each of these nutrients helps to metabolize omega-3 fatty acids and boost omega-3 status. Clinical trials have documented benefit of just 25mg of zinc and 500mcg of folic acid added on top of anti-depressant medications (versus placebo). Dietary antioxidants are also important to help preserve omega-3 fatty acids and prevent free radical damage to the lipid components within nerve cells.

Conclusion
Various branches of scientific investigation have clearly established that EPA and DHA have the potential to influence brain physiology and structure. While the precise mechanisms whereby omega-3 fatty acids may alleviate depression remain unknown, and we have much more to learn, the initial results are more than encouraging. The results of the recent clinical trials reinforce the epidemiological, laboratory and experimental studies, and certainly underscore the importance of adequate omega-3 and nutritional co-factors in those with depression.

The long-term studies of fish oil supplements in the area of cardiovascular health, some spanning more than three years, have shown that they are safe and well-tolerated. Depression is a serious and potentially life-threatening illness, so obviously omega-3 fatty acids are not a substitute for appropriate mental health evaluation and care. However, the emerging research along with the collateral health benefits, such as that in heart health, should encourage patients with depressive symptoms to discuss omega-3 fatty acids with their healthcare providers.

References


