Omega-3 fatty acids for managing mood disorders

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A decade ago research indicated a likely causal link between low levels of omega-3 fatty acids (FAs) and a higher prevalence of mood disorders, and also provided quite strong support for omega-3 FAs as both an antidepressant monotherapy and an augmentor of formal antidepressant drugs. Recent research is somewhat less convincing about their antidepressant efficacy but is nevertheless furthering our understanding by quantifying differential efficacy across the FAs.

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Omega-3 and omega-6 fatty acids (FAs) are regarded as 'essential' polyunsaturated lipids because they cannot be synthesised within the body but must be obtained from the diet, and are required for normal growth and development.[1] The parent omega-3 and omega-6 FAs are alpha-linolenic acid and linoleic acid, respectively. The human liver modifies these parent FAs into longer chain unsaturated fatty acids, with the key polyunsaturated FAs being eicosapentaenoic acid (EPA; omega-3), docosahexaenoic acid (DHA; omega-3) and arachidonic acid (omega-6). These are incorporated into phospholipids and, as cell membrane constituents throughout the body, mediate a range of physiological effects. Each of the FAs has differing properties and it is their optimal combination (particularly the omega-3 to omega-6 ratio) rather than any one FA 'family' contribution that impacts on health.

EPIDEMIOLOGY OF FATTY ACIDS

Diets hundreds of years ago were judged to have a relatively equal ratio of omega-3 to omega-6 FAs, but modern diets have progressively distorted the ratio so that omega-6 FA intake is disproportionately higher, with a commonly suggested ratio of 10:1.[2,3] Although our diet was once rich in omega-3 FAs via fish, wild game and certain leafy plants and plant oils (such as flaxseed, chia and canola), it has changed to one that is rich in omega-6 FAs, which are found in commonly used vegetable and nut oils (such as safflower, sunflower and corn) as well as meat from domesticated animals, poultry and dairy products.

In humans, alpha-linolenic acid conversion to EPA and DHA is extremely low and is in competition with linoleic acid for the same converting enzymes. Thus the provision of these long-chain omega-3 FAs is best achieved by direct consumption of fish and

seafood, such as salmon, mackerel, sea trout and sardines. Our modern western diet has been quantified as providing an average daily EPA plus DHA intake of 100 to 135 mg/day, whereas the recommended standard is 250 to 300 mg/day.[2,4]

HOW LOW LEVELS OF OMEGA-3 FATTY ACIDS MIGHT CONTRIBUTE TO MOOD DISORDERS

Although changes in the omega-3 to omega-6 ratio have been known to influence a number of nonpsychiatric conditions (including cardiac and arthritic problems, and alteration in brain growth in general), their potential contributory role to depression has also been postulated to reflect reduced EPA and DHA levels in the brain. In the brain, as well as the rest of the body, they modulate cellular functions by, for example:

- promoting cell membrane fluidity thereby influencing transmembrane protein activity
- impacting on receptors, enzymes and ion channels
- participating in intracellular metabolic pathways
- influencing gene expression.

Adequate DHA is required for normal dopaminergic and serotonergic neurotransmission and induces the expression of brain-derived neurotrophic factor (BDNF), which impacts on neurogenesis, plasticity and synaptic transmission within the brain. BDNF has been shown to be reduced in patients with depressive and bipolar disorders, whereas antidepressant medications stimulate BDNF expression. Furthermore, both EPA and DHA may suppress cytokine production and have protective anti-inflammatory effects, which is of relevance when there is increasing evidence implicating inflammatory processes in causing and advancing depressive episodes. Proinflammatory eicosanoid molecules generated from omega-6 FAs compromise neurotransmitter metabolism, stimulate the hypothalamic–pituitary–adrenal axis and inhibit neuronal growth and plasticity. Those generated from omega-3 FAs are either less inflammatory or anti-flammatory.[2]

Several animal studies have been instrumental in helping clarify the relation between omega-3 FA status, neuronal function and behaviour, as well as researching the effects of omega-3 supplementation in ameliorating the physiological responses to stress and a reduction in depressive behaviours.[2,5,6]

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CLINICAL STUDIES LINKING FATTY ACID ABNORMALITIES WITH MOOD DISORDERS

In 2006, the authors reviewed the relevance of omega-3 FAs to mood disorders, reporting a number of quite positive causal and treatment studies.[7] The epidemiological studies quantified higher rates of depression, postnatal depression and bipolar disorders (but not schizophrenia) in countries with low seafood consumption. Some studies indicated that people with clinical depression were more likely to have lower omega-3 and higher omega-6 levels and thus a higher omega-6 to omega-3 ratio. Furthermore, several treatment studies indicated that augmentation of antidepressant drugs with omega-3 FAs was associated with a greater and faster improvement than use of antidepressants alone, and some quantified benefit from omega-3 monotherapy. One of these studies involved children and adolescents, which is particularly important in respect to concerns about use of formal antidepressant medications in young subjects.

Although there have been several studies examining the use of omega-3 preparations in treating people with bipolar disorder, most studies were negative, and the few positive studies indicated that any benefits appeared limited to the depressive phase, with no effects on the hypomanic or manic phases, albeit still positioning omega-3 FAs as an antidepressant.

In a recent review, the authors focused on subsequent treatment studies and on the clinical priority of clarifying the relative antidepressant efficacies of omega-3 preparations varying in relative contents of EPA and DHA.[2] The review considered a number of meta-analyses that showed some inconsistencies in quantification and conclusions. The firmer findings included EPA-weighted omega-3 preparations having some therapeutic benefit whereas the use of DHA preparations alone or preparations with equivalent DHA and EPA levels appeared less effective, which is intriguing as DHA is the major omega-3 FA that benefits the brain. The latter finding has been interpreted as DHA actually blocking the beneficial effects of EPA when the two are prescribed with a 1 to 1 dose ratio.

As FA levels can be measured in red cells, plasma and adipose tissue, research studies for people with mood disorders potentially have far greater precision (in comparison with other psychiatric domains) in examining any impact of fish oil as a treatment. Unfortunately, most studies tend to examine its effectiveness in unrestricted clinical samples rather than examining whether it may only be potentially beneficial in those with deficient omega-3 levels.

WHY RECOMMEND OMEGA-3 SUPPLEMENTATION?

As already noted, the potential contribution of omega-3 FAs to managing mood disorders now appears less distinctive. This could reflect a common sequence in science whereby the initially published studies tend to report positive results only. The progressive accrual of a number of negative studies is now providing a counter-balancing argument and one that can be wedded with clinical observations. It is actually rare for patients to report that taking fish oil as a form of supplementation has had a distinctive impact on their mood. This could simply reflect fish oil being used generally as an augmenting strategy rather than as monotherapy or the time it takes for any beneficial biological changes to accrue. However, it does not marry with early studies claiming faster improvement with fish oil augmentation.

Fish oil supplementation has a distinctive acceptability to patients with mood disorders as they view it as 'natural' and at variance with their views on formal antidepressant medication. As it has few side effects and there is some support for its use in mood disorders, it does appear reasonable for practitioners to commend it to patients as an augmenting strategy. We generally recommend a dose of about 1000 mg of omega-3 a day (with preparations that have an EPA to DHA ratio of 180 mg:120 mg). For people seeking dietary sources of omega-3 FAs, the general recommendation is two to three serves of fish (especially cold water fish) or seafood per week (includes canned fish such as tuna). Vegetarians and vegans may consider the following alternatives: flax seed or flax seed oil; chia seeds; hemp seeds; mustard oil; seaweed (e.g. spirulina); beans such as mung beans; winter squash; leafy greens such as spinach and kale; berries such as blueberries; wild rice; fruits such as mangoes and honeydew; and other vegetables such as cabbage, cauliflower and broccoli.

A key at-risk group is pregnant women because their requirements for omega-3 FAs increase as the developing baby tends to divert maternal omega-3 to its developing brain. If increasing the supply of omega-3 FAs can be demonstrated to be beneficial in pregnant women by reducing the chance of perinatal mood disorders (particularly in those who have already had episodes of clinical depression), this would be a particularly useful and safe strategy as there are risks associated with formal antidepressant drugs when used during pregnancy. It would appear a 'no-brainer' to advise adequate dietary intake or supplementation of omega-3 FAs to pregnant women because of their increased needs and those of the baby. For patients with a history of depression or with the potential for postnatal depression, this recommendation can be even more strongly supported.

CONCLUSION

It currently still appears reasonable to recommend omega-3 supplementation to people with a biological mood disorder (e.g. melancholia bipolar or depression) or those at risk of such a condition (pregnant women with a history of a mood disorder and at risk of a postnatal relapse). EPA-weighted preparations appear to have the most distinctive benefit but the overall therapeutic 'signal' is less distinctive than indicated in the literature a decade ago. MT

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COMPETING INTERESTS: Professor Parker has received fish oil capsules from several pharmaceutical companies to use in controlled trials and has shares in a company that manufactures fish oil capsules. Dr Brotchie: None.