

LE Magazine October 2007

REPORT

Fighting Depression and Improving Cognition with Omega-3 Fatty Acids

By Laurie Barclay, MD



Antidepressant drugs continue to raise concerns about their side effects, which include suicide, clinical worsening of depression, and unusual changes in behavior in adolescents and children.

Recently, the FDA instructed all drug manufacturers to add black box warnings (the most serious warning label for a prescription medicine) to their antidepressant drugs.

In light of these findings, doctors and patients are seeking safer alternative therapies. New research reveals that omega-3 fatty acids may effectively alleviate depression without dangerous side effects.

In this article, we unveil the growing evidence base for omega-3s in improving mood and restoring structural integrity to brain cells that are critical in performing cognitive functions.

Already well known for their ability to protect against heart disease, cancer, and diabetes,¹ the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be highly effective in preventing and managing depression and cognitive decline, according to a growing body of evidence.²⁻⁴

The American Psychiatric Association's treatment recommendations for the use of omega-3 fatty acids bears testament to this strategy. Joseph R. Hibbeln, MD, from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) tells Life Extension magazine, "The strongest evidence was found for managing major depressive symptoms, with the effect of omega-3s being at least as great, if not greater than, antidepressant medications." Regarding these powerful fatty acids, Dr. Hibbeln further notes, "...deficient intakes may increase risk for mental distress."

OMEGA-3 FATTY ACIDS AND DEPRESSION

Consuming plenty of omega-3 fatty acids may offer powerful protection against depression. A large Norwegian study of nearly 22,000 participants revealed that those who regularly took cod liver oil, which is rich in omega-3 fatty acids, were about 30% less likely to have symptoms of depression than those who did not. The longer the participants took cod liver oil, the less likely they were to have high levels of depression.²

Omega-3 fatty acids may also help improve mood in those who already suffer from depression. In a recent study at the Royal College of Surgeons in Ireland, the effect of omega-3 fatty acid supplementation was studied in 49 patients with repeated episodes of harming themselves. In addition to standard psychiatric care, study subjects were randomly assigned to receive 1200 mg EPA plus 900 mg DHA, or placebo, for 12 weeks. At the end of the treatment period, the group receiving omega-3 fatty acids had significantly greater improvements compared with the placebo group in scores for depression, suicidality and daily stresses.⁵

Furthermore, other studies suggest that people who are still depressed despite use of antidepressant medications may have reduced intensity of depression, anxiety, sleep disturbances, and sexual dysfunction when supplementing with omega-3 fatty acids.^{3,4}

HOW OMEGA-3S FIGHT DEPRESSION

Scientists are intensely examining how omega-3 fatty acids work to promote a healthy mood.

A new study sought to shed some light on how omega-3 fatty acid deficiency may aggravate depressed mood. Researchers looked at plasma levels of essential fatty acids and neurosteroids, which are neuroactive chemicals implicated in several neurophysical and disease processes. Study subjects included 18 healthy men and 34 men with alcoholism, depression, or

both. In the group of all 52 subjects, lower level of omega-3 essential fatty acids was associated with higher levels of neuroactive steroids.⁶

It appears that a lack of DHA has far-reaching hormonal effects, increasing corticotropin-releasing hormone, a hormone that moderates emotionality. This may in turn contribute to hyperactivity within the hypothalamic pituitary adrenal (HPA) axis, an important neuroendocrine system that regulates mood, aggression and “fight-or-flight” responses associated with anxiety.



“The [evidence] is becoming quite compelling that increasing omega-3 fatty intake enhances many aspects of brain function, including the control of mood and aspects of personality,” Brian M. Ross, MD, Associate Professor of Medicine, Chemistry and Public Health at the Northern Ontario School of Medicine of Lakehead University, tells Life Extension. “For example, combining the results of a series of clinical trials clearly shows that supplementation with omega-3 fatty acids, in particular the long-chain varieties EPA and DHA, helps reduce the symptoms associated with clinical depression. Other provocative data suggest that boosting omega-3 fatty acid intake increases attention and reduces aggression, probably by enhancing cognitive processes.”

According to a hypothesis recently presented by Dr. Ross, deficiency of omega-3 fatty acids in major depressive disorder may reflect the interaction between a diet lacking these essential polyunsaturated fatty acids (PUFAs), and a genetically determined abnormality in their metabolism, such that cellular uptake of omega-3 PUFAs is decreased. Low level of omega-3 fatty acids could thus be a risk factor for depression, while dietary supplementation with omega-3 fatty acids might be a useful and well-tolerated treatment for major depressive disorder.⁷

Given that brain tissue is rich in omega-3 fatty acids, particularly in the membranes of three different types of brain cells, this link between omega-3 fatty acids and brain health is hardly surprising. These essential fatty acids are required for proper growth, development, and function of brain tissue.⁸

“The human brain is 60% fat, and omega-3 fatty acids are the fatty acid of choice for the structure of certain parts of brain cell membranes and brain intercellular nerve connections,” Douglas London, MD, Research Associate in Psychiatry at the Psychopharmacological Research Laboratory of McLean Hospital and medical faculty at Harvard Medical School, tells Life Extension.

“Lack of dietary omega-3 forces the brain cells to utilize other fatty acids on hand, resulting in cells constructed with inferior building material,” Dr. London says. “Lack of available omega-3s affects brain function and is associated with cognitive and emotional disorders. There is growing evidence that a significant proportion of the US population is at risk for omega-3 fatty acid deficiency.”

OMEGA-3 LEVELS AFFECT MOOD AND BRAIN FUNCTION

Further evidence to strengthen the link between dietary lack of omega-3 fatty acids and depressed mood was presented in March 2007 at the American Psychosomatic Society’s annual meeting held in Budapest, Hungary.

One of the studies presented in Budapest by Sarah M. Conklin, PhD, a postdoctoral scholar in Cardiovascular Behavioral Medicine, Department of Psychiatry at the University of Pittsburgh, showed that in healthy adults of average age 45 years, low levels of EPA were associated with high levels of impulsive behavior, hostility, and cynical ideas. Low levels of either EPA or DHA predicted high degrees of angry feelings and outbursts.^{9,10}

“The omega-3 fatty acids have widespread biological functions in the body including the brain,” Dr. Conklin tells Life Extension. “Our research has shown that individuals who have higher levels of these fats in their blood are less likely to report symptoms of depression. Similarly, those who have lower levels of these fats in their blood score higher on measures of impulsiveness.”



Even more exciting, Dr. Conklin presented a second study in Budapest showing that the amount of omega-3 fatty acid consumed in the diet may actually cause beneficial anatomical changes in areas of the brain that regulate emotion. Fifty-five healthy adults provided information about their typical daily consumption of omega-3 fatty acids and had MRI scans to determine the volume of gray matter in specific brain regions. The higher the intake of omega-3, the larger was the volume of gray matter in the anterior cingulate cortex, a brain area controlling emotion and mood and implicated in depression.¹¹

After making adjustments for age, sex, race, total gray matter volume, smoking status, alcohol use, and IQ, gray matter volume in a specific region of the anterior cingulate cortex decreased as scores on a depression scale increased. This observation supports the role of this brain region in depression, and uncovers a possible mechanism by which omega-3-fatty acids act as

antidepressants.

“We were able to show that individuals who consumed more omega-3 fatty acids in their diets had more gray matter volume in areas of the brain important for regulating mood,” Dr. Conklin explains. “These results suggest that these specific fats, certainly not fat in general, may confer a protective effect against depression and other mood-related problems.”

Interestingly, autopsy studies of brains from patients with major depressive disorder show selective deficits in DHA in the orbitofrontal cortex, another brain region implicated in depression and mood disorders.¹²

OMEGA-3 FATTY ACIDS AND DEPRESSION: WHAT YOU NEED TO KNOW

- Brain tissue is rich in omega-3 fatty acids, which are of vital importance within cell membranes and in connections between nerves.⁸
- Low dietary intake of beneficial omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is linked to depressed mood, hostility, and impulsive behavior.^{7,9,10}
- High intake of EPA and DHA is associated with increased gray matter volume in brain regions controlling depression and mood.¹¹
- Low levels of omega-3 fatty acids are linked to poor performance on cognitive and memory tests, and more rapid cognitive decline with aging.^{13,14} High intake of omega-3 fatty acids during pregnancy is associated with better neurodevelopmental outcomes later in childhood.^{19,20}
- In controlled clinical studies, depressed patients randomly assigned to receive omega-3 fatty acids have demonstrated greater improvement compared with those assigned to placebo.^{33,34}

COGNITIVE BENEFITS OF OMEGA-3S

A third study presented in Budapest by Dr. Conklin’s group revealed that low levels of DHA and high levels of the detrimental arachidonic acid were associated with poor cognitive performance on tests of delayed memory, logical memory, and ability to draw designs from memory.¹³

Earlier work by Dr. Conklin and colleagues showed that relative deficiency of omega-3 fatty acids was associated with depression and antisocial behavior. In adults with high cholesterol, depressed mood, neurotic tendencies and impulsivity were linked to low levels of omega-3 fatty acids and high levels of the omega-6 fatty acids.

Dr. Conklin adds, “[Omega-3] fatty acids are abundant in only a handful of very specific marine foods such as salmon, some other fish and mollusks, and increasing evidence is suggesting that it is important to ensure that we consume adequate amount of these omega-3 fatty acids.”

There is further promising evidence that putting omega-3 into our diets is associated with improved outcomes for other mental health disorders, such as impaired cognition and perhaps even Alzheimer’s disease.

Research findings from the Netherlands suggest that consuming more fish and omega-3 fatty acids protects against cognitive decline. The Zutphen Elderly Study followed a group of 210 men 70 years and older, examining them in 1985 and testing their cognitive ability in 1990 and 1995.¹⁴

Men who did not eat fish experienced measurable cognitive decline from 1990 to 1995 that was four times greater than that of men who ate fish regularly. Strikingly, there was a dose-response relationship between intake of EPA and DHA and loss of cognitive ability. The investigators concluded that “a moderate intake of EPA plus DHA may postpone cognitive decline in elderly

men.”¹⁴

Mood and mental function are inextricably linked, with depression impairing cognitive ability. In fact, Alzheimer’s disease and other dementias often first appear as changes in outlook and personality. Not surprisingly, deficiency of omega-3 fatty acids has also been implicated in cognitive impairment, whereas diets supplemented with omega-3 fatty acids appear to benefit cognitive function.¹⁵

Animal studies further suggest that dietary supplementation with DHA may protect against the type of brain damage seen with Alzheimer’s disease.¹⁶ Some scientists also believe that a diet rich in omega-3 fatty acids may help prevent Alzheimer’s disease and other dementias,¹⁷ and that they may be of modest benefit in some patients with mild Alzheimer’s disease.¹⁸



REPORT

Fighting Depression and Improving Cognition with Omega-3 Fatty Acids

By Laurie Barclay, MD

BENEFITS OF OMEGA-3S IN PREGNANCY

At the other end of the age spectrum, eating seafood during pregnancy is linked to better neurodevelopmental outcomes in childhood. To some extent, these findings were unexpected, given concerns about potential harm to the baby from the mercury content in some fish. Researchers evaluated data from 11,875 pregnant women taking part in the Avon Longitudinal Study of Parents and Children.¹⁹

Surprisingly, women who followed their doctor's recommendation to limit their seafood intake during pregnancy to 340 grams weekly had a 48% greater risk that their children would be in the lowest quarter of verbal IQ scores, compared with mothers who ate more than 340 grams of fish weekly. Mothers who ate less seafood also had a greater risk that their children would have problems with social behavior, motor skills, communication, and social development.



Translating these findings to clinical studies, researchers at the University of Western Australia randomly assigned 98 pregnant women to receive either high-dose fish oil (2200 mg DHA plus 1100 mg EPA daily) or placebo (olive oil) from 20 weeks of pregnancy until delivery. Neither the women nor the scientists knew which women were assigned to fish oil until the study was complete.²⁰

Although children in both groups had similar growth rates at 2.5 years of age, those whose mothers received fish oil during pregnancy had significantly better eye-hand coordination.

The benefits of omega-3 also extend to infants born prematurely. They have been found to have decreased levels of DHA in brain cortex. Both preterm and term infants fed DHA have enhanced cortical visual acuity and cognitive outcomes.²¹ In fact, some infant formulas are now enriched with omega-3 fatty acids in response to recommendations that pregnant and nursing women maintain an

adequate dietary intake of DHA to meet their own increased needs as well as those of the fetus or infant.²²

HOW MUCH IS ENOUGH?

America's obsession with thinness over the past three decades has led us to spurn all dietary fats, including beneficial omega-3 fatty acids such as EPA and DHA. The result has been a tidal wave of depression, attention-deficit/hyperactivity disorder (ADHD), and other psychiatric diagnoses.^{23,24} The incidence of depression has climbed higher with each decade of the twentieth century, as have health care costs for antidepressant medications and other mental health treatment.²⁵

In North America today, the average daily intake of EPA plus DHA is only 130 mg, falling far short of the daily 1000-2000 mg total omega-3 fatty acids recommended by some clinicians for optimal health, mood, and cognitive function. Based on clinical trials, dosages of 1000-4000 mg may offer maximal benefits for those with depressed mood.²⁶

"Although the precise mechanism of action is still unknown, accumulating evidence suggests that 1000-2000 mg daily of EPA may be useful in the treatment of mild to moderate depression," Dr. Yamina Osher, lead author of a recent review of 12 clinical trials of PUFAs in depression, bipolar disorder, and other mood disorders²⁷ and a member of the Faculty of Health Sciences at Ben Gurion University in Beer Sheva, Israel, tells Life Extension.

FURTHER RESEARCH

Researchers are currently investigating whether a diet deficient in omega-3 essential fatty acids increases the risk for depression, aggression, and suicide associated with alcoholism. Scientists are comparing the effect of omega-3 fatty acids with that of placebo in aggressive alcoholics, women with depression during pregnancy, and suicide attempters.

Additional therapeutic benefits are being explored, including the use of omega-3 in attention deficit disorder and in autism, but there is still insufficient evidence on which to base firm conclusions.

IMPLICATIONS FOR TREATMENT

Despite this unfinished picture, the Committee on Research on Psychiatric Treatments of the American Psychiatric Association invited scientists to participate in the Omega-3 Fatty Acids Subcommittee. This expert panel convened in 2006 to review published studies and those presented at scientific meetings that evaluated the effect of omega-3 fatty acids in major depressive disorder, bipolar disorder, schizophrenia, dementia, borderline personality disorder and impulsivity, and ADHD.



Their conclusions, which were approved by three separate committees of the American Psychiatric Association, declared that population-based studies and tissue studies support a protective effect of omega-3 essential fatty acid intake, particularly EPA and DHA, in mood disorders. A review of the randomized controlled trials showed negligible risks and a statistically significant benefit of omega-3 fatty acids in both major depression and in bipolar depression, with less evidence of benefit in schizophrenia.^{33,34}

“The evidence suggests that omega-3 fatty acids are important for optimal human health and brain function,” Marlene P. Freeman, MD, lead author of the American Psychiatric Association review, tells Life Extension. “In some studies, investigators have demonstrated a beneficial effect of omega-3 fatty acids on mood disorders, and more research is underway. Individuals with serious mental health disorders should always receive a full evaluation and know their treatment options.”

“As professionals, we encourage anyone with depression or other disorders to get the medical attention that they deserve,” says Dr. Freeman, who is also Director of the Women’s Mental Health Program and Associate Professor of Psychiatry, Obstetrics and Gynecology, and Nutritional Sciences at the University of Arizona’s College of Medicine. She concludes, “Omega-3 fatty acids may be an important part of the treatment of some psychiatric disorders, and at this time researchers are figuring out where they fit in to treatment. They may be an effective treatment for some individuals, with important medical benefits.”



INTERACTIONS

Omega-3 fatty acids from fish oil may have anti-thrombotic effects. Individuals who have bleeding disorders and those taking warfarin (Coumadin®) should only use fish oil in consultation with a physician.³⁵

CONCLUSION

Essential for healthy brain structure and function, omega-3 fatty acids may be critical for maintaining healthy mood and keeping mental distress at bay. These powerful fatty acids are essential throughout life—helping ensure healthy brain development in infants, maintaining a healthy mood in adulthood, and protecting the aging brain against cognitive decline and dementia.

Optimizing your intake of omega-3 fatty acids is not only essential for a healthy body, but also for a healthy mind.

If you have any questions about the scientific content of this article, please call one of our Health Advisors at 1-800-226-2370.

References

1. Assisi A, Banzi R, Buonocore C, et al. Fish oil and mental health: the role of n-3 long-chain polyunsaturated fatty acids in cognitive development and neurological disorders. *Int Clin Psychopharmacol*. 2006 Nov;21(6):319-36.
2. Raeder MB, Steen VM, Vollset SE, Bjelland I. Associations between cod liver oil use and symptoms of depression: The Hordaland Health Study. *J Affect Disord*. 2006 Dec 18.
3. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry*. 2006 Jan;188:46-50.
4. 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 Oct;59(10):913-9.
5. Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. *Br J Psychiatry*. 2007 Feb;190:118-22.

6. Nieminen LR, Makino KK, Mehta N, et al. Relationship between omega-3 fatty acids and plasma neuroactive steroids in alcoholism, depression and controls. *Prostaglandins Leukot Essent Fatty Acids*. 2006 Oct;75(4-5):309-14.
7. Ross BM. Omega-3 fatty acid deficiency in major depressive disorder is caused by the interaction between diet and a genetically determined abnormality in phospholipid metabolism. *Med Hypotheses*. 2007;68(3):515-24.
8. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. *J Nutr Health Aging*. 2006 Sep;10(5):386-99.
9. Conklin SM, Harris JI, Manuck SB, et al. Serum omega-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. *Psychiatry Res*. 2007 Jul 30;152(1):1-10.
10. Conklin SM, Manuck SB, Yao JK, Hibbeln JR, Flory JD, Muldoon MF. Serum phospholipid polyunsaturated fatty acids are associated with mood, behavior and personality in healthy community adults. American Psychosomatic Society annual meeting, March 2007, Budapest, Hungary, abstract 1718.
11. Conklin SM, Gianaros PJ, Brown SM, et al. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neurosci Lett*. 2007 Jun 29;421(3):209-12.
12. McNamara RK, Hahn CG, Jandacek R, et al. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol Psychiatry*. 2006 Dec 21.
13. Muldoon MF, Conklin S, Ryan CM, Yao J, Hibbeln J, Manuck SB. Cognitive function and omega-6 and omega-3 fatty acid balance. American Psychosomatic Society annual meeting, March 2007, Budapest, Hungary, abstract.
14. van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *Am J Clin Nutr*. 2007 Apr;85(4):1142-7.
15. Pinilla FG. The impact of diet and exercise on brain plasticity and disease. *Nutr Health*. 2006;18(3):277-84.
16. Cole GM, Frautschy SA. Docosahexaenoic acid protects from amyloid and dendritic pathology in an Alzheimer's disease mouse model. *Nutr Health*. 2006;18(3):249-59.
17. Saugstad LF. Are neurodegenerative disorder and psychotic manifestations avoidable brain dysfunctions with adequate dietary omega-3? *Nutr Health*. 2006;18(2):89-101.
18. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol*. 2006 Oct;63(10):1402-8.
19. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*. 2007 Feb 17;369(9561):578-85.
20. Dunstan JA, Simmer K, Dixon G, Prescott SL. Cognitive assessment at 21/2 years following fish oil supplementation in pregnancy: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2006 Dec 21.
21. 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 Oct;75(4-5):329-49.
22. Vidailhet M. Omega 3: is there a situation of deficiency in young children? *Arch Pediatr*. 2007 Jan;14(1):116-23.
23. Bruinsma KA, Taren DL. Dieting, essential fatty acid intake, and depression. *Nutr Rev*. 2000 Apr;58(4):98-108.
24. Wells AS, Read NW, Laugharne JD, Ahluwalia NS. Alterations in mood after changing to a low-fat diet. *Br J Nutr*. 1998 Jan;79(1):23-30.
25. Weissman MM, Klerman GL. Depression: current understanding and changing trends. *Annu Rev Public Health*. 1992;13:319-39.
26. Logan AC. Omega-3 fatty acids and major depression: a primer for the mental health professional. *Lipids Health Dis*. 2004 Nov 9;3:25.

27. Osher Y, Belmaker RH, Nemets B. Clinical trials of PUFAs in depression: State of the art. *World J Biol Psychiatry*. 2006;7(4):223-30.
28. Appleton KM, Hayward RC, Gunnell D, et al. Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. *Am J Clin Nutr*. 2006 Dec;84(6):1308-16.
29. Holtzheimer PE, III and Nemeroff CB. Emerging treatments for depression. *Expert Opin Pharmacother*. 2006 Dec;7(17):2323-39.
30. Jorm AF, Allen NB, O'Donnell CP, et al. Effectiveness of complementary and self-help treatments for depression in children and adolescents. *Med J Aust*. 2006 Oct 2;185(7):368-72.
31. Keck PE, Jr., Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry*. 2006 Nov 1;60(9):1020-2.
32. van Strater AC, Bouvy PF. Omega-3 fatty acids in the treatment of affective disorders: an overview of the literature. *Tijdschr Psychiatr*. 2007;49(2):85-94.
33. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006 Dec;67(12):1954-67.
34. Freeman MP. Omega-3 fatty acids and perinatal depression: a review of the literature and recommendations for future research. *Prostaglandins Leukot Essent Fatty Acids*. 2006 Oct;75(4-5):291-7.
35. Available at: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/fis_0106.shtml. Accessed July 19, 2007.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.