

evidence-based alternative therapies for mental illness

OMEGA-3 FATTY ACIDS AND SAM-E

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Exercise and a healthy diet have long been recognized as important adjuncts to talk therapy and drug therapy for the treatment of mental illness. Recently, omega-3 fatty acids (primarily from fish oil and flaxseed oil) and s-adenosylmethionine (SAM-e) have been used to treat symptoms of mental illness, particularly depression. An evidence base now is being developed for these two “alternative” remedies.

A recent article by Adriane Fugh-Berman, M.D. and Jerry M. Cott, Ph.D. has documented the current evidence base for the use of alternative therapies for mental illness.¹ Since alternative remedies are used by about half of mental health consumers, it is essential that this information be widely disseminated so that consumers and families affected by mental illness and providers of mental health care can properly discuss and evaluate these alternatives as part of the treatment dialogue.

The alternative therapies which Fugh-Berman and Cott recognized as evidence-based for treatment of mental illness were:

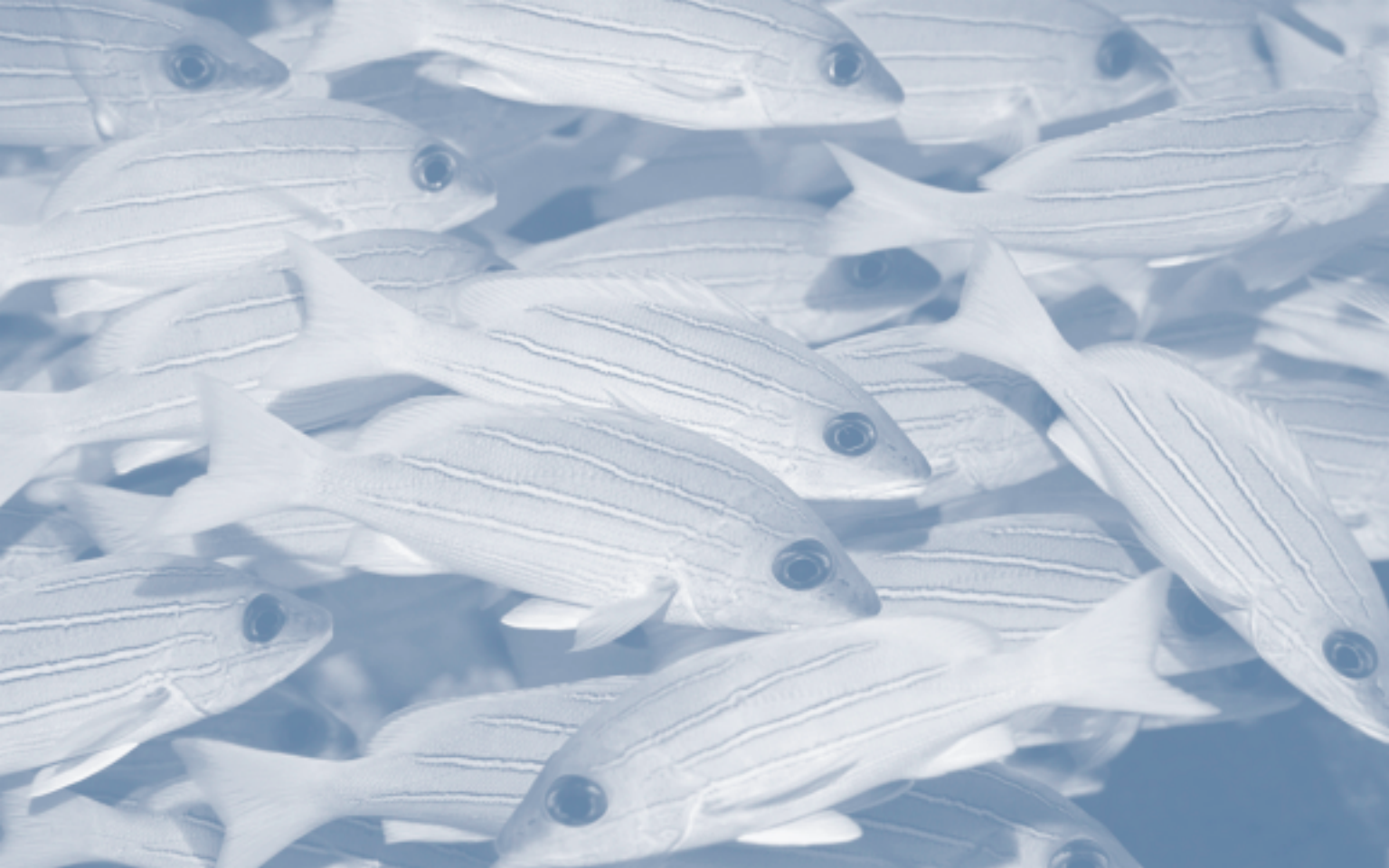
- St. John's wort (*hypericum perforatum*) for depression.
- Ginkgo (*ginkgo biloba*) for mild dementia.

- Kava (*piper methysticum*) for anxiety and stress.
- Valerian (*valeriana officinalis*) for insomnia and stress.
- Omega-3 essential fatty acids (fish oil and flaxseed oil), for major depression, bipolar disorder, and other psychiatric disorders.
- S-adenosylmethionine (SAM-e) for depression.
- Folate, tryptophan and phenylalanine to enhance the effectiveness of conventional antidepressants.

The article concluded that, although the effects of herbal therapies are milder than many prescription medications, there is a substantial evidence base for the use of St. John's wort, ginkgo, kava and valerian, for relief of some symptoms of mental illness and for some people. In a 2000 pamphlet, the National Association of Mental Health Planning and Advisory Councils (NAMHPAC) described the evidence base for these herbal therapies. A recent JAMA-reported study (Shelton, *et al.*, 2001)² found a minimum treatment effect for St. John's wort in chronic, severe depression. However, there is strong evidence of its effectiveness in mild to moderate depression. Ongoing studies should help resolve the controversy. Evidence for the use of the remaining listed alternative therapies is promising, but not yet as strong. Evidence for omega-3 fatty acids and SAM-e is summarized in this pamphlet. The other alternative therapies evaluated but not found to be evidence-based at this time for treatment of mental illness included: ginseng, passion flower, skullcap and mega-vitamins.

This pamphlet is not intended to encourage the use of alternative therapies for mental illness. However, since many users of alternative therapies do not inform their physicians of their use, this pamphlet is intended to help open a dialogue between consumers and families affected by mental illness and providers of mental health care, based on the evidence that is now available. Counseling about side effects and herb-drug interactions is very important to avoid potential trouble. Based on the evidence now available, physicians should be prepared to discuss use of omega-3 fatty acids and SAM-e with persons and families affected by mental illness. Consumer autonomy and family responsiveness are best fostered in an atmosphere of understanding and candor.





Omega-3 fatty acids

Because of the concern about the health effects of excessive consumption of fats, we have for too long ignored the critical function of the essential fatty acid (omega-3/omega-6) balance in our diet. This balance of essential fatty acids is necessary to regulate the cell membranes in our bodies, and particularly our brains, which are composed of 60% fat. This pamphlet seeks to summarize important recent studies suggesting that additional ingestion of omega-3 essential fatty acids may be an important remedy to the detrimental dietary changes that have come about in recent years. These changes have emphasized omega-6 and partially hydrogenated (*trans*-) fat consumption and may have made modern societies more prone to serious mental illness as a result.

This research is still ongoing, and these conclusions are not universally accepted. This pamphlet should not be read as making such a claim. However, Andrew L. Stoll, M.D., Director, Psychopharmacology Research Laboratory, McClean Hospital Faculty, Harvard Medical School, recently asserted in his groundbreaking and comprehensive book, [The Omega-3 Connection](#) (Simon & Schuster, New York 2001), “we are learning that restoring the body’s natural balance of omega-3 oils may improve a multitude of medical disorders, including coronary artery disease, major depression, and bipolar disorder (also called manic-depressive illness).” Stoll added that: “other research suggests that omega-3 fatty acids may yield new treatments for postpartum depression, schizophrenia, [and] attention deficit-

hyperactivity disorder.... Furthermore, it is possible that omega-3 fatty acids may actually prevent these disorders from developing as well.”³

The National Institutes of Health convened a 1998 conference on “Omega-3 Essential Fatty Acids and Psychiatric Disorders” (see <http://nimh.nih.gov/events/omega.htm>). Although the NIH was careful not to express an opinion, eminent researchers from a range of disciplines unanimously supported lowering the ratio of omega-6 to omega-3 fatty acids (currently as much as 25:1 in American diets) to promote optimum health and linked psychiatric disorders to relative omega-3 deficits.

A SHORT COURSE IN LIPIDS

Fatty acids are a primary portion of human nutritional requirements, subdivided into saturated, monounsaturated, polyunsaturated and *trans*- varieties. In this terminology, the term “saturated” means a fat molecule with no double bonds between the carbon atoms. The distinction is important because when they are packed together, molecules with double bonds resist compacting. The long-chain, omega-3 and omega-6 polyunsaturated fatty acids are called “essential” fatty acids because they or their precursors cannot be made by human bodies and must be found in our diet.⁴ These fatty acids are carbon chain compounds with several double bonds, subdivided into those whose first double bond occurs on the third carbon from the methyl end (omega-3 essential fatty acids) and those whose first double bond occurs on the sixth carbon from the methyl end (omega-6 essential fatty acids).

From the beginning of human evolution up until about 1920, the human diet consisted of between a 1:1 and a 2:1 ratio of omega-6 to omega-3 essential fatty acids.⁵ The modern (American) diet has shifted this balance to between 10:1 and 30:1, as omega-3 essential fatty acids have declined due to (1) the prevalent use of omega-6 seed oils (especially corn) instead of omega-3-rich plants to feed the animals that make up our animal protein, (2) decline of fish consumption and general lack of flaxseed oil, canola oil, walnuts, and leafy green vegetables in our diet, (3) hydrogenization of oils for use in processed foods, thus increasing *trans*-fatty acid intake which interferes with fatty acid synthesis (4) loss of cereal germ by modern milling processes, and (5) increase in sugar intake which interferes with the enzymes of fatty acid synthesis.⁶

Alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentanoic acid (EPA) are the missing omega-3-rich essential fatty acids needed to restore this balance. ALA is an essential fatty acid, and DHA and EPA are derivatives, sometimes referred to as “conditionally essential fatty acids”⁷ because they are dietary essentials for some people, especially those with metabolic deficiencies. DHA (written as 22:6n-3, meaning twenty-two carbon atoms, six double bonds, and the first double bond at the third carbon) is the brain’s principal long chain omega-3 fatty acid. DHA also is found in high amounts in the mitochondria of nerve cells. Of equal importance, EPA (written as 20:5n-3) is the active anti-inflammatory omega-3 essential fatty acid. EPA can be synthesized by the body from ALA, and DHA can be synthesized by the body from EPA. ALA has the formula 18:3n-3.

The clinical studies thus far have generally used fish oil (about 3:2 EPA to DHA), except for one study that used a pharmaceutical grade of pure EPA.⁸ There is no clear evidence of the relative contribution of EPA and DHA to the observed outcomes. Stoll asserts that EPA appears to be “the most mood stabilizing component” in fish oil, and cites anecdotal data that suggest that too much DHA relative to EPA may actually worsen mood.⁹ However, this statement requires scientific validation.

It has been suggested that depletion of omega-3 essential fatty acids impairs membrane function. The brain uses its cell membranes to control the movement of electrically charged ions such as sodium and potassium and organizing the activities of the brain at the cellular level. The “lipid bilayer” forms the membrane around brain cells and is shaped by phospholipids, containing two fatty acids for each phospholipid molecule. It is theorized by Stoll that a 1:1 ratio of omega-6 to omega-3 essential fatty acids in the diet promotes an optimal balance of phospholipids in cell membranes. Stoll concludes that: “lipid bilayers composed of proper amounts of omega-3 fatty acids appear to function best.”¹⁰ He theorizes that the greater fluidity of cell membranes rich in omega-3 essential fatty acids may account for this conclusion.¹¹ In addition, neurotransmitter receptors lie embedded in the matrix of all membranes, and their 3-dimensional conformation is dependent on the essential fatty acids, which give structure to the membranes through their multiple double bonds.

Additional data are accumulating that suggest an association between essential fatty acids and the “mood” neurotransmitter, serotonin. Severely depressed patients have lower levels of serotonin

metabolites.¹² Both cholesterol lowering therapies and low cholesterol levels have been associated with an increased risk of suicide. The prevailing theory holds that low cholesterol levels lower serotonin utilization.¹³ However, drug and diet therapies to lower cholesterol also alter essential fatty acid levels. Cholesterol levels may be only a surrogate marker for changes in essential fatty acids.

Stoll concludes that: “the implications of omega-3 deficiency on the brain are profound and span the entire human life cycle. Beginning in pregnancy, premature birth and its potential neurologic complications may result from omega-3 deficiency. Babies who are bottle-fed or born from omega-3 deficient mothers will lack the omega-3 fatty acids necessary for optimal cognitive and visual development. Children deprived of omega-3s may have less ability to pay attention and control impulsive behavior and may be at higher risk for depression. Teenagers and adults with omega-3 deficiency may be more prone to hostility or violence. In aging, the loss of omega-3 fatty acids in the brain may result in a higher risk of stroke, memory problems, or dementia. Individuals of *any age* without adequate amounts of omega-3 fatty acids in the brain and body may also be at higher risk for depression, bipolar disorder, and possibly other psychiatric disorders.”¹⁴

DEPRESSION

It has been theorized that omega-3 essential fatty acids may reduce the development of depression, since depressive patients show significant depletion of omega-3s. There appears to be an inverse relationship between the prevalence of major depression and the amount of fish consumed per capita

worldwide.¹⁵ There are at least four studies showing reduced levels of omega-3 essential fatty acids in the blood of depressed patients.¹⁶ Uncontrolled clinical trials of omega-3 essential fatty acid supplements have shown promise in the treatment of major depression, and several controlled trials are underway.¹⁷

POSTPARTUM DEPRESSION

Depletion of maternal omega-3 essential fatty acids also has been noted during pregnancy. The physiology of pregnancy involves the mobilization of essential fatty acids from maternal stores to the fetus and especially the developing brain and nervous system. Supplementation with omega-3 essential fatty acids may ensure adequate supplies for the needs of the mother and the developing fetus and should be as common as folic acid supplementation--now an almost universal health precaution to prevent birth defects (e.g. *Spina bifida*).

Without dietary supplementation, levels of omega-3 essential fatty acids may remain low for some time postpartum, particularly in lactating women since considerable amounts of omega-3s are found in breast milk. Thus, it is possible that maternal omega-3 essential fatty acids depletion may contribute to postpartum depression. Joseph Hibbeln of the National Institute of Alcohol Abuse and Alcoholism of the National Institute of Health conducted an elegant 1998 epidemiological study showing an inverse relationship between fish consumption and major depression that suggests a causal relationship.¹⁸ Double-blind clinical studies are needed to confirm this suggestion.

BREAST MILK AND INFANT FORMULA

Breast milk, unlike infant formula, has relatively high concentrations of omega-3 and omega-6 essential fatty acids. The World Health Organization recommends that essential fatty acids be added to infant formulas. European infant formulas are routinely fortified, and the FDA has only recently allowed the addition of fatty acids to infant formulas sold in the United States. It goes without saying that lactating mothers should also consider taking omega-3 essential fatty acid supplements as long as they are breast-feeding. Omega-3 essential fatty acids are crucial in the development of the fetal and neonatal brain and nervous system. One study showed that intellectual development may also suffer in infants deprived of these fatty acids.¹⁹

BIPOLAR DISORDER

Bipolar disorder (manic-depressive illness) is a common neuropsychiatric illness with a high morbidity and mortality. Despite the use of mood-stabilizing drugs, including lithium and valproate, there are high rates of recurrence. All of the currently available mood-stabilizing drugs appear to affect neuronal signal transduction (or second messenger) mechanisms. Biochemical studies have shown that dietary treatment with omega-3 essential fatty acids leads to the incorporation of these compounds into the membranes crucial for cell signaling. This mechanism may be similar to some of the actions of lithium and valproate.

A recent double-blind study by Andrew Stoll, M.D., *et al.* (1999) demonstrated that dietary supplementation with omega-3 essential fatty acids resulted in marked mood-stabilizing activity for persons with bipolar disorder. Significant group differences in favor of fish oil were seen on the Hamilton Depression Scale, the Global Assessment Scale and the Clinical Global Impression. The authors concluded that omega-3 essential fatty acids were well tolerated and improved the short-term course of the illness.²⁰

SCHIZOPHRENIA

There is increasing evidence that neuronal injury due to oxidative stress (excess oxygen radicals) contributes to the pathophysiology of schizophrenia. Considerable effort has been directed towards determining the respective roles of increased oxidative stress (resulting in increased fatty acid breakdown) versus dietary deficiencies or defective metabolic pathways on membrane fatty acid concentration.²¹ It is likely that both processes are important for the development of a pathological state.

In an uncontrolled study, dietary supplementation with concentrated fish oil led to significant improvement in negative (alogia, flat affect, anhedonia, apathy, motor retardation) but not positive symptoms (hallucinations, disorganized thought) as rated by the Positive and Negative Syndrome Scale. Improvement in clinical symptoms was related to increased levels of omega-3 essential fatty acids in the blood.²² Thus, it is conceivable that dietary supplementation with antioxidants and omega-3 essential fatty acids at the initial stages of illness may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia.

ADVERSE EFFECTS AND INTERACTIONS

No adverse effects of omega-3 essential fatty acid supplementation are known, other than “fishy” reflux or loose stools with higher doses. Persons taking an anti-clotting agent such as warfarin or high doses of aspirin should be monitored for safety while taking omega-3 supplements, since the supplements reduce platelet aggregation and could increase bleeding time. Theoretically, there could be a mechanical interaction with lipid lowering drugs that could be “binding” with dietary fats. If these medications are used, they should not be taken at the same time as the supplements. **No one should taper off or discontinue any medications without the advice of a physician.**

DOSAGE

Stoll recommends careful choice of omega-3 essential fatty acid supplements, avoiding fish liver oil (which may contain excessive environmental pollutants) and emphasizing a high EPA-to-DHA ratio. However, as stated above, fish oil (about 3:2 EPA to DHA) is the only scientifically validated product at this point. Stoll recommends one to two grams of total omega-3 essential fatty acids (EPA plus DHA) for health, mood or cognitive enhancement and clinical doses of from two to five grams per day (up to 9.6 grams per day was used in the bipolar disorder study described above).²³

SAM-e (s-adenosylmethionine)

S-adenosylmethionine is approved for use as a prescription drug in Germany, Italy, Spain and Russia, and has been in use in Europe for over three decades for relief from symptoms of depression. Unlike long-chain omega-3 essential fatty acids, SAM-e is a substance normally produced by the human body. Thus, it is not an essential nutrient, and does not have to be ingested. Its precursors are readily available. However, it does play a role in regulating the activity of norepinephrine, dopamine and serotonin, the neurotransmitters implicated in major depression.²⁴

Spurred by European acceptance, recent studies have shown promising, though not conclusive, evidence of effectiveness of SAM-e in treating depression. Specifically, a comprehensive 1994 meta-analysis published in *Acta Scandinavica Neurologica* assembled data from twenty-five double-blind studies (fourteen against other antidepressants and eleven against placebo) to show the efficacy of SAM-e.²⁵ It found that the anti-depressant response rate ranged from seventeen to thirty-eight percent better for SAM-e than for the placebos, and that the effect was comparable to that of other antidepressants.

Since SAM-e is poorly absorbed from the stomach, most of the studies have used large doses (200-400 mg/day by intravenous injection or 800-1600 mg/day orally), well beyond the dosages commonly taken

without a prescription. SAM-e has an important role in the structure of the lipid bilayer in cell membranes, perhaps altering their electrical properties.²⁶ This in turn appears to affect mood.

ADVERSE EFFECTS AND INTERACTIONS

Mild and transient anxiety, insomnia, loose bowels and heartburn are the only noted physical effects. However, SAM-e can induce mania in patients with bipolar disorder.²⁷ Thus, bipolar disorder needs to be ruled out before initiating use of SAM-e. A careful psychiatric evaluation is the appropriate way to make this differential diagnosis.

DOSAGE

Since the clinical trials employed very high doses, dosage is the major remaining controversy concerning use of SAM-e in treating depression. The expense may also be an issue since the cost is not reimbursed. Advice of a physician is essential in the current state of medical knowledge, as there remain serious questions about dosage and negative side effect potential for SAM-e.

CONCLUSION

In conclusion, use of omega-3 fatty acids and SAM-e for depression and for some other symptoms of mental disorder is supported by a basic neurobiological rationale and by some clinical evidence. The evidence thus far looks very promising. However, for SAM-e, dosage needs to be monitored, and coun-



seling to avoid triggering a manic episode is very important. Use of alternative treatments should be discussed between a person desiring to use them and any professional providing treatment, as part of an effective treatment regimen. Professionals need to recognize that consumers have ready access to alternative treatments and that failure to discuss them may lead to failures in the treatment process. Candid discussion of these and other evidence-based alternative treatments should become a routine aspect of contemporary treatment of mental disorders.

Acknowledgments

The state mental health planning and advisory councils have joined together to form the National Association of Mental Health Planning and Advisory Councils (NAMHPAC). Federal law requires the establishment of mental health planning councils to review state applications for block grant funding, to serve as advocates for adults with serious mental disorders and children with serious emotional disturbance, and to monitor and evaluate state mental health planning systems. Although these activities are mandated, many states do not provide funding to support them. In many cases, this lack of funding, combined with council members' often short tenures, prevent these organizations from making their full impact on service delivery and consumer and family empowerment. NAMHPAC provides technical assistance to these organizations in the areas of exemplary practices, organizational development, and information sharing. In addition, NAMHPAC provides a national presence on mental health policy issues on behalf of the state planning and advisory councils.

Joseph N. de Raismes, III, J.D., Past Chair of NAMHPAC, and Jerry M. Cott, Ph.D., former Chief of the Psychopharmacology Research Program of the National Institute of Mental Health, prepared this brochure for NAMHPAC. This pamphlet has been underwritten by the Thendara Foundation (Cincinnati, Ohio). Their assistance is gratefully acknowledged.

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