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The Impact of Omega-3 Fatty Acids on Depressive Disorders and Suicidality: Can We Reconcile 2 Studies With Seemingly Contradictory Results?

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Investigation into the psychotropic efficacy of the omega-3 fatty acids has grown tremendously in the past decade and a half. Since publication of the Stoll et al[1] study of omega-3 for treatment of bipolar disorder, many clinical trials, in adults and children, have examined the omega-3s in unipolar major depressive disorder (MDD), postpartum depression, bipolar disorder, attention-deficit disorder, psychotic disorders, obsessive-compulsive disorder, and borderline personality disorder.[2–5] Psychiatric clinical trials of omega-3 fatty acids in mood disorders now number in the 30s, and various meta-analyses and systematic reviews have generally, but not unequivocally, suggested benefit.[2,6–16] These efficacy findings are consistent with what is being learned about antidepressants in general, with the growing availability of unpublished studies and databases.[17]

Interpretation of the omega-3 data is complicated by several factors:

1. Preparations of the psychiatrically relevant omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), range from pure EPA or DHA to combinations of the 2 at different ratios. Most studies have used EPA alone or a combination of EPA and DHA[2]; few studies have used pure DHA.[18,19] The possible EPA to DHA ratios are varied, and thus far there is no clear advantage for any 1 preparation.
2. Doses in studies have ranged from less than 1,000 mg/d to 10 g/d. With regard to unipolar depression, the data generally support doses in the range of 1–2 g/d,[2] although studies with higher doses have also shown benefit. Optimal doses have yet to be characterized.
3. The EPA to DHA ratio, which varies widely in commercial preparations, may be important when considering the clinical effects of omega-3, but we do not know whether there is an optimal ratio for humans. Likewise, omega-6 fatty acids, which people from industrialized countries consume in high levels, may also be relevant. Some studies that have found therapeutic windows for EPA and DHA suggest an optimal omega-6/omega-3 ratio for humans. For example, our study of EPA monotherapy[20] found an association between lowering of the omega-6/omega-3 ratio and clinical improvement in subjects who received EPA, but we did not find a significant association in our smaller study of DHA.[19]
4. The omega-3 fatty acids are vulnerable to oxidation and may be affected by dietary and consumptive practices. Investigators often attempt to control for this by excluding smokers and people who already consume high amounts of omega-3 in the diet.[21,22] However, these methods are not 100% reliable; patients may lie or may minimize or exaggerate lifestyle factors to be admitted into studies.
5. Diagnostic criteria vary, with some studies requiring *DSM-IV* MDD and others having more liberal diagnostic requirements; depressive severity may also vary; and certain comorbid conditions and concurrent medications may or may not determine exclusion.

The body of omega-3 data is therefore heterogeneous, which makes it difficult to compare and contrast studies in a systematic manner that provides practical information for investigators and clinicians, not to mention the general public.

The Journal of Clinical Psychiatry recently published 2 excellent, meticulously crafted reports online examining the clinical impact of omega-3 fatty acids. Both of these reports are included in the current issue of *The Journal*. Lewis and colleagues[23] performed a case-control study of suicide deaths among active-duty military, in which higher serum DHA demonstrated a protective effect against suicide; surprisingly, EPA appeared to confer no significant protective effect. A meta-analysis by Sublette and colleagues[24] examined the relative effects of EPA and DHA for MDD and found that EPA, rather than DHA, appeared to have the main antidepressant effect.

Can these seemingly contradictory findings be reconciled? Let us first contrast the 2 studies:

1. Lewis and colleagues[23] selected a specific, unambiguous outcome: suicide death. In contrast, Sublette and colleagues[24] examined depressive improvement, an outcome more subject to patient and investigator bias.
2. Lewis and colleagues[23] examined a narrow segment of the population: active-duty, predominantly male military personnel serving during the post-9/11 era—a population that may be especially vulnerable to psychiatric disorders. Sublette and colleagues,[24] on the other hand, examined studies with depressed individuals

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of both genders (presumably with a more balanced distribution than in the Lewis sample) and from many walks of life, which would make their sample more representative of the general population with depression, although not necessarily of the population as a whole, since their reviewed studies did not include healthy controls.

3. While Lewis and colleagues[23] focused on dietary *serum levels* of omega-3, Sublette and colleagues[24] examined a wide range of omega-3 *supplementation regimens*, including monotherapy, augmentation (including 1 study with psychotherapy as the baseline treatment), different doses and EPA to DHA ratios, and different treatment durations. Diagnoses included MDD of different severities, bipolar disorder, dysthymia, depressive episode, Parkinson's, and coronary heart disease. Again, this heterogeneity may limit generalizability with regard to MDD per se.
4. Both studies reported difficulty controlling for medical and psychiatric comorbidity, including substance abuse and posttraumatic stress disorder, which may be especially relevant in a military population. Soldiers who had witnessed extreme violence, for example, had a greater suicide risk than those who had not. Although access to comorbidity data was limited in the Sublette meta-analysis,[24] the studies reviewed typically allowed some comorbid disorders (except for active substance abuse), provided that they did not constitute the primary complaint. We cannot be sure whether substance abuse and/or posttraumatic stress disorder were contributing factors to suicide in the Lewis study.
5. Lewis and colleagues[23] broke down their serum omega-3 findings into octiles, allowing for a wide range of comparisons. The authors observed that their sample had an unusually low serum DHA status compared to the general population, which may make detection of an association more difficult and yield results less generalizable to the population at large. Sublette and colleagues[24] designed their meta-analysis with a binary dose schedule: EPA at levels of greater than or less than 60%, relative to DHA. They provide a strong rationale for their dichotomy, based on the observation that all significant positive studies had at least 60% EPA and all studies with less than 60% EPA were negative. They could not, however, examine the impact of blood levels of omega-3, which were not obtained in many of their studies. It is not clear how blood levels may relate to levels in the brain, where the omega-3s presumably carry out their psychotropic effects.

These issues make the studies difficult to compare on a head-to-head basis and could explain any apparent differences in their findings. But are these findings contradictory? One study says that DHA is protective against suicide and EPA is not; the other says that EPA is more effective than DHA for alleviating depression.

These findings of Lewis et al[23] and Sublette et al[24] are not mutually exclusive:

1. Although the relationship between depressive disorders and suicide is well established, suicidal ideation or completed suicide should not be considered as a proxy measure for MDD. Only 15% of people with depression will commit suicide,[25] and at least 40% of suicides consist of people without diagnosed depression.[26] Suicide may be influenced by many factors, eg, situational stressors that can be difficult to systematically assess and quantify in study samples. Therefore, conclusions about suicide and about depression cannot necessarily be commingled.
2. Although EPA did not significantly associate with suicide in the Lewis study,[23] there was a trend toward significance ($P < .08$), suggesting that EPA may in fact have a benefit, albeit more modest. Other fatty acids that are seemingly unrelated to mood also appeared to have protective effects against suicide: dihomo-γ-linolenic acid, palmitoleic acid, *cis*-vaccinic acid, and stearic acid. Therefore, the overall clinical impact of the different fatty acids and their ratios, in oral preparations and in the blood, is difficult to fully elucidate within the limitations of these studies.
3. Serum levels of omega-3 may not necessarily reflect brain levels; EPA is a precursor of DHA and may indirectly increase brain DHA or cause secondary effects, such as in the inflammatory system, that could ultimately impact on the brain. While Sublette and colleagues[24] suggest that DHA could block the effects of EPA, this scenario seems unlikely given everything else that is known about DHA's impact on mood and suicidality.
4. Posttraumatic stress disorder in the Lewis sample, even if not formally diagnosed, may have influenced suicidality. Also, psychiatric pathology in general, measured indirectly by a greater number of outpatient and inpatient mental health visits, may have also conferred a greater suicide risk for these soldiers. Interestingly, substance abuse visits were not associated with increased suicide risk, although it is possible that many individuals were underdiagnosed in this regard.

Considering the above, these studies should not be viewed as contradictory and can in fact be reconciled. EPA may have benefits for the overall constellation of symptoms known as *DSM-IV* MDD that exceed those of DHA. On the other hand, DHA may impact the mechanism(s) in the brain that regulate suicidal behavior, independent of MDD status. These findings should encourage investigators who study omega-3s, as well as other antidepressants, to closely scrutinize suicidal symptoms in addition to performing standard efficacy analyses based on depressive symptoms as a whole.

On a final note, our group at Massachusetts General Hospital, in collaboration with Emory University, is nearing

completion of a 3-arm randomized clinical trial comparing EPA, DHA, and placebo for MDD, including analysis of plasma polyunsaturated fatty-acid levels as moderators and mediators of response. We hope that our findings will help to shed further light on the comparative efficacy of EPA and DHA.

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