Is there anything “fishy" about using omega-3 fatty acids for anxiety? A review of the current literature surrounding fish oil supplementation for improving anxiety symptoms.

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Objectives

By the end of the presentation, the audience should be able to:
1. Differentiate between symptoms of anxiety and anxiety disorders
2. Describe the potential mechanisms between omega-3 fatty acids and neuropsychiatric health
3. Formulate evidence-based recommendations for the use of omega-3 fatty acid supplements in anxiety disorders
Anxiety Disorders

I. Epidemiology of anxiety disorders
   a. In the United States (U.S.), anxiety disorders comprise the most common mental illness – affecting nearly 40 million adults\(^1\)\(^3\)
      - Higher prevalence in females (2:1 female to male ratio)
      - Specific phobias are most commonly reported source of anxiety
        ▪ Prevalence: specific phobias > social anxiety disorder > generalized anxiety disorder > panic disorder
   b. Approximately 31.1% of U.S. adults experience any anxiety disorder at some time in their lives (includes obsessive compulsive disorder and post-traumatic stress disorder)\(^1\)
   c. Anxiety disorders are associated with a lower health-related quality of life and an increased risk of all-cause mortality\(^4,5\)

II. Anxiety symptoms and definitions
   a. Anxiety is often muddled with other symptoms and conditions
   b. Anxiety is a broad term used to encompass a variety of psychological, behavioral, and physical symptoms\(^3\)
   c. Definitions
      - Anxiety is broadly defined as an emotion characterized by worried thoughts, feelings of tension, and physiological changes\(^6\)
        ▪ An emotional response to the anticipation of a future threat\(^7\)
      - Symptoms of anxiety can manifest as thoughts, feelings, and physiological changes (eg. sweating, increased blood pressure, jitteriness/trembling, dizziness, rapid heart rate)\(^7,8\)
      - Other anxiety-related terminology\(^6,8\)
        ▪ Worry = a state of anxiety and uncertainty
        ▪ Fear = an emotional response to a threat, real or perceived
        ▪ Stress = a state of mental or emotional strain or tension resulting from adverse or demanding circumstances

III. Formal diagnosis and characterization of anxiety disorders
   a. The grouping of anxiety disorders includes generalized anxiety disorder (GAD), panic disorder (PD) with/without agoraphobia, and social anxiety disorder\(^7,9\)
      - These disorders differ from one another by the types of objects/situations that induce fear, anxiety, or avoidance behavior and the associated cognitive ideation\(^7\)
   b. Diagnosed per 2013 Diagnostic and Statistical Manual of Mental Disorders, 5\(^{\text{th}}\) Edition (DSM-5)\(^7\)
      - Different from developmentally normative or transient, often stress-induced, fear/anxiety due to excess or persistence (i.e. typically lasting ≥6 months)
      - Symptoms cause significant distress and impair social or daily functioning
      - Symptoms not attributable to substance use, other medication, or another medical/mental health condition
   c. Under the previous DSM-IV, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) were grouped under anxiety disorders\(^7,9\)
      - In DSM-5 these were separated out to other categories of trauma and stressor-related disorders and obsessive-compulsive and related disorders, respectively
d. Anxiety disorders often overlap with one another and are comorbid with other psychiatric conditions
   - Treatment may be complicated in patients who present with an overlap of more than one anxiety disorder
   - Anxiety or related symptoms can exist individually or in combination with another psychiatric disorder
     ▪ Most patients with anxiety present with another psychiatric condition, commonly depression
     ▪ Anxious distress has been noted as a prominent feature of both bipolar disorder and major depressive disorder (MDD)

IV. Pathophysiology
   a. Complexity of development of anxiety disorders includes genetics, neurobiological changes, personalities, and experiences\textsuperscript{7,10}
      - Twin studies up to 50% heritability
      - Primarily thought to be a brain stem and limbic system disorder
        ▪ Integration of mood modulation and cognitive functioning
        ▪ Fine balance between excitation and inhibition
   b. There are various mechanisms that aim to describe the pathophysiology behind anxiety disorders\textsuperscript{7,10}
      - Dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis with excess cortisol release
      - Imbalances in gamma-aminobutyric acid (GABA) and/or serotonin (5-HT), which play a large role in modulating the activity of the limbic system and brain stem
        ▪ GABA is primary inhibitory neurotransmitter and 5-HT modulates GABA
      - Changes in hippocampal volume and neurogenesis in the limbic system are implicated in stress sensitivity and resiliency

V. Management/treatment
   a. Psychotherapy
      - Psychotherapy is considered a first-line treatment for all anxiety disorders\textsuperscript{3,7}
- Interpersonal treatment with a focus on cognitive and behavioral techniques for managing symptoms of anxiety
  - Cognitive behavioral therapy (CBT)
  - Psychotherapy is strongly recommended for PTSD – trauma-focused psychotherapy always first-line treatment

b. Pharmacotherapy
- Antidepressants are the primary pharmacological agents used for treatment of anxiety disorders
  - Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacological agents
    a. Varying Federal Drug Administration (FDA) indications for different anxiety disorders, but SSRIs can be used off-label for other anxiety disorders based on clinical data
    b. Lack of head-to-head trials for superiority of one SSRI vs. another
    c. Meta-analysis in GAD suggests fluoxetine may have better efficacy and sertraline with better tolerability compared to other SSRIs
  - Alternative antidepressant selection may include serotonin/norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs), mirtazapine
    a. SSRIs and SNRIs typically preferred over TCAs, MAOIs, and mirtazapine due to their side effect profiles
    b. See Appendix A for a list of antidepressant agents
  - A full antidepressant response takes longer, and the response rate is lower compared to patients with depression
    a. May take up to 12 weeks for maximum effect
    b. During the initial 2-week period, patients are likely to experience increased anxiety symptoms
      i. This may affect treatment adherence
      ii. Recommended to provide adequate counseling and establish expectations
    c. Additional improvement in GAD symptoms is not likely with an agent and/or dose if partial response is not seen at 4 weeks
  - It is usually recommended to start antidepressants at half the initial dose used in depression to minimize initial worsening of anxiety symptoms
- Other non-antidepressant treatment options may include antihistamines, atypical antipsychotics, GABA modulators, and much more
  - See appendix B for a list of specific agents
  - NOTE: benzodiazepines may be used, but should be restricted to the lowest effective dose and not to exceed 4 weeks in duration
    a. Concerns for abuse, dependence, tolerance, and potentially dangerous or distressing withdrawal, among others
    b. Not recommended for PTSD also because of interference with psychotherapy
- Considerations in patients who are pregnant or nursing
  - GAD with highest prevalence during pregnancy (8.5-10.5%)
    a. An uncontrolled or poorly controlled anxiety disorder involves risks to the mother and fetus
b. Associated with increased risk of postpartum depression\textsuperscript{15}

- **Treatment considerations\textsuperscript{7,61}**
  a. Encourage psychotherapy
  b. Weight risk vs. benefit of pharmacotherapy and patient preferences
  c. Transplacental exposure is high for most antidepressants\textsuperscript{15,16}
    i. Avoid paroxetine during pregnancy
      1. Crosses the placenta with increased risk of teratogenic effects
      2. Additional non-teratogenic effects the newborn may experience could include respiratory depression, seizures, apnea, cyanosis, etc.
    ii. Sertraline and fluoxetine are the most well-studied antidepressants in pregnancy and usually preferred
    d. Antidepressant exposure through breastfeeding is generally considered to be less than transplacental exposure, but data is limited\textsuperscript{16-18,52,53}
      i. SSRIs generally considered safe for breastfeeding mothers, but lack robust evidence
      ii. Most SSRIs categorized as Hale's Lactation Category L2 (probably compatible)
  c. Patient-preference plays a role in choosing psychotherapy +/- pharmacotherapy\textsuperscript{3,7,9}
    - Similar efficacy for acute treatment of anxiety\textsuperscript{3}
    - Combination treatment is ideal, but there has been no clear evidence to suggest superiority of combination therapy vs. monotherapy for anxiety long-term outcomes\textsuperscript{3}
      - Exceptions to this include:
        a. In treatment of PD and OCD, combination therapy is more efficacious\textsuperscript{11}
        b. Specific phobias and SAD typically treated with psychotherapy\textsuperscript{7}
        c. Limited evidence supporting augmentation strategies in SAD
      - Some guidelines specifically recommend first-line therapy as CBT +/- antidepressant therapy – British Association for Psychopharmacology and National Institute for Health and Care Excellence
  d. Goal of treatment is remission of anxiety symptoms
    - The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial provided clinical definitions for response and remission with treatment\textsuperscript{19}
      - **Response** = \( \geq 50\% \) reduction in symptoms
      - **Remission** = near-absence of symptoms (eg. Hamilton Anxiety Scale [HAM-A] score <7)
    - If treatment goal not achieved with first-line pharmacotherapy using an SSRI, alternative options may include:\textsuperscript{3}
      - Switching from one SSRI to another
      - Switching from SSRI to SNRI, or vice versa
      - Switching to TCA
      - Augmentation with alternative agent
    - Oftentimes for anxiety, response and remission rates remain low despite psychotherapy and/or pharmacotherapy\textsuperscript{3}
    - Various mental health assessments may be used to quantify and track progress
      - *See appendix C for a list of various rating scales*
  e. Major therapeutic phases for treatment of anxiety disorders\textsuperscript{3,7}
Figure 2. Therapeutic phases for pharmacological treatment of anxiety disorders

- Similar therapeutic phases to treatment of depression
- Recommended to continue treatment for at least 1 year after achieving response
- Early discontinuation is associated with a high risk for relapse of symptoms
- When appropriate, discontinuation should be slow and gradual to minimize risk of precipitating withdrawal symptoms
    - May consider discontinuation after 12 months of treatment
    - May taper agents up to 12 weeks – similar to treatment initiation

f. Natural and herbal remedies

- Agents with potential benefit in anxiety may include passionflower, valerian, St. John’s wort, kava, L-lysine, L-arginine, B vitamins, and folic acid
  - Kava linked to hepatotoxicity – FDA warns against use
  - St. John’s wort with many drug-drug interactions
- Recent evidence has suggested omega-3 fatty acids may provide antidepressant and anxiolytic effects

Omega-3 Fatty Acids

I. Types of fat and fatty acids

a. There are 2 types of fat: saturated and unsaturated fats

   - Unsaturated fats are further subdivided into polyunsaturated and monounsaturated fats
   - Under the polyunsaturated fats category, there are a few different types of polyunsaturated fatty acids (PUFAs) – omega-6 and omega-3 fatty acids
   - Omega-6 (n-6) fatty acids
     - Implicated in pro-inflammatory processes
     - Different types of n-6 fatty acids:
       a. Linoleic acid (LA)
          i. Essential fatty acid, which can only come from dietary intake
          ii. From certain plants – flaxseed, soybean, walnut, canola oil
       b. Arachidonic acid (AA)
          i. From animal sources – poultry, eggs
          ii. Abundant in brain, muscles, and liver

   - Omega-3 (n-3) fatty acids
     - Anti-inflammatory biological role
     - Play a fundamental role in brain structure and function
     - Different types of n-3 fatty acids:
       a. Alpha-linolenic acid (ALA)
          i. Essential fatty acid, which can only come from dietary intake
ii. Other n-3 fatty acids are converted from ALA
iii. From certain plants – flaxseed, soybean, walnut, canola oil
b. Docosahexaenoic acid (DHA)
   i. From marine sources – fish, shellfish, fish oil, krill oil
   ii. High storage concentration in brain, retina, and sperm
c. Eicosapentaenoic acid (EPA)
   i. From marine sources – fish, shellfish, fish oil, krill oil
   ii. Dietary intake more efficient than metabolic conversion of ALA
d. Docosapentaenoic acid (DPA)
   i. From marine sources (particularly salmon), grass-fed beef, and
      found abundantly in human milk
   ii. Most abundant n-3 fatty acid in the brain after DHA
   iii. May serve as a storage depot for EPA and DHA in the body

II. Diet vs. supplementation of n-3 fatty acids
   a. n-3 fatty acids are available as over-the-counter (OTC) or prescription supplementation
      - Commonly referred to as “fish oil” as per DHA and EPA sources in most supplements
      - Concentrated EPA, DHA, or a combination of the two are commercially available in
        various formulations
      - Concentrated DPA not commercially available – undergoing research
      - NOTE: ~3 salmon meals/week roughly equivalent to 1 g/day of n-3 fatty acid
        supplementation
      - Side effect profile of fish oil supplementation is virtually non-existent
        - “Fishy burps” or fishy aftertaste
        - Gastrointestinal upset
        - Potential to increase in bleeding risk, albeit debated in the literature
          a. Bleeding time may be prolonged at doses >3g/day
          b. Overall, limited clinical evidence of prolonged bleeding
      - Dosing regimens for n-3 fatty acids range between 1-4 g/day
        - For triglyceride-lowering effects, doses typically 2-4 g/day EPA + DHA
      - Drug-drug interactions (DDIs)
        - No DDIs between fish oil and psychotropic medications
   b. Dietary and supplement recommendations for intake of n-3 fatty acids
      - The American Heart Association recommends for people without cardiovascular disease
        (CVD) to eat foods rich in n-3 fatty acids at least twice/week
      - Recommended daily intake of EPA + DHA 500 mg/day per International Society for the
        Study of Fatty Acids and Lipids (ISSFAL)
      - The Omega-3 Fatty Acids Subcommittee of the Committee on Research on Psychiatric
        Treatments of the American Psychiatric Association (APA) recommends eating fish ≥2
        times/week for healthy adults and 1g/day of n-3 fatty acid supplementation (EPA + DHA)
        for patients with mood, impulse control, or psychotic disorders
Omega-3 Fatty Acids & Mental Health

I. Nutritional psychiatry
   a. “Food and mood”
      - Mental health is closely tied to nutrition
        ▪ Essential vitamins, minerals, and fatty acids may have a critical role in overall brain functions, as well as, a role more specifically in neurotransmitter synthesis and function\textsuperscript{41}
        ▪ The brain requires essential nutrients for proper function
        ▪ Additionally, some foods may produce free radicals and can damage brain tissue
          - A “healthy diet” consisting of high intakes of fruit, vegetables, fish, and whole grains may decrease risk of depression\textsuperscript{39}
          - In countries with a higher consumption of fish, it has been observed that there is a lower prevalence of MDD and bipolar disorder\textsuperscript{35,42,43}
          - In animal models, it has been found that diet manipulation can affect brain plasticity\textsuperscript{44}
          - Diet is likely just as important to psychiatry as it is to endocrinology, cardiology, and gastroenterology\textsuperscript{45}
   b. A diet rich in vitamins in minerals can be mimicked with certain supplements
      - There is growing evidence for the select use of nutrient-based supplements to address deficiencies or augment therapy\textsuperscript{45}
      - Vitamin D and n-3 supplementation for mood and behaviors has been a hot topic of research in recent years

II. Proposed mechanism of n-3 fatty acids in mood and anxiety
   a. Anti-inflammatory action
      - Decrease inflammation in neural tissues and directly affect cell membrane properties related to neurotransmitter signaling\textsuperscript{46}

Figure 3. n-3 fatty acids proposed health benefits\textsuperscript{32-37}
- Enhance cell membrane fluidity and neurogenesis
  - Thought to be related to a decrease in prostaglandins derived from arachidonic acid (n-6), which can lead to decreased brain-derived neurotrophic factor levels and/or alterations in blood flow to the brain
  - Inflammation ↓ serotonin activity
  - EPA (n-3) ↓ brain inflammation and helps ↑ neuronal release of serotonin
  - DHA (n-3) sensitizes serotonin receptors by improving cell membrane structure and function in post-synaptic neurons

b. Cell membrane mechanisms
  - Lipid rafts are highly organized structures in the cell membrane rich in lipids, cholesterol, and various signaling molecules (including G-protein)
  - Antidepressant and antipsychotic drugs have been shown to accumulate in lipid rafts
  - n-3 incorporated in membrane lipid rafts and/or involved in G-protein translocation
  - Modification of membrane signaling domains and/or modification of G-protein withi in the signaling domains
    a. Antidepressants activate adenyl cyclase more efficiently resulting in increased levels of cyclic adenosine monophosphate (cAMP)
    b. Related to the above, n-3 fatty acids may have antidepressant effects via association with lipid raft structure and release of raft-associated proteins into non-raft sections of the membrane

III. n-supplementation and other psychiatric disorders
  a. Larger body of evidence evaluating n-3 supplementation as an adjunctive therapy in MDD
  - Cited in the APA treatment guidelines for depression as an augmentation treatment option
    - Adjunctive EPA or combination of EPA + DHA n-3 supplements
    - n-3 supplements with higher EPA percentages (i.e. ≥60%)
  b. Possible association of n-3 supplementation inducing mania in patients with bipolar I disorder
    - Bipolar depressive symptoms, but not manic symptoms, may be improved by adjunctive administration of n-3 fatty acids

Evaluation of the Literature

**Clinical question #1:**
Are anxiety disorders associated with low dietary intake of n-3 fatty acids?

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>To evaluate whether high-consumption of n-3 fatty acids may be associated with lower prevalence of anxiety disorders</td>
</tr>
</tbody>
</table>
| Participants | **Inclusion**
  - Adults living in Brazil |
|              | **Exclusion**
  - Use of n-3 or n-6 fatty acid supplements
  - Previous bariatric surgery
  - Consumed <500 or >4000 calories/day
  - Patients with missing information for main variables |

Methods

- Cross-sectional data from the baseline examination of the ELSA-Brasil study August 2008-December 2010 (separate longitudinal study with main study outcomes evaluating type-2 diabetes and myocardial infarction)
- Food frequency questionnaire (FFQ) measuring dietary exposure over 12 months – quantified daily intake of fish and seafood (g/day), n-6 (g/day), n-3 (g/day), and the n-6:n-3 ratio
- Brazilian healthy eating index (BHEI) to evaluate dietary quality from current nutritional recommendations
- Revised Clinical Interview Schedule (CIS-R) to diagnose mental disorders following ICD-10 codes; included anxiety diagnoses of GAD, PD, SAD, phobia, or OCD
- Fasting labs to evaluate lipid panel and C-reactive protein (CRP)
- Other comprehensive questionnaires, tests, and measurements included demographics, physical activity, alcohol intake, height, weight, body mass index (BMI), blood pressure, plasma glucose, and A1c

Intervention

- n/a: observational study

Outcome(s)

- Association between PUFA consumption and anxiety disorders

Statistical analysis

- Two-sided tests with α 0.05 for statistical significance
- Categorical variables compared with Chi-square test
- Continuous variables compare using ANOVA with post hoc Bonferroni for parametric and Kruskal-Wallis test for non-parametric variables
- Triglycerides reported as natural scales, but log-transformed for comparison
- Diet variables measured in g/day were adjusted for total energy intake and categorized into quintiles
- Log regression models to compare n-3, n-6, and the n-6:n-3 ratio
- Partially adjusted model (Model 2) for certain variables, such as physical activity, cardio risk factors, dyslipidemia, etc., and a fully adjusted model (Model 3) with all variables an additional adjustment for diet quality and MDD
- Sensitivity analyses performed and a Holm-Bonferroni test to adjust for multiple comparisons

Results

- Total participants n=12,268 (1893 with anxiety disorders [15.4%] and 10375 without [84.6%])
- Statistically significant differences in baseline characteristics included: age, sex, race, BMI, exercise, smoking, alcohol intake, and systolic blood pressure
- Similar rates of hypertension, diabetes, and dyslipidemia between groups
- Participants with anxiety were primarily women with slightly higher BMI, less vigorous physical activity, higher frequency of smoking, and lower frequency of current use but higher frequency of past use of alcohol

<table>
<thead>
<tr>
<th>Table 1a. PUFA intake and anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median n-3 and n-6 intake (interquartile range [IQR])</td>
</tr>
<tr>
<td>LA, g/day</td>
</tr>
<tr>
<td>AA, g/day</td>
</tr>
<tr>
<td>ALA, g/day</td>
</tr>
<tr>
<td>EPA, g/day</td>
</tr>
<tr>
<td>DPA</td>
</tr>
<tr>
<td>DHA, g/day</td>
</tr>
<tr>
<td>PUFA, g/day</td>
</tr>
<tr>
<td>n-3 total</td>
</tr>
<tr>
<td>n-6 total</td>
</tr>
<tr>
<td>n-6:n-3 ratio</td>
</tr>
</tbody>
</table>
- Association of lower overall n-3 total intake (including EPA, DPA, DHA, but not ALA) and higher n-6:n-3 ratio in participants with anxiety
- Additional variables were tested (including depression), but all associations lost significance after multivariate adjustment

**Author’s conclusions**
- Inverse association between total n-3, EPA, DPA, and DHA intake and anxiety
- Cross-sectional analysis with a calculated prevalence of 15.4% of participants with anxiety similar to previously reported rates of anxiety in Brazil
- Similar results as compared to previous literature in anxiety and anxiety-related disorders

**Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>- Diagnosis of anxiety disorder</td>
<td>- Diet measured at single point in time (at baseline)</td>
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<tr>
<td>- Large sample size</td>
<td>- Diet self-reported – recall bias</td>
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<tr>
<td>- Review of baseline characteristics in those with vs. without anxiety</td>
<td>- Study not performed in U.S.</td>
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<tr>
<td>- Adjustments with multivariate analysis</td>
<td>- Mental health diagnoses assessed by lay interviewers</td>
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<tr>
<td></td>
<td>- Included OCD in anxiety disorder cohort (separate in DSM-5)</td>
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<td></td>
<td>- Not looking at n-3 fatty acid supplementation outside of diet</td>
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<td></td>
<td>- Multivariate analysis lost significance</td>
</tr>
</tbody>
</table>

**Take home points**

There was an inverse association between n-3 dietary intake and the presence of anxiety and an association between the n-6:n-3 ratio and anxiety. But there was not a strong association noted for n-6 intake alone and anxiety. After adjusting for depression and multivariate analyses associations lost significance, which may be related to anxiety and depression often co-occurring. It is difficult to discern whether differences in baseline characteristics confound the associations; cross-sectional analysis does not give us causality, only associations.

**Table 2. Additional literature for dietary intake of n-3 fatty acids in anxiety**

<table>
<thead>
<tr>
<th>Primary Literature</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacka, et al. (2013)</td>
<td>- Observational cross-sectional analysis of Australian women (n=935)</td>
</tr>
<tr>
<td></td>
<td>- Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition assessed depressive and anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>- Significant association for low total n-3 fatty acids, DPA, EPA, and DHA with anxiety disorders (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>- Inverse, linear association between intake of DHA and rates of anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>- Relationship between DHA and depressive disorders may be non-linear</td>
</tr>
</tbody>
</table>

**Clinical question #2:**
Is supplementation with n-3 fatty acids an appropriate treatment consideration for managing anxiety symptoms?

<table>
<thead>
<tr>
<th>Study design</th>
<th>Parallel group, placebo-controlled, double-blind randomized control trial (RCT) in U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>To determine whether n-3 decreases proinflammatory cytokine production and depressive and anxiety symptoms in healthy young adults</td>
</tr>
</tbody>
</table>
| Participants | **Inclusion**
- First and second-year medical students
**Exclusion**
- High fish intake
- Fish oil or flaxseed supplementation
- Smoking, alcohol, or drug abuse
- Chronic illness inflammatory/endocrine
- Lipid-altering drugs
- Beta-blockers, steroids, ACE-inhibitors
- Regular use of non-steroidal anti-inflammatory drugs (NSAIDs)
- Use of psychoactive medications |
| Methods      | – August 2007-December 2009; block randomization to intervention or placebo
– Baseline 2 visits (3 weeks apart): visit 1 lower stress time/non-exam, visit 2 day before an exam/high stress; additional 4 visits after randomization x 12 weeks
– Baseline height, weight, central adipose tissue
– FFQ reported, Pittsburgh Sleep Quality Index with Pittsburgh Sleep Diary, and 7-day Physical Activity Recall at first and last visits
– Modified version of the Health Review administered every visit assessing side effects
– Center for Epidemiological Studies Depression Scale (CES-D) and Beck Anxiety Inventory administered at each visit
– Fasting labs at each visit to assess cytokine assays (interleukin 6 [IL-6] and tumor necrosis factor alpha [TNF-α]) and fatty-acid analyses |
| Intervention | – 2.5 g/day n-3 fatty acid supplement (OmegaBrite® 7:1 EPA/DHA) vs. matching placebo
– Adherence measured via pill pack/unused pills at follow-up visits |
| Outcomes     | **Primary (1’) – inflammatory:** changes in serum and stimulated IL-6 and TNF-α production
**Secondary (2’) – mood:** changes in anxiety and depressive symptoms |
| Statistical analysis | – Two-sided tests with α 0.05
– Mixed models test effects of supplementation, unstructured variance-covariance estimate error, natural log transformation for residual not normally distributed
– Differences in adverse effects were evaluated using Fischer’s exact test
– James’ blinding indices used to assess effectiveness of blinding |
| Results      | **Table 3a. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Mean age, years (Standard Deviation [SD])</th>
<th>23.65 (1.87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex, %</td>
<td></td>
<td>44%</td>
</tr>
<tr>
<td>Race, %</td>
<td>White 67.6%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Black 3%</td>
<td>17.7%</td>
</tr>
<tr>
<td></td>
<td>Asian 17.7%</td>
<td>Other 11.7%</td>
</tr>
<tr>
<td>Sagittal abdominal diameter, cm</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Median Beck Anxiety (Interquartile range [IQR])</td>
<td>placebo 2.5 (1-4.5)</td>
<td>supplement 3.5 (2-6)</td>
</tr>
<tr>
<td>Median CES-D (IQR)</td>
<td>Placebo 5.25 (3.5-7.5)</td>
<td>supplement 6.25 (4-8)</td>
</tr>
</tbody>
</table>
- No significant differences in baseline characteristics
- No significant differences in self-reported diet via FFQ from baseline to 12 weeks
- Reported meds other than intervention (did not differ between groups): multivitamins, birth control, antihistamines, and antibiotics
- 99% of participants completed the 12-week study
- >95% adherence in each arm; no differences between groups
- No significant differences in side effects between supplement vs. placebo
- Blinding considered adequate; evaluated using James’ blinding indices (0.55)
- Baseline EPA or DHA similar in labs at baseline between groups; 6-fold (with n-3 supplement) and 0.5-fold (placebo) increase in plasma levels by 3-weeks of intervention
- 14% reduction in the geometric mean of IL-6 cytokine stimulation, but no significant correlations with anxiety or depression scores in the supplement or placebo groups
- 20% reduction in the geometric mean of anxiety symptoms
- Significant negative correlation between plasma n-3 levels and anxiety (r= -0.39, p=0.0006) and positive association between n-6:n-3 ratio and anxiety (r=0.34, p=0.001) vs. no significant associations in placebo group

### Table 3b. Outcomes for n-3 supplementation vs. placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Outcome</th>
<th>n-3 supplement (n=34)</th>
<th>Placebo (n=34)</th>
<th>Group difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1’</td>
<td>Serum cytokines log(IL-6)</td>
<td>0.051 (0.069)</td>
<td>0.054 (0.070)</td>
<td>-0.0033 (0.900)</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>log(TNF-α)</td>
<td>0.54 (0.027)</td>
<td>0.61 (0.028)</td>
<td>-0.076 (0.039)</td>
<td>0.06</td>
</tr>
<tr>
<td>1’</td>
<td>Stimulated cytokines log(IL-6)</td>
<td>10.9 (0.050)</td>
<td>11.1 (0.051)</td>
<td>-0.15 (0.072)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>log(TNF-α)</td>
<td>7.3 (0.060)</td>
<td>7.4 (0.061)</td>
<td>-0.15 (0.086)</td>
<td>0.08</td>
</tr>
<tr>
<td>2’</td>
<td>Beck Anxiety, log</td>
<td>0.93 (0.076)</td>
<td>1.2 (0.075)</td>
<td>-0.23 (0.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>2’</td>
<td>CES-D, log</td>
<td>1.6 (0.098)</td>
<td>1.6 (0.097)</td>
<td>0.012 (0.14)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Author’s conclusions
- n-3 supplementation can reduce inflammation and anxiety in healthy, young adults
- Reduction in anxiety symptoms associated with n-3 supplementation may link to anxiolytic benefits for individuals without an anxiety disorder diagnosis

Critique

**Strengths**
- Double-blind RCT with matching placebo
- Assessed symptoms of anxiety and depression
- Assessed adherence of n-3 supplementation

**Limitations**
- Healthy, young adults
- No clinical diagnosis of anxiety or depression
- Not taking antidepressants or other psych-related drugs
- Adherence likely not reflective of real world
- Small sample size
- Not widely generalizable

Take home points
Statistically significant improvement in anxiety symptoms, but not clinically significant. The measured ratio of n-6:n-3 was lower and stimulated cytokines were lower in patients taking the n-3 supplement. This study gives us an indication that n-3 supplementation may improve anxiety symptoms in patients with a formal diagnosis of anxiety, but this study population was healthy, young adults without a diagnosis of a mental health condition.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Systematic review and meta-analysis from various countries (U.S., Japan, France, Italy, Germany, Poland, Iran, Sweden, United Kingdom, Netherlands, Israel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>To evaluate the anxiolytic effects and efficacy of n-3 fatty acid treatment in participants with elevated anxiety symptoms, irrespective of diagnosis</td>
</tr>
<tr>
<td>Participants</td>
<td>Inclusion: - Human clinical trials - Placebo or non-placebo-controlled trials - Healthy volunteers, patients with psychiatric illness, and patients with physical illnesses other than psychiatric illnesses</td>
</tr>
<tr>
<td></td>
<td>Performed manual search of review article reference lists in this subject area</td>
</tr>
<tr>
<td></td>
<td>Duplicates removed, titles and abstract were screened for eligibility, then full-text review analyzed and 3rd author discussed inconsistencies for final consensus</td>
</tr>
<tr>
<td>Intervention</td>
<td>n-3 fatty acid treatment vs. without n-3 fatty acid treatment (placebo or non-placebo)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary (1st): changes in anxiety symptoms</td>
</tr>
<tr>
<td></td>
<td>Secondary/subgroups (2nd): changes in anxiety symptoms for those with or without a “specific clinical diagnosis,” mean n-3 fatty acid daily dosage, mean age, and EPA percentage</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Random-effects meta-analysis to account for heterogeneity and Q statistic + corresponding p values inter-study variation and I^2 statistic evaluating intra-study variation</td>
</tr>
<tr>
<td></td>
<td>Hedges g with 95% confident intervals (CI) for effect sizes and 2-sided p values &lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Variance imputation for mean and SD before and after treatment</td>
</tr>
<tr>
<td></td>
<td>Intention-to-treat for participant count, or per-protocol numbers if trials only reported values for participants who completed</td>
</tr>
<tr>
<td></td>
<td>Quality of blinding, randomization, and risk of bias evaluated with Jadad score</td>
</tr>
<tr>
<td></td>
<td>Duval and Tweedie’s trim-and-fill test for adjusting effect sizes for potential publication bias with funnel plots and Egger regression for further assessment</td>
</tr>
<tr>
<td></td>
<td>Sensitivity testing for confounding effects and potential study outliers</td>
</tr>
<tr>
<td></td>
<td>Meta-regression and subgroup meta-analyses conducted for additional outcomes/differences</td>
</tr>
</tbody>
</table>

Results | 19 articles; n=2240 participants (1203 n-3 treatment and 1037 without n-3 treatment) |
|         | 16 studies placebo-controlled and 3 studies did not use placebo |
|         | Recruited studies mean Jadad score (SD) = 3.8 (1.0) |
|         | Significant heterogeneity between trials (Cochran Q 178.820, df 18, I^2 89.934%; p <0.001) |

Table 4a. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n-3 fatty acids (n=1203)</th>
<th>Control (n=1037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>43.7</td>
<td>40.6</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>
No significant differences in baseline characteristics of mean age or female sex
− No significant association for drop-out rate in n-3 treatment group (p=0.71) or duration of treatment (p=0.17)
− No significant publication bias via Egger regression and no adjustment needed per trim-and-fill test
− Overall mean n-3 fatty acid dosage = 1605.7 mg/day

Table 4b. Outcomes for n-3 supplementation vs. control

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hedges g (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall n-3 fatty acid treatment and reduction in anxiety symptoms</td>
<td>0.374 (0.081-0.666)</td>
<td>0.01</td>
</tr>
<tr>
<td>Placebo-controlled subgroup</td>
<td>0.372 (0.032-0.712)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-placebo-controlled subgroup</td>
<td>0.399 (0.154-0.643)</td>
<td>0.001</td>
</tr>
<tr>
<td>“Specific clinical conditions” subgroup</td>
<td>0.512 (0.119-0.906)</td>
<td>0.01</td>
</tr>
<tr>
<td>Without “specific clinical conditions” subgroup</td>
<td>-0.008 (-0.266-0.250)</td>
<td>0.95</td>
</tr>
<tr>
<td>n-3 supplement doses &lt;2 g/day subgroup</td>
<td>0.457 (-0.077-0.991)</td>
<td>0.09</td>
</tr>
<tr>
<td>n-3 supplement doses &gt;2 g/day subgroup</td>
<td>0.213 (0.031-0.395)</td>
<td>0.02</td>
</tr>
<tr>
<td>EPA &lt;60% subgroup</td>
<td>0.485 (0.017-0.954)</td>
<td>0.04</td>
</tr>
<tr>
<td>EPA ≥60% subgroup</td>
<td>0.092 (-0.102-0.285)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Author’s conclusions
− n-3 fatty acid supplementation may be associated with anxiety reduction – maybe placebo effect, but appears to be some improvement in anxiety symptoms
− Anxiolytic effects appear to be stronger in patients with “specific clinical conditions”
− Additional trials are warranted to evaluate use of n-3 fatty acid supplementation as monotherapy and as augmentation in anxiety

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First meta-analysis/review evaluating n-3 supplementation in anxiety</td>
<td>Broad inclusion criteria (anxiety disorders, anxiety symptoms, PTSD, OCD)</td>
</tr>
<tr>
<td>Broad inclusion criteria</td>
<td>Selection bias</td>
</tr>
<tr>
<td>Various scales evaluating symptoms</td>
<td>Two articles appear to drive results</td>
</tr>
<tr>
<td>Thorough literature search and analysis</td>
<td>Heterogenous population</td>
</tr>
</tbody>
</table>

Take home points
First thorough review of current literature evaluating effects of n-3 fatty acid supplementation and anxiety symptoms. However, “specific clinical conditions” were not always a diagnosis of anxiety. This analysis provides information for selecting doses of n-3 supplementation and EPA concentration for anxiety. Further research is warranted for n-3 supplementation in specific subgroups of anxiety disorders.
### Table 5. Case of n-3 fatty acid supplementation and increase in symptoms of anxiety

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Key Information</th>
</tr>
</thead>
</table>
| Blanchard, et al. (2015)\(^{56}\) | – 54-year-old man on fluoxetine and n-3 supplement for MDD with remission of depressive symptoms  
– n-3 supplement (6:1 EPA to DHA) dosing: 2x 1g soft gels/day  
– Tapered off fluoxetine; continued n-3 supplement  
– Increase in general anxiety and insomnia/nighttime awakenings  
– Symptoms resolved with discontinuation of n-3 supplement |

### Table 6. Additional trials for n-3 fatty acids in anxiety and anxiety-related disorders (previously in DSM-4)

<table>
<thead>
<tr>
<th>Primary Literature</th>
<th>Key Information</th>
</tr>
</thead>
</table>
| Fux, et al. (2004)\(^{58}\) | – Placebo-controlled, cross-over trial with a small sample of 11 patients with OCD on stable maximally tolerated dose of SSRI treated with matching placebo vs. 2g/day n-3 supplement (96% EPA) x 6 weeks  
– Baseline Hamilton Rating Scales for depression (HAM-D) and HAM-A scores of 11.3 (±7) and 14.3 (±8) respectively – no diagnosis of major depression and mild anxiety  
– Statistically significant/clinically insignificant change in Yale–Brown Obsessive-Compulsive Scale (YBOCS) (mean 17.6 [±6] by week 6 on placebo and to 18.5 [±4] on EPA, p=0.001); no changes in HAM-D or HAM-A |
| Zeev, et al. (2005)\(^{59}\) | – Open-label trial with a small sample of 6 patients with PTSD  
– Continued psychotropics + 2g/day n-3 supplement (96% EPA) x 12 weeks  
– 2 dropouts during first 4 weeks and “the only statistically significant change was a marked worsening of the avoidance subscale in all three of the four patients who demonstrated a general tendency towards worsening scores on all scales.” |
| Buydens-Branchey, et al. (2008)\(^{60}\) | – Double-blind, randomized trial with a small sample size of 22 patients undergoing substance abuse outpatient treatment program treated with placebo vs. combination n-3 supplement 5 caps/day (EPA+DHA) x 12 weeks (after completing 12 weeks of initial rehab)  
– Patients with diagnosis of MDD or bipolar disorder excluded  
– Significant decreases in anger and anxiety scores with large effect sizes (f=0.0506 and f=0.567, respectively) |
| Lesperance, et al. (2011)\(^{56}\) | – High-EPA n-3 fatty acid supplementation reduced depressive symptoms only in patients without comorbid anxiety |

**Conclusions and Evidence-based Recommendations**

I. A diet rich in n-3 fatty acids is inversely associated with anxiety disorders\(^{49,51,58-59,61}\)

II. May consider n-3 fatty acid supplementation as below; see Figure 4\(^{49-51,56-60}\)

   a. Monitoring
      - Track changes in anxiety symptoms through mental health assistants (eg. GAD-7)
      - No efficacy lab monitoring recommended for clinical practice with n-3 fatty acid supplementation
      - Monitor for signs or symptoms of unusual bruising/bleeding
         - Bleeding time may be prolonged at n-3 doses >3g/day\(^{31}\)
         - Possible increased risk of bleeding in combination with SSRI

III. Further research is warranted using n-3 fatty acids in a patient population with a formal diagnosis of an anxiety disorder (eg. GAD)
Would recommend healthy, balanced diet and dietary consistency
- Increase consumption of fresh fruits, vegetables, whole grains, and n-3 fatty acids (anti-inflammatory fatty acids)
- Limit consumption of processed foods (pro-inflammatory n-6 fatty acids)
- Consider referral to nutritionist for meal planning and additional nutritional education (e.g., Mediterranean diet)

Would consider n-3 fatty acid supplementation for the following
- Consider trial of n-3 fatty acid supplementation:
  - GAD, substance-induced anxiety disorder, unspecified anxiety disorder, other anxiety disorder, or anxiety due to another medical condition (particularly CVD): consider antidepressant +/- psychotherapy +/- n-3 supplement augmentation
  - PD or OCD: consider with antidepressant +/- psychotherapy +/- n-3 supplement augmentation
  - For patients unwilling to trial antidepressants or other anxiolytics (except PD or OCD): consider psychotherapy +/- n-3 supplementation
- Consider for patients interested in natural supplementation
- Consider for patients who are pregnant or nursing
  - Fish oil supplement preferred over many dietary marine sources of n-3 fatty acids
  - Avoid mercury-containing fish during pregnancy
  - High-quality fish oil – purified, without concerns for mercury
  - n-3 supplement with safe side effect profile

Would NOT recommend/exercise caution with n-3 fatty acid supplementation for the following
- PTSD due to possible worsening of symptoms (particularly with high EPA concentration n-3 supplements)
- SAD or specific phobias due to lack of evidence supporting augmentation; typically treated with psychotherapy alone
- Would not recommend n-3 supplements with high EPA concentration – ≥60% EPA in treatment of anxiety disorders
- Patients with comorbid bipolar I disorder
  - n-3 supplementation may induce mania, similar to most antidepressants; no improvement in mania
  - If using in patients with bipolar disorder, recommend n-3 supplementation in combination with a mood stabilizer
- Patients with high risk of bleeding or history of bleeding
  - In combination with serotonergic drugs, bleeding risk may be increased
- Patients with poor adherence
  - High pill burden for doses ≥2 g/day
  - Minimize compromising primary antidepressant pharmacotherapy or move focus away from mainstays of therapy

Figure 4. Evidence-based recommendations when considering n-3 fatty acid supplementation in anxiety disorders
References

19 Blevins


### Appendix A. Antidepressant classes and agents

| Selective Serotonin Reuptake Inhibitors (SSRIs) | Citalopram, escitalopram, fluoxetine, paroxetine, sertraline |
| Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) | Duloxetine, venlafaxine, levomilnacipran, desvenlafaxine, milnacipran |
| Norepinephrine/Dopamine Reuptake Inhibitor (NDRI) | Bupropion |
| Tricyclic Antidepressants (TCAs) | Amitriptyline, imipramine, nortriptyline, desipramine, doxepin, amoxapine, clomipramine, maprotiline, protriptyline, trimipramine |
| Monoamine Oxidase Inhibitors (MAOIs) | Isocarboxazid, phenelzine, selegiline, tranylcypromine |
| Other/Atypical Antidepressants | Vortioxetine, trazodone, nefazodone, mirtazapine, vilazodone |

### Appendix B. Additional pharmacological agents for treatment of anxiety disorders

| Hydroxyzine | Sedating, first-generation antihistamine Usually short-term acute treatment of GAD, up to 4 weeks |
| Beta-blockers | Atenolol or propranolol or pindolol May provide relief for physical symptoms of anxiety, such as tremor, palpitations, and shortness of breath |
| Buspirone | Anxiolytic Usually short-term acute treatment of GAD |
| Anticonvulsants | Gabapentin Valproic acid |
| Pregabalin | Structural analog of gamma-aminobutyric acid (GABA) Monotherapy or augmentation of antidepressants in GAD |
| Quetiapine | Second-generation/atypical antipsychotic Monotherapy in GAD or augmentation of antidepressants in OCD or PTSD Typically reserved for treatment-resistance |
| Benzodiazepines | Clonazepam, lorazepam, alprazolam, diazepam, chlordiazepoxide, temazepam Rapid symptomatic relief for acute distress LIMIT USE |

### Appendix C. Symptom rating scales for GAD

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Anxiety Scale (HAM-A)</td>
<td>Gold standard for GAD symptoms; 14-item scale Clinician-rated</td>
<td>Mild: 0-17 Mild-moderate: 18-24 Moderate-severe: 25-30</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder 7-item Scale (GAD-7)</td>
<td>Commonly used in practice for GAD; 7-item scale Patient self-report (assess symptoms over last 2 weeks)</td>
<td>None: 0-5 Mild: 6-10 Moderate: 11-15 Severe: 16-21</td>
</tr>
<tr>
<td>Beck Anxiety Inventory (BAI)</td>
<td>Distinguishes anxiety (GAD) from depression; 21-item scale Patient self-report</td>
<td>Minimal: 0-7 Mild: 8-15 Moderate: 16-25 Severe: 26-63</td>
</tr>
</tbody>
</table>