Omega-3 Fatty Acids in Autism and other Neuropsychiatric Disorders

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The Prevalence of Autism Increased Dramatically during the Last Quarter Century

A traditional diet in the Arctic regions of North America provides 15-19 grams/day of EPA + DHA (omega-3 fatty acids).

In the U.S. < 1 gram/day of omega-3 fatty acids are consumed.
Number of Scientific/Clinical Papers\textsuperscript{1} on Omega-3 Fatty Acids Published per Year

\begin{itemize}
  \item 1963-2004
  \item Only research papers on Medline are reported.
\end{itemize}
Nutritional Deficiencies in Developed, Western Nations

- The modern Western diet is profoundly depleted of essential fatty acids (omega-3 >> omega-6).¹
- A recent study suggests that the modern Western diet is also profoundly depleted of essential trace minerals²
  - Compared the mineral content of 40 different fruits and vegetables from the UK between 1930s and 1980s
  - Marked reductions in Ca++, Mg++, Cu++, Na+ in vegetables
  - Marked reductions in Mg++, Fe++, Cu++, K+ in fruits

² Mayer A-M. Historical changes in the mineral content of fruits and vegetables. *British Food Journal* 1997;99:207-211.
OMEGA-3 FATTY ACIDS IN BIPOLAR DISORDER: Study Design

• Double-blind placebo-controlled 4-month trial
• N = 30 bipolar outpatients (mostly Type I)
• All subjects had mania/hypomania within past 1 year
• Randomized to 9.6 g/day omega-3 vs. placebo (olive oil)
• Concomitant meds left unchanged
• 8 entered study on no other drug therapy
• Main outcome measures:
  - Recurrence or lack of response
  - SCID Status at end of trial

Investigators
- Andrew L. Stoll, M.D.  
  Harvard Medical School
- Emanuel Severus, M.D., Ph.D.  
  Free University of Berlin
- Lauren Marangell, M.D.  
  Baylor College of Medicine
- Marlene Freeman, M.D.  
  University of Arizona
Survival Analysis (hypothetical)

A perfect result: all patients make it through the 4 month study without a recurrence of symptoms.

A lousy result: nearly all of the patients had a recurrence of symptoms during the 4 months of the study.

Proportion remaining well (%) vs. Time (days)

- 50% relapsed by day 30
OMEGA-3 IN BIPOLAR DISORDER: Survival Analysis

Survival Analysis

Time (days)

p = 0.002 (Mantel-Cox)

Proportion of patients remaining in study (%)

Stoll et al. Arch Gen Psychiatry 1999

omeg-3
N = 14

olive oil
N = 16
OMEGA-3 FATTY ACID MONOTHERAPY: Survival Curve

Survival Curve

Cumulative Survival (%) vs Time (days)

- omega-3
  - N = 4
- olive oil
  - N = 4

p = 0.04 (Mantel-Cox)

Stoll et al. Arch Gen Psychiatry 1999
OMEGA-3s IN SCHIZOPHRENIA

- Evidence for phospholipid abnormalities in schizophrenia\(^1\).
- Open-label data suggest benefits of EPA\(^2\).\(^3\).
- EPA (n=15) superior to placebo (n=14) & DHA (n=16) in a 3-month, add-on, double-blind trial\(^4\).
- EPA (n=14) superior to placebo (n=12) in medication-free subjects in a separate 3-month trial\(^4\).
- Outcome in schizophrenia better in fish consuming nations.\(^5\)

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\(^1\) Horrobin *Schizophr Res* 1998;30:193-208.
OMEGA-3 FATTY ACIDS in UNIPOLAR DEPRESSION

Considerable Indirect Efficacy Data Exists

1. 4 studies reported lower blood omega-3 fatty acids (usually EPA) in patients with major depression.
2. Epidemiological evidence points to lack of omega-3 fatty acids as world-wide risk factor for depression.
3. The neurochemical effects of omega-3 depletion are consistent with models of depression.
4. Abnormalities in the omega-3 dependant eicosanoid and cytokine pathways are present during major depression.
5. Open-label case series reporting antidepressant effects.
6. Double-blind data reporting the antidepressant effects of fish oil in bipolar disorder.
7. Reduced rates of seasonal mood shifts in Iceland and Japan.
Omega-3s in Unipolar Depression

Direct Evidence of Efficacy

Efficacy of EPA >>> DHA

4 double-blind, placebo-controlled trials
- EPA add-on in unipolar depression\(^1\) ................. effective
- EPA add-on in recurrent unipolar depression\(^2\) .......... effective
- EPA + DHA (3:2) add-on in unipolar depression\(^3\) .... effective
- DHA monotherapy in unipolar depression\(^4\) .............. ineffective


FISH CONSUMPTION AND MAJOR DEPRESSION AROUND THE WORLD

- New Zealand (5.8%)
- Canada (5.2%)
- France (4.5%)
- W. Germany (5.0%)
- USA (3.0%)
- Puerto Rico (3.0%)
- Korea (2.3%)
- Taiwan (0.8%)
- Japan (0.12%)

$r = -0.84$
$p < 0.005$

Adapted from: Hibbeln JR. *Lancet* 1998
OMEGA-3 FATTY ACIDS: Critical in Brain Development

- Concentrated in breast milk (not in U.S. formula).
- DHA is one of the most abundant lipids in brain.
- DHA crucial for visual system development.
- DHA improves cognitive function in infants. (explains breast-fed vs. bottle-fed disparity)
- World-wide rates of major depression and schizophrenia outcome inversely correlated with national fish consumption.
- Omega-3 fatty acids are depleted in the U.S. diet.
OMEGA-3 FATTY ACID DEPLETION IN POST-PARTUM WOMEN

- After 1 child: Low DHA
- After 2 children: Lower DHA
- After 3 children: Lowest DHA
- Triplets > twins:
- Triplets:
- Lactation: At 16 weeks, decreased DHA
OmegaBrite™ (EPA:DHA = 7:1) in Huntington’s Disease

**10-Dec-00:**
HD patient W, in the EPA Study, began taking OmegaBrite for 2 grams of EPA/day (6 capsules)

**28-Feb-01:**
William wrote this note to his wife.

**27-Apr-01:**
William wrote this note for his wife.

IDEAL CHARACTERISTICS OF A FISH OIL SUPPLEMENT

- Maximum concentration
  - >90% now available
- No heavy metal or organic carcinogens
  - Any concentrated fish oil (> 50%) is convincingly safe
- No fishy aftertaste, smell, or “repeat”
  - Mitigated by encapsulating under nitrogen to minimize oxidation
- EPA >> DHA
  - The data points to EPA as the active ingredient

Locke CA, Stoll AL. World Rev Nutr. 2001
**OmegaBrite**

**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size: 3 capsules</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
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<tbody>
<tr>
<td>Calories</td>
<td>15</td>
<td></td>
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<tr>
<td>Calories from fat</td>
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<tr>
<td>Total fat</td>
<td>1.5 g</td>
<td>2%*</td>
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<tr>
<td>Polyunsaturated fat</td>
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<tr>
<td>Cholesterol</td>
<td>0 g</td>
<td>0%*</td>
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<tr>
<td>Vitamin E (as d-a-tocopherol)</td>
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<tr>
<td>EPA (eicosapentanoic acid)</td>
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<tr>
<td>DHA (docosahexanoic acid)</td>
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<tr>
<td>Other omega-3 fatty acids</td>
<td>90 mg</td>
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<tr>
<td>Omega-6 fatty acids</td>
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<td></td>
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<tr>
<td>Other fatty acids</td>
<td>60 mg</td>
<td></td>
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</tbody>
</table>

*Percent Daily Values are based on a 2,000 calorie diet.*

Daily value not established.

Ingredients: fish oil, gelatin, glycerin and vitamin E (as d-a-tocopherol).

Distributed by Omega Natural Science, Inc. Waltham, MA 02451 www.omegabrite.com
OMEGA-3 FATTY ACIDS Usage Guide

- Fish oil preferred to flaxseed oil at this time.
- **Adult starting dosage**: 1 g EPA/d (or 1-2 g EPA + DHA/d)
- **Usual dosage range**: 1 - 6 g/d of EPA (or EPA + DHA).
- **BID schedule optimal** (qd, TID also ok).
- Food increases omega-3 absorption.
- Highest content of EPA desirable.
- Antioxidants (vitamins C 250-500 mg/d & E 200-400 IU/d) may prevent in vivo degradation of omega-3s.
- If GI upset: Divide dose, ginger root, Daikon radish
- **Caution**: Xenical; Anticoagulants or high-dose NSAID?

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1 If pregnant or nursing, higher amounts of DHA are required for optimal brain and visual system development in the baby. The 3rd trimester is crucial, because most brain growth occurs then. A typical EPA:DHA ratio of 3:2 is usually suggested here.
POTENTIAL ADVERSE EFFECTS: Fish oil

• **Fishy aftertaste** (the “repeat”)
  – Due to rancidity of fatty acids through oxidation

• **Gastrointestinal disturbance**
  – Benign and generally only seen at high dosage

• **Hypervitamosis A**
  – Only if high-dose cod liver oil used

• **Impaired platelet function**
  – Theoretical risk of bleeding only. Unlike aspirin, EPA binds platelets reversibly and inhibits aggregation only partially

• **Exposure to heavy metals or chemical pollutants**
  – **not** an issue with concentrated fish oils due to distillation(s) and other purification steps
  – It is an issue with fish
FLAX OIL
(\(\alpha\)-Linolenic acid)

Advantages

- More palatable than fish oil
- Native flax oil more concentrated than native fish oil
- May be used in recipes (but not as a frying oil)

Drawbacks

- Limited conversion of ALA to longer chain omega-3 in humans
- No controlled data in neuropsychiatric disorders
- May cause more manic switch than fish oil

Usage: 1 tablespoon (~7 g of ALA) qd-TID or use capsules. Omega-3 dosage with flax oil should be the same or higher as that used for fish oil, due to the incomplete conversion of ALA to EPA.
FLAXSEED BENEFITS

• Oil contains a high concentration of a-linolenic acid (ALA, a short-chain omega-3), and likely has many health benefits.
• Excellent treatment for constipation:
  – Seed husks are a good fiber source.
  – Oil has mild laxative effect.
• Keep dosage below 3-4 tablespoonfuls per day

Simopoulos A. 1999
FLAXSEED TOXICITY!? 

- Inexplicable link of ALA to prostate cancer:
  - At least 4 epidemiological studies associated ALA content of blood with elevated rates of prostate cancer.\(^1\)\(^-\)\(^4\)
  - In vitro data also suggests ALA promotes prostate cancer.\(^5\)
  - Omega-6 fatty acids also promote tumorigenesis.\(^5\)
  - In contrast, adequate EPA **inhibits** tumorigenesis.\(^5\)

- The seed husks of flaxseeds (also lima & cassava beans) contain cyanogen, which is converted to thiocyanate. Thiocyanate inhibits iodine uptake by thyroid, possibly leading to goiter. Cyanogen is destroyed during cooking. Flaxseed **oil** is free of cyanogen.\(^6\)

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\(^3\) Harvei et al. *Int J Cancer* 1997;71:545-551
\(^6\) Simopoulos A. 1999
Dietary Patterns of Early Modern Humans

- 25-50% of dietary protein came from aquatic sources\(^1\)
  - Freshwater or Marine: fish, crustaceans, mollusks, waterfowl
- Methodology
  - Direct
    - \(^{13}\)C and \(^{15}\)N isotope measurements of femur collagen\(^1\)
    - Paleoarcheological samples: fish & shellfish remains
    - Dental wear patterns
  - Indirect
    - Cave art
    - Artifacts: weapons, nets, fish jewelry
- Inland-dwelling Neandertals relied on large herbivores

\(^1\)Richards et al. *Proc Nat Acad Sci.* 2001
Why not just eat more fish?

WILD FISH: Classifications

• Locale
  – Freshwater fish: No body of water in No. America is safe.
    • Assume all fish are contaminated.
  – Saltwater fish
    • Less predictable contamination

• Size and place in the food web
  – Small prey fish: Short-lived, plentiful, and prey to bigger fish
    (anchovies, sardines, menhaden, etc.): Little or no contamination
  – Large Predators: Long-lived and predatory (tuna, salmon, cod,
    etc.): Risk of pollutant accumulation

• Lipid storage
  – Fish that store lipids in liver (e.g. cod, swordfish, etc.):
    • Flesh is relatively clean, but little or no omega-3s.
  – Fish that store lipids in muscles (e.g. salmon, tuna, etc.):
    • Flesh is the omega-3 source, but variable pollution effects.

www.fda.gov
Isn’t Farmed Fish Safe?

- **Aquaculture economics**
  - Improving, but still more expensive than commercial fishing

- **Environmental impact**
  - Improving in developed countries due to regulations & technology.
  - Worsening in developing countries

- **Farmed fish species: Food value**
  - **Salmon**: Generally good omega-3 source. Salmon require omega-3 fatty acids for growth, but the amount is variable and could be less or more than in wild salmon. Dye is added to farmed salmon to make them pink & appealing. The dye is chemically similar to the pigment that makes wild salmon pink (from a shellfish prey’s shell). There is NO current requirement for industry to disclose contamination or omega-3 content.
  - **Catfish, Talapia, Shrimp**: No omega-3s at present

- **Contamination**
  - Recent reports of high mercury and PCBs in farmed fish due to almost universally contaminated feed[^1].

TERRESTRIAL SOURCES OF OMEGA-3 FATTY ACIDS

- Flaxmeal or flaxseed oil
- Perilla Oil
- Chia
- Borage seed oil
- Hemp oil: Too much omega-6 (n6:n3 = 4:1)
- Wild game
- Omega-3 enriched eggs\(^1,2,3\)

\(^2\)Three omega-3 enriched eggs = 1 serving fatty fish.
\(^3\)The Country Hen. Box 333, Hubbardston, MA 01452  [www.countryhen.com](http://www.countryhen.com)
Omega-3s and Autism: State of the Science

- Still no double-blind, placebo-controlled trials of omega-3s in autism.
- However, indirect data continues to mount, indicating that omega-3s may be helpful in autism.
  - The epidemiological evidence of a rapidly rising incidence of autism is consistent with the progressive depletion of omega-3s in the 20th C.
  - Blood levels of omega-3 fatty acids appears to be lower in children with Autism.
  - The biochemical effects of omega-3s are consistent with some of the leading hypotheses regarding the pathophysiology of autism, especially inflammatory mechanisms.
  - Omega-3s, in controlled studies, have been shown to be helpful in every neuropsychiatric disorder tested to date.
INDIRECT EVIDENCE FOR OMEGA-3 DEFICIENCY IN AUTISM

• Reduced frequency and shorter duration of breastfeeding in autistic children compared to their normal siblings\(^1,2\).
• Abnormal heart rate variability\(^3\).
• High rates of stereotyped behaviors in omega-3 deficient rhesus monkeys\(^4\).
• High rate of inflammatory bowel disease.

Vancassel et al.  
Plasma fatty acid levels in autistic children.  

- **Purpose:** To compare the phospholipid fatty acids in the plasma of a population of autistic subjects compared to mentally retarded controls.

- **Results:**
  - Autistic children had a 23% lower blood level of 22:6n-3 (DHA), when compared to MR controls.
  - Autistic children had a 20% lower blood level of total omega-3 (n-3), without a significant reduction in omega-6 fatty acids (n-6), when compared to MR controls.
  - This led to a 25% increase in the omega-6: omega-3 ratio.

- **Purpose**: To compare behavior, learning, and health problems in 2 groups of boys ages 6 to 12.
  - #1: Low blood levels of omega-3 or omega-6 fatty acids.
  - #2: High levels of omega-3 or omega-6 fatty acids.

- **Results**:
  - A greater number of behavior problems, assessed by the Conners' Rating Scale, temper tantrums, & sleep problems were reported in subjects with lower blood omega-3 levels.
  - More learning and health problems were found in subjects with lower blood omega-3 levels.
  - More colds and more antibiotic use were reported by those subjects with lower total omega-6.

- There is increasing evidence that abnormalities of fatty acid and membrane phospholipid metabolism play a part in many neurodevelopmental and psychiatric disorders.

- ADHD, dyslexia, dyspraxia and autism fall within a *phospholipid spectrum of disorders*.

- This proposal could explain:
  - The high degree of co-morbidity between these conditions,
  - Their aggregation within families (through a genetically-linked biochemical abnormality).
  - Effect of our changing diet (ω-3s) on a population level
Clinical Experience with Omega-3s in Autism

- Informal surveys of past DAN! audiences.
- Numerous e-mail descriptions and testimonials.
- Dr. Paul Hardy has treated several hundred children with autism and related neurodevelopmental disorders with omega-3 fatty acids¹.
  - He reports a “dramatic response” in ~ 50% of kids.

WE DESPERATELY NEED CONTROLLED STUDIES!

¹Personal communication with Dr. Hardy on 3-21-05
PHASES OF MEDICAL RESEARCH

Scientific hypothesis

Clinical observation

Preliminary “open-label” or uncontrolled trial

Preliminary controlled study

Definitive controlled study
The Importance of Preliminary “Open-Label” or Uncontrolled Studies

- “Open-label” means both the patient and clinician/researcher know that the patient is receiving the “active” drug.
- This is where major discoveries are made.
- Inexpensive
- Huge, double-blind, placebo-controlled studies are crucial for confirmation of initial findings
The Importance of Scientifically Controlled Research

- Evaluates preliminary uncontrolled findings
- Permits other researchers to replicate methods
- Permits patients, families, and clinicians to evaluate the merits & drawbacks of a new treatment
- Permits insurance companies, the FDA, and other regulatory agencies to evaluate the merits and drawbacks of a new treatment
OMEGA-3 FATTY ACIDS IN AUTISM: Unanswered Questions

• Are omega-3s truly effective in autism?
• If so, which omega-3(s) is the active component (EPA, DHA, ALA) - or are all 3 active?
• What is the proper dosage?
• Oral vs. IV?
• Are there biological markers that will predict omega-3 response?
• Are there subtypes of autism that preferentially respond to omega-3s?
FINANCIAL DISCLOSURE
Andrew L. Stoll, M.D.
Dir., Psychopharmacology Research Lab., McLean Hospital
Assistant Professor of Psychiatry, Harvard Medical School

- **Current Research Grant support:** The Stanley Foundation.
- **Past Research Grant support:** The Poitras Charitable Fund, and the Hirschhorn Foundation. Abbott Laboratories, Janssen Pharmaceutica, Eli Lilly & Co., Solvay, NIH (NCCAM) and Harvard Medical School,

- **Current Speaker's Bureau:** Harvard Medical School (Dept. Of Continuing Medical Education), Abbott Laboratories, Bristol-Myers Squibb, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica,

- **Past Speaker’s Bureau:** Astra-Zeneca, Smith-Kline Beecham, Eli Lilly & Co., Organon, Pfizer (Parke-Davis), and Wyeth-Ayerst.

- **Current consulting:** Omega Natural Science, Inc.

- **Past Consultant:** Abbott Laboratories, Bristol-Myers Squibb, Glaxo, Eli Lilly & Co., Pfizer (Parke-Davis), and CX Research, Inc.

- **Major Stockholder:** None.

- **Other:** Dr. Stoll has published a book on omega-3 fatty acids: "The Omega-3 Connection" (Simon and Schuster, 2001). His wife, Carol A. Locke, M.D. creates nutraceutical products for psychiatry and general medicine and is the Founder and CEO of Omega Natural Science, Inc. (OmegaBrite™).