

## What's so fishy? The health benefits of fish oil on disease prevention and health maintenance

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## Objectives/Goals

- Review the various omega-3 fatty acids (DHA, EPA, ALA) and their sources
- Discuss the proposed health benefits of omega-3 fatty acids
- Review the adverse events and interactions associated with the use of omega-3 fatty acids

## Fish Oil

- Omega-3 Fatty Acids
  - Appropriately termed n-3 polyunsaturated fatty acids (n-3 PUFA)
- Major "omega-3s"
  - Docosahexaenoic acid (DHA)
  - Eicosapentaenoic acid (EPA)
  - Alpha linolenic acid (ALA)
- EPA/DHA are the predominant omega-3s in fish oil



Image from <http://www.alispagnola.com/Free/fishbowl4.jpg>

## Omega-3 Sources

- **DHA/EPA**
  - Herring, salmon, tuna, mackerel and lake trout recommended by the American Heart Association
  - Cod liver oil, shellfish, shark liver oil
  - Cold water algae (DHA)
- **ALA**
  - Flaxseeds, walnuts, soybeans, and canola oil



AHA. Fish and omega-3 fatty acids. Accessed Dec 2009.  
Anderson BJ, et al. *Lipids in Health and Disease* 2009; 8:331-1-20.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.

## Reported Uses of Fish Oil

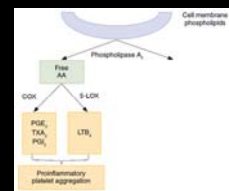
- FDA approved
  - Hypertriglyceridemia
- Likely effective
  - Cardiovascular disease
- Possibly effective
  - Age-related maculopathy, angioplasty, asthma, atherosclerosis, ADHD, cachexia, cancer, depression, inflammatory bowel disease, neuroprotective, obesity, osteoporosis, rheumatoid arthritis, skin-aging, stroke, etc



Image from <http://inbaandradokh.files.wordpress.com/2008/07/health.gif>  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Rupp H. *Adv Ther* 2009; 24(7):675-690.

## Process of Inflammation

- Arachidonic acid (AA) is a n-6 PUFA stored in cell membranes in immune cells
- Converted to proinflammatory agents by COX and 5-lipoxygenase (5-LOX)

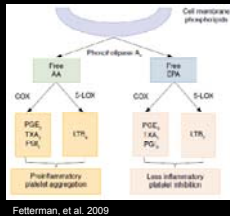


Fetterman, et al. 2009

Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. *UpToDate*. 2009.  
Rupp H. *Adv Ther* 2009; 24(7):675-690.

## Anti-inflammatory Actions

- EPA and DHA consumption
  - Replaces arachidonic acid available for conversion
  - Competes with AA for COX and LOX
    - Mainly EPA
    - Converted to prostaglandin E3 (PGE<sub>3</sub>), thromboxane A3 (TXA<sub>3</sub>), and leukotriene B5 (LTB<sub>5</sub>)



Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. *Lipidology*. 2009.  
Rupp H. *Adv Ther* 2009; 26(7):675-690.

## Anti-inflammatory Actions

- PGE<sub>3</sub>, TXA<sub>3</sub>, and LTB<sub>5</sub>
  - Less proinflammatory effects
  - May be antagonistic
- EPA and DHA decrease production of inflammatory cytokines
  - Interleukins
  - Tumor necrosis factor- $\alpha$

Calder P. *Am J Clin Nutr* 2006; 83:1505S-15S.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. *Lipidology*. 2009.

## Anti-inflammatory Actions

- Asthma
  - Fish oil decreases production of these cytokines and improves symptoms
  - Predominantly seen in patients with exercise-induced asthma
- Crohn's disease
  - Increased remission rates and decreased steroid use
- Rheumatoid arthritis
  - Improvement in joint tenderness, swelling, duration of morning stiffness, and grip strength
  - Decreased NSAID use



Image from <http://www.elsevier.com/locate/jplip>  
Calder P. *Am J Clin Nutr* 2006; 83:1505S-15S.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009;66:1169-79.

## Cardiovascular Benefits



- Benefits first documented in Greenland Eskimos
- Small trials and case reports have shown up to a 23% reduction in overall mortality and 32% reduction in death from CV causes
  - For comparison, statins reduce by 13% and 22% respectively
- DHA has shown to have greater benefit than EPA

Breslow J. *Am J Clin Nutr* 2009; 83:1477S-82S.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.

## Cardiovascular Benefits

- Decrease blood lipids
  - Triglyceride reduction up to 25% - 30%
- Reduce blood pressure and heart rate
  - 3-5 mm Hg systolic and 2-3 mm Hg diastolic
  - HR reduction of 1-2 bpm
- Improve cardiac relaxation, filling, and output
  - By reducing HR, more time is allotted to diastolic filling, allowing greater cardiac output

Breslow J. *Am J Clin Nutr* 2009; 83:1477S-82S.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
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## Cardiovascular Benefits

- Antiplatelet/anticoagulant effects
  - Reduce TXA<sub>2</sub> production
- Antiarrhythmic effects
  - DHA/EPA inhibit calcium channels
  - Hyperpolarize myocytes
  - Decreasing arrhythmic occurrences



Breslow J. *Am J Clin Nutr* 2009; 83:1477S-82S.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Rupp H. *Adv Ther* 2009; 26(7):675-690.

Image from [http://www.hopewellvet.com/images/business-ekg\\_nflay.jpg](http://www.hopewellvet.com/images/business-ekg_nflay.jpg)

## Neuroprotective Benefits

- Reduce neurotransmitter excitability and injury following ischemia
- DHA shown to be effective in reducing functional and anatomical changes in nerve cells
- Evidence to suggest that n-3 PUFAs may reduce oxidative stress
  - A chief cause of neuronal damage



Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. UpToDate. 2009

Parker G, et al. *Am J Psychiatry* 2006; 163(6):969-77.

Image from <http://www.legaljuice.com/homer-simpson-brain2.jpg>

## Neuroprotective Benefits

- Alzheimer's disease
  - Patients have low serum and brain cell membrane levels of DHA
  - Animal studies showed diets low in DHA resulted in impaired learning and cognition
    - Reversed with DHA supplementation
  - May reduce the accumulation of  $\beta$ -amyloid over 70%

Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. UpToDate. 2009

Parker G, et al. *Am J Psychiatry* 2006; 163(6):969-77.

## Side Effects

- Number one complaint: fishy taste/breath
  - May be improved by chilling or freezing capsules
  - Consider enteric coated, odorless capsules
- Dose-dependent gastrointestinal upset
  - Nausea, heartburn, indigestion, upset stomach, diarrhea



Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. UpToDate. 2009

Top image from <http://i51.photobucket.com/albums/i374/guppy/thehuman/sinkyfish.gif>  
Lower image from [http://www.dumbadum.org/images/pic-sounds/letter-u/upset\\_stoma](http://www.dumbadum.org/images/pic-sounds/letter-u/upset_stoma)

## Side Effects

- Small increases in glucose levels and LDL seen
  - Clinically insignificant
- Allergic reactions
  - Swelling, itching, shortness of breath

Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. UpToDate. 2009

## Drug Interactions

- Antiplatelets and anticoagulants
  - With more than 3 grams per day
- Antihypertensives
  - Fish oil can decrease blood pressure
- Orlistat (Xenical®, Alli®)
  - May decrease fish oil absorption



Image from <http://drugrecallwatch.files.wordpress.com/2009/08/alli-imagebox.jpg>  
Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.  
Mozaffarian D. UpToDate. 2009

## Which Supplement to Choose?

- Concerns about mercury contained in fish oil
  - Look at fish source, smaller fish (anchovies, sardines) have decreased exposure to contaminants
- Pay attention to the amount of DHA and EPA, not just the amount of total fish oil or omega-3 fatty acids
  - Best ratios are DHA:EPA 2:3 to 3:2
  - Doses have ranged from as low as 500 mg and up to 12000 mg total fish oil per day
  - Doses under 3 grams per day given "generally recognized as safe" (GRAS) status by the FDA



Image from <http://www.sustainablefish.net/wp-content/uploads/2008/12/sardine.jpg>  
Anderson B, et al. *Lipids in Health and Disease* 2009; 8(33):1-20.  
Felleman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.

## Which Supplement to Choose?



[http://images01.ox.com.ph/ua/1/05/21/03/00421\\_1.jpg](http://images01.ox.com.ph/ua/1/05/21/03/00421_1.jpg)



[http://www.walgreens.com/dmimages/cache/07431216887\\_220x220\\_s.jpg](http://www.walgreens.com/dmimages/cache/07431216887_220x220_s.jpg)

## Which Supplement to Choose?

- Go for the "USP Verified" brand
  - Pharmavite®, Sunmark®, Berkley & Jensen®, Equaline®, Nutri Plus®, Nature Made®, Kirkland®
- Set standards for purity and quality
  - Random "off-shelf" testing



Image from [www.usp.org/images/dsvp\\_mark.gif](http://www.usp.org/images/dsvp_mark.gif)  
Anderson B, et al. *Lipids in Health and Disease* 2009; 8(33):1-20.  
Fetterman J, et al. *Am J Health-Syst Pharm* 2009; 66:1169-79.

## Lovaza® (formerly Omacor®)

- Only prescription omega-3 fatty acid
  - 1000 mg omega-3
  - 465 mg DHA
  - 375 mg EPA
- Highly purified
  - Do not freeze
- 4 capsules daily (4 grams) in 1 – 2 doses



Image from <http://www.lovaza.com>  
Lovaza [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.  
Rupp, H. *Adv Ther* 2009; 26(7):675-690.

## Take Home Points

- DHA and EPA are the chief omega-3s in fish oil
- Major beneficial effects related to cardiovascular diseases, inflammatory states, and neurologic diseases
  - Much of the data gained from small trials and case reports/series; large, randomized controlled trials are lacking
- Recommend supplements based on total DHA/EPA with a ratio around 1 and "USP Verified"
  - Up to 3 grams per day of total fish oil is GRAS
  - AHA recommends two 3-oz servings of fatty fish per week or 1000 mg of total DHA/EPA daily for cardiovascular disease

## True or False?

- The most important factor in selecting the appropriate omega-3 fatty acid supplement is the total amount of omega-3 fatty acids per unit dose.
- The American Heart Association recommends consumption of fatty fish, such as mackerel and lake trout, for the natural source of fatty acids.
- Cold water fish, such as salmon or tuna, provide sufficient amounts of the three omega-3 fatty acids (DHA, EPA, and ALA) that the human body cannot synthesize.

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