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Omega-3 fatty acids

- Go to www.vitacost.com and search for either "MegaEFA" or "Nordic Ultimate Omega"; discuss with Dr. Wilson
- Background
    - Essential polyunsaturated fatty acids (PUFA); essential fatty acids (humans cannot make these on their own
    - Include:
        - eicosapentaenoic acid (EPA)
            - may have more antidepressant qualities
            - may not have anti-suicide properties
            - precursor to DHA
        - docosahexaenoic acid (DHA)
            - may have more anti-manic qualities
            - may have anti-suicide properties
            - selectively concentrated in synaptic neuronal membrane
            - contributes to unique biophysical properties that mediate receptor activity and signal transduction
    - Found in:
        - Coldwater fish (e.g., salmon, halibut)
        - Plant sources rich in alpha-linolenic acid, which can be converted in tissue to EPA/DPA:
            - Canola oil—high amounts of alpha-linolenic acid and linoleic acid, which can be converted to arachidonic acid (see below)
            - Flax seed
            - Mungo bean
        - Seed oils—high amounts of omega-6 fatty acids
            - Soybean oil—high amounts of omega-6 fatty acids
            - Corn oil
    - Functions by:
        - First, a critical component is increasing the ratio of omega-3 to omega-6 fatty acids and omega-3 fatty acids to arachidonic acid
        - In central nervous system:
            - Increases serotonergic neurotransmission
            - Alters dopaminergic neurotransmission
            - Regulates corticotrophin-releasing factor
            - Inhibits phosphokinase-C
            - Suppresses phosphatidylinositol-associated second messenger activity (like lithium)
            - Increases dendritic arborization and synapse formation

        - Prevents neuronal pre-programmed death (apoptosis)
        - Improved cerebral blood flow
        - Regulates gene expression (e.g., increases production of gene product BDNF (brain-derived neurotrophic factor
    - May reduce certain harmful cytokines (part of the bodies immune/inflammatory response); these cytokines can stimulate the stress/cortisol response (potentially damaging neurons in the hippocampus) and worsen depression and anxiety
    - Vasodilatory
    - Anti-inflammatory, thus, with increased amounts of EPA/DPA, can outcompete arachidonic acid to reduce the production of eicosanoids and cytokines (see below)
        - The time it takes for EPA/DPA to outcompete arachidonic acid varies from 2 weeks to 12 weeks to 2-3 years (especially in the brain)
    - increase ketogeneis, producing ketone bodies that could bypass glucose utilization and improve energy supply to the brain
    - EPA (more than DHA) is a strong activator of peroxisome proliferator-activator receptor alpha, an important regulator of energy homeostasis and fatty acid beta-oxidation
- Arachidonic acid (AA) is an omega-6 PUFA that competes with EPA/DPA for membrane space and conversion to potent eicosanoids, increasing the eicosanoids which are pro-inflammatory and exacerbate dysfunction in:
    - Cardiovascular system
    - Kidneys
    - Bones
    - Central nervous system
- Benefits, general
    - Essential omega-3 fatty acids
        - May prevent and treat cardiovascular illnesses
            - Decreased risk of arrhythmias
            - Decreased risk of thrombosis
            - Decreased triglycerides
            - Decreased atherosclerotic plaque growth
            - Improved endothelial function
            - Possible improvement in hypertension
            - Reduced inflammatory response
            - Modulates heart rate variability via vagal mechanism
            - AHA recommends:
                - Eat fish at least twice-weekly
                - For general cardiovascular health: 400 mg to 1 g of EPA PLUS DPA/day;
                - If have coronary artery disease: 1 gram of EPA PLUS DPA/day
                - If hyperglyceridemia: 2-4 gram of EPA PLUS DPA/day
                - If more than 3 g/day, should be monitored by physician since can increase risk of bleeding

- Prevents and treats gastrointestinal, rheumatologic, bone, and respiratory illnesses
- May decrease the risk of breast, prostate, and lung cancer
- Lower tissue levels of omega-3 essential fatty acids are associated with
    - depression
    - suicide
    - cardiovascular disease
    - inflammatory disease
    - a genetic variant of phospholipase A2 that increases risk of interferon-induced depression
    - greater hostility and omega-3 supplementation decreased violence in inmates
- In utero exposure and supplementation in infant formula are associated with improved cognitive and visual performance in children
    - Adequate maternal intake of omega-3 essential fatty acids necessary for optimal in utero brain and nervous system development
    - DHA is selectively transferred to the developing fetus in utero
    - Omega-3 essential fatty acids decrease progressively during normal pregnancy
    - Intake by pregnant and lactating women in the US reaches only 20-60% of recommended intake
    - Inadequate intake increases the risk of intrauterine growth retardation and visual problems among children
    - EPA PLUS DHA at 2.7 g/day was superior to placebo in lengthening gestational age at delivery
- Central nervous system
    - In countries with lower per capita fish consumption, there is a 30- to 60-fold increased rates of :
        - Major depression
        - Post-partum depression
        - Bipolar disorders
    - In countries with higher per capita fish consumption, there is a lower prevalence of
        - Depressive symptoms
        - Seasonal affective disorder
        - Poorer course in schizophrenia
    - DHA may lower risk of dementia
    - Suggestions re: dose ranges:
        - EPA 1-2 g/day, OR
        - EPA >2 g/day PLUS DPA
    - Rates of homicide are higher in areas of the world with less fish consumption

- Evidence
    - Depression

- Gertsik et al, 2012: 1.2 g added to Celexa better than placebo
- Meta-analysis of the effects of EPA in Depression (Sublette, et al, 2012); 15 trials, 916 participants
    - supplements where EPA was greater or equal to 60% of the total dosage of EPA and DHA demonstrated benefit in depression
    - supplements where EPA was less than 60% of the total dosage of EPA and DHA were ineffective in depression
    - effective doses of EPA (in excess of DHA) were in the range of 200-2000 mg/d
- **Nemets et al, 2006; 28 children aged 6-12 yo with depression (first episode), RCT, omega 3 fatty acids 1000 mg (400 mg EPA and 200 mg DHA) vs. placebo for 16 weeks**
    - **Response rate 70% with omega-3 and 0% with placebo**
    - **Remission rate 40% with omega-3 and 0% with placebo**
- Sublette et al, 2006: low DHA is associated with increased suicidal behavior over 2 years in depressed patients
- Silvers et al, 2005: 77 adults with depression, 12 weeks, adjunctive, 0.6 g EPA PLUS 2.4 g DHA vs. placebo: both groups improved
- Su et al, 2003: 22 adults with depression, 8-week, adjunct, 4.4 g/d EPA PLUS 2.2 g/d DHA (elsewhere listed as a total of 9.6 g/d):effective
- Marangell et al, 2003: 25 adults with depression, 6 weeks, DB, 2 g/d DHA monotherapy, ineffective
- Peet and Horrobin, 2002: 70 adults with treatment-resistant depression, 12 weeks, add on therapy; 1, 2, or 4 g EPA
    - 1 g/day EPA effective
    - 2 or 4 g/day ineffective
- Nemets et al, 2002: 20 adults with depression, 2g/d EPA, 4 weeks, adjunct: effective
- Benefits, when present in some studies, occurred within two weeks
- Overall, 1-2 g/day supported as effective; optimal dose not clear; optimal ratio of EPA:DHA not clear
- No side effects in these studies

- Bipolar disorder
    - Sarris et al, 2012, meta-analysis, helpful for bipolar depression but not (statistically) for mania
    - Frangou et al, 2006: RCT, DB, EPA in bipolar depression, 1 g/d EPA OR 2 g/day EPA OR placebo; 12 weeks: some solid benefits
    - Osher, 2005: 12 adults with bipolar I were treated with open-label add-on omega 3 fatty acids (1.5-2 g/day of EPA)—80% achieved response with no side effects.
    - Post, 2003: EPA 6 grams/day failed to show benefit in bipolar depression.
    - Keck et al, 2002: RCT, DB, adjunctive EPA 6 g/d, 16 weeks, bipolar depression or rapid cycling: no differences
    - Stoll et al, 1999: 30 adults with bipolar I disorder; 16-week, adjunct, 6.16 g EPA and 3.36 g DHA: effective, mainly in depression

- Perinatal depression
  - Open-label, flexible-dose trial, EPA PLUS DHA at ~1.9 g/day, in depression during pregnancy: effective
  - RCT, DB, 0.5-2.8 g/day of EPA PLUS DHA, in post-partum depression: improvement but not different from placebo
  - Two negative studies:
    - Small open-label study of EPA PLUS DHA
    - DHA 200 mg/d
- Prevention or delay in psychosis
  - Amminger, 2010; 1.2 g/day, 12 weeks
- Schizophrenia
  - Vienna Omega-3 Study, high risk patients (13-25 yo), Amminger et al, 2015
    - No prior history of antipsychotic use
    - 12 weeks 1.2 g (700 mg EPA/480 mg DHA)
    - 10% of those receiving omega-3's converted to psychotic disorder
    - 40% of those receiving placebo converted to psychotic disorder
    - Those receiving omega-3's, at 90 months
      - 53% no psychiatric diagnosis vs. 32% placebo
      - 57% required inpatient care vs. 68% placebo
      - 17% required outpatient care vs. 26% placebo
      - 70% had full time job vs. 63% placebo
      - 69% with high GAF vs. 59% placebo
  - Emsley et al, 2002: RCT, DB, EPA 3 g/d: EPA > placebo in symptoms and in tardive dyskinesia
  - Peet et al, 2002: RCT, DB, EPA 1, 2 or 4 g/d: effective, greatest at 2 g/d
  - Peet et al, 2001: RCT, DB, EPA 2 g/d vs. DHA 2 g/d vs. placebo: EPA > DHA, EPA > placebo
  - Peet e al, 2001: RCT, DB, EPA 2 g/d vs. placebo: EPA > placebo and → less antipsychotic use
  - Fenton et al, 2001: RCT, DB, EPA 3 g/d: EPA = placebo
- Borderline personality disorder
  - Zanarini and Frankenburg: 30 adults with borderline personality disorder, 8 week, monotherapy, 1 g EPA, ineffective overall but improves aggression
- ADHD/learning disorders
  - 2006—pilot studies suggesting efficacy
  - Richardson and Puri: RCT, 12 weeks, monotherapy, essential fatty acids (480/d DHA PLUS 186 mg/d EPA PLUS 864 mg cis-linoleic acid PLUS 96 mg gamma-linolenic acid (GLA) PLUS 42 mg/d AA PLUS 60 IU vitamin E (as d,l-alpha tocopherol) or placebo: active treatment effective

        - Stevens et al: fatty acids (480/d DHA PLUS 80 mg/d EPA PLUS 96 mg GLA PLUS 40 mg/d AA PLUS 24 mg alpha-tocopherol acetate) vs. placebo: effective
        - Richardson and Montgomery: fatty acids (174 mg DHA PLUS 558 mg EPA PLUS 60 mg GLA PLUS 9.6 mg vitamin E) vs. olive oil placebo, RCT, DB: effective
        - 3 studies of fish oil PLUS primrose oil: effective
        - 2 published RCT, DB studies of supplemental DHA: negative
        - No adverse side effects
    - Autism
        - 2006—pilot studies suggesting efficacy
    - Dementia
        - Inconsistent results
- Side effects and risks:
    - loose stools
    - mild upset stomach
    - belching
    - fishy aftertaste and fishy breath
    - thins blood (so notify internist of use)
- Adding vitamin E may further reduce cytokine production
- Dosing (as ADJUNCT; NOT as primary treatment)
    - Depression:
        - EPA 1-2 g/day, OR
        - EPA >2 g/day PLUS DPA
    - Bipolar disorder:
        - 9-9.6 g/day (e.g., one 3000 mg cap three times-a-day) added to standard treatment
        - 2-6 g/day for bipolar spectrum disorders
    - Metabolic syndrome
        - 2 g/d EPA and 0.7 g/d DPA may reduce risk
    - ADHD/learning
        - 80-558 mg/d EPA and 174-480 mg/d DHA
            - Ratios (of EPA:DHA) studied: 1:2, 1:6, 4:1
        - 60-96 mg GLA
        - 9.6 mg or 60 IU vitamin E
    - Other
        - Schizophrenia/tardive dyskinesia: 2 g EPA/day
        - Rheumatoid arthritis and inflammation: 2.7 g/d EPA
        - Inflammatory bowel disease: 2.7-7 g/day EPA
        - Preterm labor/rate of miscarriages:
            - 2.7 g EPA/DPA reduced risk of preterm labor in pregnancy
            - 1 g/d DPA had similar effects in another study
    - Animi-3 (by prescription)
        - DHA/EPA
        - Folic acid
        - Vitamin B6
        - Vitamin B12

Please see http://bipolarchild.com/newsletters/0501.html

A Randomized Controlled Trial of Individual Family Psychoeducational Psychotherapy and Omega-3 Fatty Acids in Youth with Subsyndromal Bipolar Disorder

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OBJECTIVE: This pilot study evaluates efficacy of omega-3 fatty acid supplementation (Ω3), individual family psychoeducational psychotherapy (IF-PEP), and their combination in youth with subsyndromal bipolar disorders (bipolar disorder not otherwise specified [BP-NOS], cyclothymic disorder [CYC]).

METHODS: This study was a 12 week, randomized trial of Ω3 versus placebo and IF-PEP versus active monitoring (AM) using a 2 × 2 design (Ω3 + PEP: n = 5; Ω3 + AM: n = 5; placebo + PEP: n = 7; placebo + AM: n = 6). Twenty-three youth ages 7-14 with BP-NOS or CYC were recruited via community advertisements and clinician referrals. Participants could be taking stable medication for attention-deficit/hyperactivity disorder and sleep aids, but no other psychotropics. Independent evaluators assessed participants at screen, baseline, and 2, 4, 6, 9, and 12 weeks. Primary outcome measures were the Kiddie Schedule for Affective Disorders (K-SADS) Depression (KDRS) and Mania (KMRS) Rating Scales, Children's Depression Rating Scale-Revised (CDRS-R), and Young Mania Rating Scale (YMRS). Ω3/placebo conditions were double-blind; independent evaluators were blind to psychotherapy condition.

RESULTS: Most participants (83%) completed the 12 week trial. Side effects were uncommon and mild. Intent-to-treat analyses indicated significant improvement in depressive symptoms (KDRS) for combined treatment relative to placebo and AM ($p = 0.01$, $d = 1.70$). Across groups, manic symptoms improved over time without significant treatment effects. Effect of IF-PEP on child depression compared with AM was medium ($d = 0.63$, CDRS-R) to large ($d = 1.24$, KDRS). Effect of Ω3 on depression was medium ($d = 0.48$, KDRS).

CONCLUSION: IF-PEP and Ω3 are well tolerated and associated with improved mood symptoms among youth with BP-NOS and CYC. Clinicaltrials.gov Identifier: NCT01507753.

Omega-3 Supplementation for Psychotic Mania and Comorbid Anxiety in Children

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OBJECTIVES: Therapeutic benefits of omega-3 fatty acids (Ω3) for mood disorders, psychosis, and anxiety have been reported in the literature. The purpose of the present article is to provide a literature review of Ω3 supplementation for affective disorders and to illustrate the benefits of Ω3 with a case presentation of a young girl with a history of bipolar disorder-type 1 with psychotic features and generalized anxiety disorder.

METHODS: Reviewed literature includes treatment studies of the impact of Ω3 on child mood disorders supplemented by review of meta-analyses within the adult mood disorders literature. The subject of this case report participated in 11 in-depth diagnostic and functional assessments over 5 years as part of an unrelated study. Three years were presupplementation and 2 years were with supplementation with no other medication changes, thus making a naturalistic multiple-baseline single-subject experiment.

RESULTS: Augmentation over a 2 year period was notable for clinically significant and sustained improvement in depressive, manic, and psychotic symptoms.

CONCLUSION: Ω3 supplementation may be a safe, adjunct intervention for treating bipolar disorder in children and adolescents, even in the presence of psychotic and anxious features. The 2 year follow-up in this case offers hope of an accumulating and enduring benefit. Further research into mechanisms of Ω3 action and of combination treatment with other well-known interventions for mood disorders would be beneficial.

Omega-3 and Omega-6 Polyunsaturated Fatty Acids in Bipolar Disorder: A Review of Biomarker and Treatment Studies

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OBJECTIVE: There is growing evidence that inflammation is an important mediator of pathophysiology in bipolar disorder. The omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acid (PUFA) metabolic pathways participate in several inflammatory processes and have been linked through epidemiologic and clinical studies to bipolar disorder and its response to treatment. We review the data on PUFAs as biomarkers in bipolar disorder and n-3 PUFA used as treatment for bipolar disorder.

DATA SOURCES: PubMed and CINAHL were searched for articles on PUFA and bipolar disorder published in the English language through November 6, 2013, with an updated search conducted on August 20, 2015. Keywords searched included omega 3 fatty acids and bipolar disorder, omega 3 fatty acids and bipolar mania, omega 3 fatty acids and bipolar depression, omega 3 fatty acids and mania, omega 3 fatty acids and cyclothymia, omega 3 fatty acids and hypomania, fatty acids and bipolar disorder, essential fatty acids and bipolar disorder, polyunsaturated fatty acids and bipolar disorder, DHA and bipolar disorder, and EPA and bipolar disorder.

STUDY SELECTION: Studies selected measured PUFAs as biomarkers or introduced n-3 PUFA as treatment.

RESULTS: We identified 17 relevant human clinical articles that either compared PUFA levels between a bipolar disorder group and a control group or used a PUFA intervention to treat depression or mania in bipolar disorder. Human studies suggest low n-3 red blood cell PUFA concentrations and correlations with clinical severity in studies of plasma concentrations in symptomatic bipolar disorder. Results of published n-3 PUFA dietary supplementation trials for bipolar

disorder indicate efficacy in treatment for mania or depression in 5 of 5 open-label trials, efficacy in treatment of depression in 1 of 7 randomized controlled trials, and a signal for treatment of depression in 1 meta-analysis.
CONCLUSIONS: Biomarker studies of PUFA and treatment studies of n-3 PUFA in bipolar disorder show promise for indicating a way forward in the study of PUFA in bipolar disorder. Investigation of the intake and metabolism of the n-3 and n-6 PUFA when supplementation is provided in treatment trials might offer clues for identification of when and how PUFA may be important for treatment in bipolar disorder.