Alternative Treatments for Emotional Dysregulation in Youth

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Disclosures

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National Trends in Visits with a Diagnosis of Bipolar Disorder as a Percentage of Total Office-Based Visits

“This increase highlights a need for clinical epidemiological reliability studies to determine the accuracy of clinical diagnoses”

Moreno et al., Arch Gen Psych, 2007
Developmental Course in Bipolar Children:
A disorder affecting preschoolers
Children often ill for years by time of referral
THE EVER CHANGING MOODS OF THE BIPOLAR CHILD
1-3% of Youth have Bipolar Disorder, Many more with Depression

Regular Kid! typical

Melancholy: sad, no pleasure, down on self, suicidal, self-destructive

Euphoric: Giddy, goofy, silly, high, “on drugs,” laughing fits

Irritability of Depression: angry, grouchy, cranky, whiny, complaining, difficult to please, short-tempered

Manic level SEVERE IRRITABILITY: swearing, disrespectful, threatening, wild, out of control with Explosions that are frequent, for 30-60+ minutes, destructive, aggressive
ultradian cycling, and fewer days euthymic (all $P<.05$). **Conclusions:** These data converge with other evidence that onset of bipolar disorder in childhood is common and often associated with extraordinarily long delays to first pharmacologic treatment. Both childhood onset and treatment delay were associated with a persistently more adverse course of illness rated prospectively in adults. These data should help foster efforts to ensure earlier and more effective treatment of bipolar illness in children and adolescents. It is hoped that appropriate early intervention would result in a more benign illness and a better prognosis in adulthood.

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Bipolar adults with childhood and adolescent onset had more lifetime suicide attempts and violence.

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881
Severe depression can occur suddenly and dramatically.

Intense feelings of self-loathing and hopelessness should always be taken seriously.
20TH-CENTURY - CHANGES IN YOUTH SUICIDE RATES
— UNITED STATES, AGES 15–24 —

Rate per 100,000

Year 1900-2000

Bipolar adults with childhood and adolescent onset have more lifetime suicide attempts
Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies


N=2769 11 studies

The weighted mean annual incidence of tardive dyskinesia for second-generation antipsychotics was 0% in the children, 0.8% (range=0.0%-1.5%) in the adults, 6.8% in the mixed adult and elderly population, and 5.3% (range=0.0%-13.4%) in the patients age 54 years and older, compared to 5.4% (range=4.1%-7.4%) in adults treated with haloperidol.

Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.
Weight Gain in 8-week Open Label Trials of Second Generation Antipsychotic Monotherapy in 116 Children with Bipolar Disorder

Biederman et al (2007), AACAP; Boston
One of the concerns about increasing the diagnosis of bipolar disorder is that it will lead to exposure to medications with unknown effects on the developing brain.

Intervening with supplementation during critical periods may enhance brain development.

Thus an agent with minimal effect on the adult brain could play a major role in the developing brain.
Number of Studies by Anti-Manic Medication Class

Traditional Mood Stabilizers: lithium, divalproex, and carbamazepine
Other Anticonvulsants: topiramate, oxcarbazepine, lamotrigine
Atypical Antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone

Number of Subjects Participating in Pediatric Anti-Manic Trials

- Traditional Mood Stabilizers: n=915
- Atypical Antipsychotics: n=1474
- Other Anticonvulsants: n=244
- Naturopathic Treatments: n=71

### Mean Change in YMRS from Baseline by Medication Class

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>YMRS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Mood Stabilizers</td>
<td>-10.99</td>
</tr>
<tr>
<td>Other Anticonvulsants</td>
<td>-11.03</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>-16.8</td>
</tr>
<tr>
<td>Naturopathic Treatments</td>
<td>-5.6</td>
</tr>
</tbody>
</table>

Omega-3 Fatty Acids

Scientific evidence suggests that omega-3 fatty acids may:

1. treat hypertension, Crohn’s disease, rheumatoid arthritis, asthma and Huntington’s Disease
2. decrease the risk of primary coronary arrest, coronary artery disease and decrease serum triglycerides
3. aid in the prevention of lung and breast cancer
Omega-3 fatty acids may be useful for treating:

1. schizophrenia
2. Attention Deficit Hyperactivity Disorder
3. dementia
4. depression
5. bipolar disorder.
Fat is present in large quantities in the brain. The essential fatty acids make up 20% of the non-H2O weight of the brain. Most of this is long chain fatty acids (20 or more carbons).
Omega-3 Fatty Acids

- Omega-3 fatty acids are found in our diet. Fish are the main source.
- Omega-3 and omega-6 fatty acids are found in algae.
- Fish eat algae and accumulate the fatty acids.
Omega-3 fatty acids are a subset of what are called “long chain (>20 carbon) polyunsaturated fatty acids (PUFA)”

- “Omega” refers to the position of the first double bond in the chain.
- Omega-3 means the first double bond begins at carbon #3
- Omega-6 means the first double bond starts at carbon #6
Omega-3 Fatty Acids

Highly **unsaturated** (a lot of double bonds) fatty acids are components of cell membranes

*No* double bonds: saturated fat
*Yes* double bonds: unsaturated fat

One double bond: mono-unsaturated fat
More than one: poly-unsaturated fat
Omega-3 Fatty Acids

• **Saturated** fats are solid at room temperature
• **Mono-unsaturated** fats are liquid at room temperature, but cloudy when cold
• **Poly-unsaturated** fats are liquid at room temperature and also when cold: they are much more fluid
Omega-3 Fatty Acids

Highly unsaturated fatty acids (like omega-3 and omega-6 fatty acids) are the precursors of eicosanoids (second messengers; hormones) which are important for cell physiology.

Omega-3 fatty acids are incorporated into cholesterol esters, phospholipids and triglycerides
Double bonds aid in the fluidity and behavior of the membrane and modulate the function of the membrane bound proteins and signal transduction systems.

In the brain, the “fluidity” of the membrane as determined by the amount of long-chain PUFAs can influence the release and reuptake of neurotransmitter, influence post-synaptic neurotransmitter actions and affect nerve conduction.
Omega-3 Fatty Acids

The main essential (we can’t make them, we must ingest them) fatty acids are:

1. Omega-3 fatty acid alpha-linolenic acid (ALA)
2. Omega-6 fatty acid linolenic acid (LA)
Omega-3 Fatty Acids

In several step processes in the liver:

ALA (omega-3) undergoes desaturation and elongation to produce

Eicosapentaenoic Acid (EPA)

Which undergoes desaturation and elongation to produce

Docosahexaenoic Acid (DHA)
Omega-3 Fatty Acids

In several step processes in the liver:

Linoleic Acid (omega-6 FA) undergoes desaturation and elongation to produce:

**Arachidonic Acid (AA)**
Lithium blocks the release of arachidonic acid in the brain. Omega-3 fatty acids can inhibit the production of arachidonic acid from dihomo-gamma-linolenic acid DGLA (DGLA is a powerful vasodilator and inhibitor of platelet aggregation and thus has an opportunity to build up).
Omega-3 Fatty Acids

• Flaxseed oil contains ALA, baby formula contains ALA, and ALA can be made into EPA and DHA.

• However, it is much more efficient to ingest EPA and DHA directly (i.e. may need 30X as much ALA to get similar amount of EPA)
Evidence that reduced levels of EPA and DHA may play a causative role in mood disorders comes from studies showing:

1. Inverse relationship between dietary intake and depression
2. Decreased blood levels of FAs in patients
3. Mood improvement with supplementation
Omega-3 Fatty Acids

Hibbeln JR *Lancet* 1998, Fish consumption and major depression

The prevalence of major depression worldwide is inversely related to the amount of fish consumed.

* e.g. The annual rate of depression in Japan (0.12%) vs. New Zealand (6%)
Omega-3 Fatty Acids

Hibbeln, 2002

• Seafood consumption and higher levels of breast milk DHA predicted for lower rates of postpartum depression.

• This may account for the 50-fold difference in prevalence rates of postpartum depression across countries.
Fish consumption, depression and suicidality

- N=3004 in Finland, 59% (N=1767) response rate
- Depression rated with BDI>10; suicidality with BDI self-harm question
- Frequent fish consumption rated as twice/wk or more
- Depression and suicidality both were lower among fish eaters
- These findings are consistent with Japanese study of 265,000 subjects which found a decreased risk of suicide among daily fish consumers
Omega-3 fatty acids are found in fish such as mackerel, trout, herring, sardines and tuna (oily fish), plus others.

Our diet is richer in omega-6 fatty acids. A decreased omega-3 to omega-6 ratio may be causative in depression due to alterations in membrane viscosity and associated neurotransmitter systems.
Omega-3 Fatty Acids

The **membrane phospholipid hypothesis** (Horrobin)

Psychiatric disturbance may be due to:

1. Decreased rate of incorporation of PUFAs into membranes and/or
2. Increased rate of loss of PUFAs from cell membranes (due to too much phospholipase A2)
The membrane phospholipid hypothesis
(Horrobin)

This would result in abnormalities in neuronal membranes and impaired functioning of neurotransmitter systems.
Studies have linked lower levels of fatty acids in plasma and red blood cells to depression. In depressed patients:

- 4 studies found reduced omega-3 levels
- 1 study found an increase in omega-6:omega-3
Omega-3 Fatty Acids

• Not clear if low fatty acid levels are a cause or an outcome of depression
• Not clear if due to diet or abnormal fatty acid metabolism
• Not clear if fatty acids are subject to more rapid depletion as a consequence of some other factor (smoking)
Omega-3 Fatty Acids

Large studies suggesting that supplementing can improve symptoms:

1. Stoll A, 1999
2. Horrobin DF, 2002
3. Nemets B, 2002

Also, a case report:
1. Puri BK, 2002
Omega-3 Fatty Acids

Stoll A, Arch Gen Psych, 1999
• Double blind randomized placebo controlled trial
• N=30 bipolar disorder
• Fish oil (6.2 g EPA, 3.4 g DHA [9.6 g combined])
• Depressive symptoms improved
• Manic symptoms did not improve, but were low at intake
• Fish oil added on to other medications
Omega-3 Fatty Acids


- N=20 MDD
- On antidepressants
- Double blind placebo controlled 4 week trial
- EPA 2 gram
- Highly significant results found: 6 of 10 patients on EPA (but only 1 of 10 patients on placebo) had 50% reduction in HAM-D
Omega-3 Fatty Acids

Horrobin DF, Arch Gen Psych, 2002
- N=70, treatment resistant depression
- On antidepressant medication
- Double blind randomized placebo controlled
- EPA at varied doses: 1g, 2g, 4g for 12 weeks
- HAM-D, MADRS, BDI
- 1 gram per day performed better than placebo on all rating scales (50% reduction on HAM-D)
This study was highly publicized in the major news media and suggest that 3 months of supplementation 1200mg (age 13-25) can have positive effects after one year on psychotic symptoms.
1998 Williams Lancet

44 infants received formula with and without supplementation with PUFA/DGA

Supplemented infants scored better on a problem solving test correlated with IQ administered 10 months of age (6 months after the supplementation ended)

Effects evident beyond the period of supplementation
Omega-3 Fatty Acids

STUDIES IN CHILDREN AND ADOLESCENTS

- Stanley Foundation funded study at Massachusetts General Hospital examining EPA+DHA monotherapy (JW PI)
- EPA+DHA is in the form of Omegabrite brand fish oil capsules (up to 6 per day or 2.6 g)
- Subjects are 20 children and adolescents age 5-18 with current bipolar disorder and YMRS>15
Our own study shows that omega-3s can treat bipolar disorder in children. This result is about 50% what we see with atypical antipsychotic medications, but without the serious or annoying side effects.
Change in Young Mania Rating Scale (YMRS) Scores in subjects treated with omega-3 fatty acid monotherapy in an open study over 8 Weeks

YMRS, Young Mania Rating Scale. LOCF, Last Observation Carried Forward *p<0.05 versus baseline

Wozniak, European Neuropsychopharmacology, 2007
Clinical Global Impression (CGI) rated improvement in mania and psychiatric comorbidity
Side Effects and Adverse Events

- GI problems
- Cold/Flu/Allergies/Infection
- Headache
- Decreased appetite
- Sleep Problems
- Skin Disturbance
- Agitation/Activation
- Respiratory Side Effects
- Tics
- Anxiety

Percent

Wozniak, European Neuropsychopharmacology, 2007
Omega-3 Fatty Acids

Adverse events? Few

- Gastrointestinal distress (diarrhea and upset stomach) at higher doses
- “Fishy” taste and smell
Omega-3 Fatty Acids

How to dose? Unclear

• Many fish oil brands exist, quality/appeal may vary
• Check nutritional information for serving size and mgs per capsule of EPA and DHA
• At least 1 gram for adults (half for children?), but up to 9.6 grams for adults (half for children?) according to Stoll study
• Maybe children need more, since they are growing
• Not clear what the ratio of EPA to DHA should be, but more recent studies utilize EPA only
Omega-3 Fatty Acids

*Omegabrite* and *Nordic Natural* Brands can be obtained over the internet.

Check ‘nutritional information’ to see what the ‘serving size’ is (1, 2, 3 caps) and how much EPA is present in each serving size. Check that the capsules are small and palatable enough for children.
Inositol is a simple sugar derivative which is a precursor for a number of second messengers important in intracellular activity. An isomer of glucose.

Common in the human diet in higher amounts in beans, grains, nuts and many fruits. There is about 1 g in a healthy daily diet.

Rationale for use: low inositol levels in the CSF of depressed patients

Inositol is key in the phosphatidyl inositol PI cycle part of the cell metabolism. This cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonin (5-HT2A and 5-HT2C) and dopaminergic D1 receptors.
Lithium and antiepileptic mood stabilizing medications affect inositol uptake suggesting that stable inositol signaling may be crucial in mood stability.

These medications decrease inositol uptake at high concentrations and increase inositol uptake at low concentrations.

The Inositol Polyphosphate Signal Suppression Hypothesis, suggests a complex regulation with a pendulum effect.
Modest clinical effect in adult bipolar disorder and depression.

Trials in children have been limited to measuring brain levels and ratios in neurochemical spectroscopic studies of treated and untreated youth (Davanzo, 2001, 2003; Moore, 1999; Silverstone, 2005; Patel, 2006)

Taken together, these neuroimaging studies suggest that inositol is implicated in the pathophysiology of bipolar disorder and that treatment with exogenous inositol or with medications which affect brain inositol levels (lithium) results in brain chemistry changes associated with clinical improvement.

First and only clinical trial examining the efficacy of inositol in the treatment of pediatric bipolar disorder or depression.

Very young children 6-12 year olds
Bipolar Spectrum with YMRS must be below 40
Combining 2 low impact treatments
INOSITOL MAY BE A PROMISING SUPPLEMENT

A study of inositol for attention deficit hyperactivity disorder in 11 children failed to demonstrate efficacy, but this study demonstrated that treatment was well-tolerated in children in doses of 200 mg per kg body weight (J. Levine, 1997).

A review of controlled trials of inositol in psychiatry reports no changes found in hematology, kidney or liver function tests (J. Levine, 1997).

There is no established recommended daily allowance for inositol. Studies of adults have used dosages ranging from 6 to 25g/d of inositol or myo-inositol given in divided doses. One study suggested that 12g/d of inositol has been shown to raise CSF inositol levels by 70% (J. R. Levine, A.; Lev, L.; Bersudsky, Y.; Kofman, O.; Belmaker, R.H.; Shapiro, J.; Agam, G., 1993).

Studies for inositol in pediatric mood disorders are lacking, but the two studies of inositol in psychiatry for children used a dose of 200mg per kg and offers initial evidence of the safety and tolerability of this dose (J. Levine, 1997).
Figure 1. Antimanic Response to Treatment

- OR=6.82
- OR=3.75
- OR=3.33
- OR=1.33
- OR=21.67
- OR=7.00
- OR=3.75
- OR=1.07
- OR=5.83
- OR=3.11
- OR=0.53
- OR=1.33

- 30% YMRS Improvement
- 50% YMRS Improvement
- YMRS<12 at Endpoint
- CGI Mania Improvement≤2

- Inositol (n=7)
- Omega-3 FA (n=7)
- Omega-3 FA + Inositol (n=10)

a: p<0.05 vs. Inositol
* p<0.05
Figure 2. Antidepressant Response to Treatment

- HAM-D SMD (Omega-3 FA vs. Inositol) = 0.51
- HAM-D SMD (Omega-3 FA + Inositol vs. Inositol) = 0.56
- CDRS SMD (Omega-3 FA + Inositol vs. Inositol) = 0.59

Inositol (n=7)  Omega-3 FA (n=7)  Omega-3 FA + Inositol (n=10)
Figure 3. Response to Treatment in Other Domains

- BPRS SMD (Omega-3 FA vs. Inositol) = 0.77
- BPRS SMD (Omega-3 FA + Inositol vs. Inositol) = 0.60
- CGI Anxiety SMD (Omega-3 FA + Inositol vs. Inositol) = 0.55
- CGI ODD SMD (Omega-3 FA + Inositol vs. Omega-3 FA) = 0.45

**Percent of Subjects**

- CGI ADHD Improvement ≤ 2
- CGI Anxiety Improvement ≤ 2
- CGI ODD Improvement ≤ 2
- 30% BPRS Improvement

**Treatment Groups**
- Inositol (n=7)
- Omega-3 FA (n=7)
- Omega-3 FA + Inositol (n=10)

**Effect Sizes**

- OR=2.37
- OR=3.11
- OR=2.50
- OR=5.83
- OR=6.00
- OR=2.40
- OR=6.82
- OR=3.46
- OR=0.67
- OR=1.25
- OR=1.88
- OR=0.45
- OR=0.45

**Graphical representation**

- Each bar represents the percent of subjects in each group.
- The bars indicate the improvement levels for each domain.
MGH NAC STUDY

STUDY OF A NATURAL TREATMENT FOR YOUNG PEOPLE WITH BIPOLAR DISORDER

Every gift matters. Please support Mass General’s initiative to study NAC in bipolar children.

DONATE
Table 1. Demographic characteristics for subjects who were exposed to the study treatment (≥2 weeks) (N=13).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed Subjects N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>9.7 ± 4.2</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>1.8 ± 1.1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Unknown or Not Reported</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Data are reported as mean ± standard deviation or n (%).
Table 2. Change in Young Mania Rating Scale, Hamilton Depression Rating Scale, Brief Psychiatric Rating Scale, and ADHD Rating Scale total scores from baseline to end point.

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>N</th>
<th>Baseline</th>
<th>End Point</th>
<th>Change</th>
<th>Test Statistic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Mania Rating Scale</td>
<td>13</td>
<td>25.4 ± 5.6</td>
<td>20.4 ± 4.9</td>
<td>-5.0 ± 5.7</td>
<td>z=-2.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>13</td>
<td>18.2 ± 5.7</td>
<td>14.7 ± 8.5</td>
<td>-3.5 ± 7.0</td>
<td>z=-1.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale†</td>
<td>10</td>
<td>48.1 ± 9.5</td>
<td>43.4 ± 12.7</td>
<td>-4.7 ± 8.8</td>
<td>z=-1.43</td>
<td>0.15</td>
</tr>
<tr>
<td>ADHD Rating Scale†</td>
<td>11</td>
<td>35.5 ± 14.9</td>
<td>34.1 ± 11.2</td>
<td>-1.4 ± 7.7</td>
<td>z=-0.87</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.
† One subject missing baseline scores for the BPRS and 2 subjects did not make it to week 6 and do not have end point scores (BPRS & ADHD-RS).
Table 3. Antimanic response to treatment (N=13)

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% YMRS Improvement</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>50% YMRS Improvement</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>YMRS &lt; 12 at End Point</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CGI Mania Improvement ≤ 2</td>
<td>3 (23%)</td>
</tr>
</tbody>
</table>

Figure 1. Antimanic response to treatment
Table 4. Antidepressant response to treatment (N=13)

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% HDRS Improvement</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>50% HDRS Improvement</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>30% CDRS Improvement</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>50% CDRS Improvement</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>CGI MDD Improvement ≤ 2</td>
<td>3 (23%)</td>
</tr>
</tbody>
</table>

Figure 2. Antidepressant response to treatment
**Table 5.** Adverse events (>1 occurrence).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomit/Diarrhea</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Dermatological</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Other (Thirsty)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>
Table 6. Change in vital signs from baseline to endpoint.

<table>
<thead>
<tr>
<th></th>
<th>N†</th>
<th>Baseline</th>
<th>End Point</th>
<th>Change</th>
<th>Test Statistic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>10</td>
<td>113.6 ± 16.3</td>
<td>114.5 ± 20.0</td>
<td>0.9 ± 17.4</td>
<td>z=0.66</td>
<td>0.51</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>10</td>
<td>71.0 ± 18.6</td>
<td>70.9 ± 17.5</td>
<td>-0.1 ± 14.1</td>
<td>z=0.71</td>
<td>0.48</td>
</tr>
<tr>
<td>Pulse</td>
<td>10</td>
<td>89.2 ± 8.5</td>
<td>89.4 ± 8.7</td>
<td>0.2 ± 11.4</td>
<td>z=-0.20</td>
<td>0.84</td>
</tr>
<tr>
<td>Weight</td>
<td>12</td>
<td>94.7 ± 60.3</td>
<td>95.5 ± 59.8</td>
<td>0.8 ± 1.7</td>
<td>z=1.50</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.
†1 subject refused all vital measurements at baseline and follow-up; 2 subjects moved around too much to take BP readings at follow-up.
“With all these omega-3 fatty acids, you’d think I’d feel better.”
Alternative Treatments for ADHD
Why alternative treatments for ADHD?

• 30% nonresponders
• Many can not tolerate side effects including decreased appetite, insomnia, motor tics, GI upset, anxiety.
• Yet concerns remain about purity, reliability, safety and toxicity of ‘natural’ treatments
Ineffective?

- St John’s Wort
- Linoleic Acid, Alpha Linoleic Acid
- DHA
open label

• Gingko Baloba Tree unique to Asia
• Bacopa Indian plant
Pycnogenol (pine bark)

- Modulates DA and NE release
- Double blind placebo controlled trial N=61 age 6-14 1mg/kg/d for one month improved ADHD symptoms with return of symptoms after discontinuation
Valerian

- Plant with sedative properties
- Used for insomnia, anxiety
- Inhibits breakdown of GABA
- TID for 3 weeks, RCT placebo N=30, positive trial
Ginseng

- Neuroprotective and anti-oxidant
- Increase DA and NE
- 1000mg BID RCT placebo controlled N=70 8 weeks
- Did not outperform MPH
Passion Flower (Passiflora)

• Traditional remedy for anxiety
• N=34  .04mg/kg/d RCT with MPH 8 weeks
• No difference except fewer side effects in parent and teacher rating scales
Vitamins and Minerals

• Magnesium 6mg/kg/d and Vit B6 0.6mg/kg/d
  8 weeks  open label 6 months
  Affects serotonin production

• Vit C + ALA, improved hyperactivity and attn

• 3 trials of Zinc 15mg-150mg 12 week RCT
  N=400 helped hyperactivity not attention (but also a negative study vs AMP)
Iron

- Cofactor in DA and NE synthesis
- Anemic children have poor attention
- RCT placebo N=23 with low iron improved in ADHD symptoms
Amino Acids

• Direct and indirect effects on neurotransmitter production (increases Ach synthesis)

• ALC (Acetyl L Carnitine) 500-1500mg BID,
  • One positive study RCT placebo, 12 months N=51
  • One negative study RCT placebo 16 weeks N=112
Others?

- Chinese herbal Yizhi 10 herbs with MPH
- Chinese herbal Jingling with MPG
- Chinese medicine Ningdong promise in Tourette’s similar to MPH in RCT
Fatty Acids-positive RCT placebo controlled studies

- N=41 EPA 186mg/DHA 480mg/ALA 96mg
- N=50 EPA 80mg/DHA 480mg/AA 40mg/GLA 96mg  attention and conduct improved
- N=132 EPA 93mg/DHA 29mg (15 week)
- N=162 EPA+DHA 120mg
- But, a negative meta-analysis

- Vayarin, a medical food, phosphatidylserine omega-3, “90 days” EPA 21.5/DHA 8.5