Integrative Medications
The therapeutic potential of omega-3 fatty acids and N-acetylcysteine

Erik Messamore, MD, PhD
emessamore@neomed.edu

Associate Professor of Psychiatry, Northeast Ohio Medical University
Medical Director, Best Practices for Schizophrenia Treatment (BeST) Center
Best Practices in Schizophrenia Treatment (BeST) Center at NEOMED

• **The BeST Center’s mission:**
  – Promote recovery and improve the lives of as many individuals with schizophrenia as quickly as possible
  – Accelerate the use and dissemination of effective treatments and best practices
  – Build capacity of local systems to deliver state-of-the-art care to people affected by schizophrenia and their families

• **The BeST Center offers:**
  – Training
  – Consultation
  – Education and outreach activities
  – Services research and evaluation

• **The BeST Center was established:**
  – Department of Psychiatry, Northeast Ohio Medical University in 2009
  – Supported by The Margaret Clark Morgan Foundation and other private foundations and governmental agencies
Integrative Medications???

- Medical illness is over-represented among individuals with severe mental illness
- Raising suspicion that certain pathophysiological processes lie at the intersection of the physical and the mental
- Agents that impact these fundamental processes (nexus points) may affect both physical and mental health
Nexus points in mental/physical maladies

<table>
<thead>
<tr>
<th>Biochemical processes</th>
<th>Psychological processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Mood</td>
</tr>
<tr>
<td>Cortisol/Stress response</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td></td>
</tr>
<tr>
<td>Glucose/Insulin</td>
<td></td>
</tr>
</tbody>
</table>
Oxidative stress

• ‘Oxidation’ = transfer of electrons from electron-rich biological substrates (e.g., DNA or cell membrane lipids) to electron-hungry oxygen atoms.

• Electron-hungry oxygen atoms are generated during metabolism (= ‘burning’ of glucose) or with the release and subsequent processing of certain neurotransmitters.

• Oxidative stress occurs when reactive oxygen production exceeds the body’s capacity to neutralize the reactive oxygen products → cellular damage

• Accumulated cellular damage becomes apparent as bodily damage (e.g. age-related disorders) or neuronal dysfunction (may manifest with neuropsychiatric symptoms)
# N-acetylcysteine or Omega-3 Fatty Acids as Integrative Medication Candidates

<table>
<thead>
<tr>
<th>N-acetylcysteine</th>
<th>Omega-3 Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative stress</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Inflammation (?)</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Impulsivity</td>
</tr>
<tr>
<td></td>
<td>Mood</td>
</tr>
</tbody>
</table>
N-Acetylcysteine: The Molecule

- A ‘nearly-natural’ substance
- Acetyl group (widely generated/used in normal metabolism)
- Cysteine (an amino acid)
- Joined by the amino (N) group of the amino acid
N-Acetylcysteine: Pharmacological Actions

- Precursor to glutathione, the body’s primary anti-oxidant compound
- Reduces the release of the neurotransmitter glutamate
- Reduces inflammatory cytokines (IL-1β, TNF-α, IL-6)

N-Acetylcysteine: Medical Uses

- Treatment of acetaminophen overdose
- Mucolytic
- Prevention of radiocontrast-induced kidney failure
- Adjunctive agent in the treatment of chronic obstructive pulmonary disease
• Glutamate levels are elevated in the anterior cingulate gyrus of cocaine-dependent adults.
• Glutamate levels in the ACC correlate with impulsivity.
• NAC normalized ACC glutamate levels in cocaine-dependent adults.

• NAC reduced cue-induced cocaine craving among 15 adults with cocaine dependence (LaRowe et al., 2007)
• Though not better than placebo at obtaining abstinence in active cocaine users, NAC produced longer times to relapse and lower cocaine cravings in users who had already achieved abstinence (LaRowe et al., 2013)


NAC, Psychiatric Uses, Tobacco

Studies suggesting efficacy of NAC at improving smoking cessation success rates:


NAC, Other Uses, Marijuana

N=116 cannabis-dependent adolescents

All received contingency management and brief weekly counseling

Cannabis-positive test was assumed for any missed visits

NAC, Other Uses, Bipolar Depression and Schizophrenia

• Reduces severity of depressive episodes in bipolar disorder (Berk et al., 2008)

• Reduces negative symptoms in schizophrenia (Berk et al., 2008; Farokhnia et al, 2013)


NAC, Psychiatric Uses, Self-Injurious Behavior

- Case report: Significantly reduced “self-injurious craving” in 25 yo woman with PTSD and Borderline PD (Pittenger et al., 2005)

- Case report: abatement of formerly daily self-cutting in a 17 yo woman with ADHD, PTSD, and eating disorder (Rus, 2017)

- Open-label pilot study: Significant reduction of non-suicidal self injury in 24 adolescent and young adult females (Cullen et al., 2017)


Open-access review article of NAC studies in neuropsychiatric illness:

NAC: Safety

<table>
<thead>
<tr>
<th>Clinical Effect</th>
<th>IV ROUTE (N=358)</th>
<th>Oral ROUTE (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (7.8%)</td>
<td>40 (20.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (6.4%)</td>
<td>29 (14.7%)</td>
</tr>
<tr>
<td><strong>Anaphylactoid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>1 (0.3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (2.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>7 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>4 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-urticarial rash</td>
<td>3 (0.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>5 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (0.3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td><strong>Other reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>10 (2.8%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Pre-syncope/syncope</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>94</td>
<td>75</td>
</tr>
</tbody>
</table>

Another nexus point: The Cell Membrane

Ion channels, reuptake proteins, and neurotransmitter receptors exist in, and are influenced by, cell membrane lipids.
Fatty Acid Composition Affects Cell Membrane Biophysics

(a) Movement of phospholipids. Lipids move laterally in a membrane, but flip-flopping across the membrane is quite rare.

(b) Membrane fluidity. Unsaturated hydrocarbon tails of phospholipids have kinks that keep the molecules from packing together, enhancing membrane fluidity.
Types of Fatty Acids

**Saturated**
All carbon atoms in the fatty acid tail carry their maximum number of hydrogen atoms.

**Mono-unstaturated**
A single pair of carbon atoms share a double bond
Oleic acid (constituent of olive oil) is a mono-unsaturated fatty acid

**Poly-unsaturated**
Multiple pairs of carbon atoms share double bonds

“Omega Number” refers to the position from the tail where the first double bond appears.
Essential Fatty Acids

• Mammals can’t create double-bonds at omega-3 or omega-6 positions
• They must be consumed from the diet
• Most important omega-3 fatty acids are EPA and DHA
• Most important omega-6 fatty acids are Arachidonic Acid and DGLA

• Approx 30% of the dry weight of the brain is from these 4 essential fatty acids
• Arachidonic acid (omega-6) and DHA (omega-3) comprise about 90% of that total.

• If the body can’t find the right EFA for a particular membrane, it will incorporate what is available instead
Consequences of essential fatty acid deficiency or imbalance

- Alterations of membrane fluidity affect function of membrane-embedded proteins - e.g., neurotransmitter receptors, reuptake pumps, ion channels
- Essential fatty acids are precursors of physiologically-active molecules
  - DGLA (omega-6) → 1-series prostaglandins
  - Arachidonic acid (omega-6) → 2-series prostaglandins; anandamide
  - EPA (omega-3) → 3-series prostaglandins
- Arachidonic acid products impact dopamine signaling
- DHA levels affect serotonin signaling
Psychiatric Patients are Substantially Over-Represented in the Lower 10% of EPA+DHA Levels

- Omega is sum of EPA+DHA as % of all fatty acids
- Inversely correlates with risk of cardiovascular disease, with >8% associated with highest degree of protection
- 45% of psychiatric inpatients had omega-3 index lower than the lowest 10% of USA population

Diet composition correlates with schizophrenia outcome

- WHO Data
- Schizophrenia prevalence is similar across countries
- Resulting disability varies significantly
- 90% of variability in resulting disability attributed to prevailing dietary pattern

EPA+DHA to prevent schizophrenia?

- 81 adolescent and young adults with sub-threshold (prodromal) psychosis
- Half get 1200 mg/d* of omega-3 fatty acids; half randomized to placebo
- 12 weeks of treatment
- Assessment at 40 weeks
- Longer-term followup at 7 years

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omega-3 fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percent with schizophrenia at 40 weeks</strong></td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Percent with schizophrenia at 7 years</strong></td>
<td>40%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>


*EPA: 700 mg/d + DHA: 480 mg/d
EPA+DHA to prevent schizophrenia?

- 304 adolescent and young adults with sub-threshold (prodromal) psychosis
- Half get 1200 mg/d* of omega-3 fatty acids; half randomized to placebo
- 24 weeks of treatment
- Assessment at completion of treatment (24 weeks) and 6 months following completion
- Additional inclusion criteria (not present in the Amminger study:
- sustained (>1 yr) low-level of social/occupational functioning
- both groups had concurrent cognitive behavioral case management (CBCM)
- Concurrent antidepressant use was 5x the level of the Amminger study

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11.2%</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

*EPA: 840 mg/d + DHA: 560 mg/d

Failed to replicate earlier study, but placebo group response was more robust

EPA Deficiency Correlates With Impulsivity & Aggression in Depression Comorbid with Substance Use Disorder


This material provided by the Best Practices in Schizophrenia Treatment (BeST) Center, Department of Psychiatry, Northeast Ohio Medical University.

330.325.6695 • www.neomedi.edu/bestcenter • bestcenter@neomedi.edu
Omega-3 Fatty Acids Appear Relevant to Treatment-Resistant Depression

- 40% of adolescents achieved remission of residual depressive symptoms with low dose (2.4 g/d) fish oil supplement.
- 100% achieved remission with high dose (16.2 g/d) fish oil supplement

Reduction of ‘Antisocial Behaviors’ in Prisoners Given Essential Fatty Acid Supplements

- Reduction versus placebo group of adjudicated in-prison offenses among prisoners (n=231) given supplemental essential fatty acid + vitamin supplement.

Paucity of Studies on Pathophysiology of Borderline PD

The Pathophysiology Knowledge Gap of Borderline Personality Disorder

Number of Medline (1946 – 2015) citations for the 'Physiopathology' modifier of the Medical Subject Heading (MeSH) headings “Schizophrenia” (6,925 publications); "Depressive Disorder" (2,182); "Bipolar Disorder" (1,325); and "Borderline Personality Disorder" (201).

Compared to other serious mental illnesses, little has been reported of the biological substrates of borderline personality disorder.
Severe Deficits of EPA and More-Severe Deficits of DHA in Borderline PD

Levels α-linolenic acid, a precursor omega-3 fatty acid, are higher in depression or BPD.

EPA levels are severely depleted in Depression and BPD.

DHA levels are even more depleted in BPD vs Depressed patients.
EPA Reduces Depression and Aggression in Borderline PD

- 20 subjects given 1 g/day ethyl-EPA
- 10 given placebo
- No other meds

Omega-3 Fatty Acid Treatment Reduced Depression, Suicidal Thoughts, Stress Tolerance in Pts with Recurrent Self-Injury

- 49 subjects who presented to an E.R. after >2 acts of self-harm
- 1220 mg/d EPA + 908 mg/d DHA for 12 weeks

Omega-3 Fatty Acids Reduce Symptoms and Improve Functioning in Adolescents with Borderline PD

• N=15 adolescents from prodromal assessment clinic, who met criteria for BPD
• Omega-3 dose was 700 mg/d EPA + 480 mg/d DHA
• Treatment was for 12 weeks

Omega-3 Fatty Acids: Safety

Table 1: Adverse Reactions Occurring at Incidence ≥ 3% and Greater than Placebo in Clinical Trials of LOVAZA

<table>
<thead>
<tr>
<th>Adverse Reactiona</th>
<th>LOVAZA (n = 655)</th>
<th>Placebo (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Eructation</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>27</td>
<td>4</td>
</tr>
</tbody>
</table>

aTrials included subjects with HTG and severe HTG.

Source: Lovaza (ethyl-EPA + ethyl DHA) prescribing information
Conclusions

- Intervening at ‘nexus points’ of pathophysiology can impact seemingly diverse expressions of illness.

- Inflammation, oxidative stress, glutamate, and cell membrane fluidity are examples of such nexus points.

- NAC or omega-3 fatty acids influence these nexus points. Each agent appears to have significant psychotropic activity that may cut across diagnostic boundaries.