Micronutrients for Mental Health: Treating Irritability and Aggression in Children with ADHD Using Micronutrients

Jeanette “Jeni” Johnstone, PhD
Licensed Psychologist and Licensed Researcher
My Background
Financial Disclosures

• The Speaker: Jeni Johnstone has no financial disclosures.

• The Planning Committee: Bita Moghaddam, Liz Stevenson, William Wilson, Neisha D’Souza, Sean Stanley, Micaela Sandoval, and Kevin Howden have no financial disclosures.
Talk Road Map

1. Historical role of diet for health
2. Concept of micronutrients
3. Mechanisms
4. Research
5. The MADDY Study
Historical Role of Diet

- Biblical times
- Ayurvedic medicine - 3000 years old, developed in India
- Traditional Chinese Medicine

**AYURVEDA AND DIET**

Contrary to western medicine one diet approach does NOT work

Food selected based on its elemental balance, taste, your doshas, effects on body, quality of food like hot/cold, heavy/light, oily.

Organic food has the most energy
Historical Role of Diet

- Running a household in Victorian England
- Recipes, and the role of food for health

“For the majority of common ailments, some slight change of diet is by far the best remedy...”
Historical Role of Diet

#1 cause of “acquired insanity? Improper nutrition
Population Health Studies
15 nutritional epidemiology studies from Australia, Spain, UK, Japan, Canada

• People who eat ‘Mediterranean’ diets have *lower rates of mood and anxiety symptoms*

• People who eat ‘Western’ ‘processed’ diets have *higher rates of mood and anxiety symptoms*

RCT of Dietary Improvement: SMILES Trial

- n = 67: 31 in diet, 25 in social support
- 12 weeks
- MDD
- 7 sessions: nutritional counseling or social support
- Dietary support > Social support
- P < 0.001, Cohen’s d = -1.16
- NNT for remission = 4.1

Consider these symptoms?

- Low mood
- Irritability
- Self-mutilation
- Apathy, lethargy
- Social withdrawal
- Inability to concentrate
Starvation

24 weeks of nutrient deprivation in normal, healthy young men \( (n=32) \) resulted in:

- Depression
- Hysteria
- Irritability
- Self-mutilation
- Apathy, lethargy
- Social withdrawal
- Inability to concentrate

Minnesota Starvation Experiments, Ancel Keys, 1950
Two Sides to Nutrition:
1. What to eat less of

- Gluten
- Casein/dairy
- Artificial additives
2. What to eat more of

- Minerals
- Vitamins
- Omega-3 fatty acids
What are Micronutrients?

- Vitamins
- Minerals
- Amino Acids
Psychiatric Disorders with Single Micronutrient Deficiencies

- Thiamine/B₁ - Wernicke’s encephalopathy, Korsakoff’s psychosis
- Cyanocobalamin/B₁₂ - psychosis of pernicious anemia
- Iodine - ‘myxedema madness’
- Niacin/B₃ (pellagra) – psychosis
Review of single micronutrient research 1920-2000

- Strongest evidence in single nutrient studies: iron, copper, zinc, vitamins B1, B6, B12, D, E and folate

- Better clinical efficacy from broad spectrum multi-ingredient treatments

Rucklidge, Johnstone, et al., BJP, 2013
Micronutrients for Mental Health Studies

• All studies on *broad spectrum* micronutrients positive
  • Designs include:
    • open-label; retrospective database analyses; case reports; reversal designs; patient preference studies; RCTs
  • >30 peer reviewed publications
Micronutrient Studies

Micronutrients reduce stress and anxiety in adults with Attention-Deficit Hyperactivity Disorder following a 7.1 earthquake
Julia Rucklidge 1,*, Jeanette Johnston 1, Rachel Harrison 1, Anna Boggs 2
1Department of Psychiatry, University of Otago, Dunedin, New Zealand
2Once Again Inc. Research & Development, Lexington, New Zealand

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Stress
Anxiety
Abstract
The role of micronutrients for resilience in the face of disaster is a topic of increasing interest. In a randomised, double-blind, placebo-controlled study, adults with Attention Deficit Hyperactivity Disorder (ADHD) were supplemented with either a high-dose micronutrient formula or placebo for 12 weeks post the 7.1 magnitude Christchurch earthquake. Participants receiving the high-dose formula showed significantly reduced symptoms of stress and anxiety compared to the placebo group. These findings suggest that micronutrients may play a role in promoting resilience during times of stress and trauma.

A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster
Jebastin John 1,2, Michael Dalton 1,2
1Department of Psychiatry, University of Otago, Dunedin, New Zealand
2Once Again Inc. Research & Development, Lexington, New Zealand

Effect of a vitamin/mineral supplement on children and adults with autism
James B. Adams 1, Tapash Audzulis, Sharran McConnell-Meem 2
1Anxiety Disorders Clinic, Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada
2Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

Adjuvant Treatment of Psychotic Disorders with Micron
Catherine Galley 1, Bonita J. Kaplan 1
1Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

Micronutrients are essential for normal development and brain function. Deficiencies in certain micronutrients have been linked to cognitive, emotional, and behavioral disorders. The role of micronutrients in the prevention and treatment of psychological disorders is an emerging area of research. Micronutrients are involved in a wide range of biological processes, including neurotransmitter synthesis, enzyme function, and cell proliferation. Micronutrient deficiencies can lead to a range of psychological symptoms, including anxiety, depression, and cognitive impairment. Micronutrient supplementation has been shown to improve mood, cognitive function, and overall quality of life in various clinical populations.
Potential Mechanisms

1. Brain metabolism
2. Mitochondrial function
3. Addressing inborn errors of metabolism
4. Reducing inflammation
5. Changing the microbiome
6. Epigenetic effects

Potential Mechanisms

Linus Pauling:

“The genes for mental illness are likely the genes that regulate brain metabolism of essential nutrients.”

Pauling, 1974, *Am J Psychiatry*; 131(11);1251-57
Pauling, 1968, *Science*; 160; 265-71
Enzyme 1.14.16.4 requires IRON
Enzyme 4.1.1.28 requires VIT. B6
Serotonin Pathway

6-Hydroxy-kynureinate

5-Hydroxy-N-formylkynurenine

5-Hydroxyindole-acetyaldehyde

Molybdenum

Iron

5-Hydroxyindole-3-carboxaldehyde

Vit. B₆

Vit. B₆

Vit. B₆

Copper

Iron

Copper

Vit. B₆

Vit. B₆

Copper

3-Formyl-aminobenzaldehyde

3-Hydroxyindolepyruvate

5-Hydroxy-L-tryptophan

Tryptophan

3-Indole-glycolaldehyde
The Brain’s Metabolic Needs

accounts for ≈ 2% of our body weight

but,

it requires 20-50% of the glucose and nutrients

What is in a broad-spectrum micronutrient formula?

- Vitamins: A, C, D, E, B₁-B₁₂, K,
- Minerals: Calcium, Iron, Phosphorous, Iodine, Magnesium, Chromium, Molybdenum, Potassium, Zinc, Selenium, Copper, Manganese, Vanadium, Boron, Nickel, Lithium
- Amino acids: dl-Phenylalanine, acetyl-L-carnitine, L-methionine, N-acetyl-cysteine,
- Herbs: Grape seed, Ginkgo biloba
- Alpha-lipoic acid
Evidence for Micronutrients in:

- Natural disaster stress
- Mood
- ADHD
Micronutrients for Natural Disaster Stress:

- September 4, 2010: 7.1 earthquake
Fig. 1. Earthquakes and aftershocks endured by participants during the duration of the study (printed with permission from The Press — Fairfax New Zealand).

749 seismic shocks
186
83

Depression, Anxiety and Stress Recovery Post-quake

Self-reported Depression Anxiety and Stress Scale (DASS)

$n = 33$

*p < 0.02

Rucklidge, et al. (2011). *Psych Research*
Evidence for Micronutrients in:

- Natural disaster stress
- Mood
- ADHD
Micronutrients for Bipolar Disorder

• 5 open label trials; 2 database analyses
  • Popper, (2001) JCP
  • Kaplan et al., (2001) JCP
  • Simmons, (2003) JCP
  • Kaplan et al., (2004) JCAP
  • Rucklidge et al., (2010) BMC Psychiatry
  • Frazier et al., (2012) JACM

Rucklidge & Kaplan, (2013). Expert Reviews
Micronutrients for Bipolar Disorder

Open label case series, $n = 11$ adults

**ES=1.97

*ES=1.22

**ES=1.07

$p < .01$

Kaplan et al., 2001, J Clin Psychiatry
Common Study Features

- Well-characterized ADHD
- Non-medicated sample
- Participants with co-morbidities
Micronutrients Studies for ADHD and Mood

• **2007: Open Label: 14 adults**

• **2009: RCT: 80 adults**

• **2012: Open Label: 14 children**

• **2014: RCT: 93 children**
Adult RCT Results

N = 80 adults:
42 micronutrients
38 placebo
Mean age = 35 years
8 week RCT

- Self and other-reported > on ADHD scales
- Clinician-rated > overall
- Improved mood
Adult ADHD RCT Results: Across 3 Raters

Total ADHD symptoms on Conners’ Adult ADHD Rating Scale (CAARS),

Rucklidge et al. (2014). BJP 204, 306-315
Adult RCT Results: Improvement in Self-Rated ADHD Symptoms

- Active: $p = 0.041$, ES = 0.47
- Placebo: $p = 0.007$, ES = 0.62

Rucklidge et al. (2014). BJP 204, 306-315
Micronutrients for Depression

Change in MADRS$^+$ scores in Adult RCT among those with depression

Rucklidge et al. (2014). BJP, 204, 306-315
Open Label, Reversal Design Study in Children with ADHD

$n = 14$, On-Off control of symptoms

Gordon et al., 2015, *J Child Adolesc Psychopharmacology*
Parent-Rated ADHD Symptoms, Combined

Conners' Parent Rating Scale: Combined Score

**ES = 0.78  **ES = 2.17  **ES = 2.18  **ES = 1.30

**significantly different from baseline (p < .001)**

$n = 14$ children

Parent-Rated Mood Dysregulation
Child Mania Rating Scale

***ES=0.88
***ES = 1.02

***sig different from baseline (p < .001)

Gordon et al., 2015, J Child Adolesc Psychopharm
The Treatment: Pill Swallowing

In divided doses, participants took:
- 1 capsule, 3x day for 3 days
- 2 capsules, 3x day for 3 days
- 3 capsules, 3x day for 3 days
- up to 12-15 capsules/day

http://research4kids.ucalgary.ca/pillswallowing

for a training video

Gordon et al., 2015, J Child Adolesc Psychopharm
RCT in Children with ADHD

\[ n = 93, \ 47 \text{ micronutrients, } 46 \text{ placebo} \]

10 weeks RCT, 10 week open label
RCT in Children with ADHD: Results

- Good retention
- 2 drop outs in both groups
- Blinding effective
Results: Safety and Side Effects

No group differences:
• Blood pressure
• Blood work
• Weight and height, $p = 0.06$, ES = .4
• Side effects

$n = 93$
$p = ns$
# RCT Primary Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Micronutrients ($n = 47$)</th>
<th>Placebo ($n = 46$)</th>
<th>Change from baseline&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post</td>
<td>Mean</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I-Overall&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44.8</td>
<td>1.0</td>
<td>37.1</td>
</tr>
<tr>
<td>Clinician ADHD-RS-IV Symptoms Total</td>
<td>44.8</td>
<td>1.0</td>
<td>37.1</td>
</tr>
<tr>
<td>Parent CPRS-R:L DSM-IV ADHD Symptoms Total</td>
<td>42.5</td>
<td>1.0</td>
<td>33.4</td>
</tr>
</tbody>
</table>

## Difference (confidence interval) <br>$p$ <br>$ES<sup>b</sup>$

<table>
<thead>
<tr>
<th>Difference (confidence interval)</th>
<th>$p$</th>
<th>$ES&lt;sup&gt;b&lt;/sup&gt;$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-0.47$ (−0.05 to −0.90)</td>
<td>0.029&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.46</td>
</tr>
<tr>
<td>$-1.43$ (−4.91 to 2.05)</td>
<td>0.415</td>
<td>0.17</td>
</tr>
<tr>
<td>$-1.29$ (−5.45 to 2.88)</td>
<td>0.540</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Results: ADHD Symptoms

ES=0.17

ES=0.13

ES=0.03

Clinician

Parent

Teacher

Score change from baseline

Active
Placebo

n = 93
p = ns

Rucklidge et al. (In Press). JCPP
Child RCT Results

*based on children entering trial with severe mood dysregulation (n=62)
## Results: Irritability, Anger

<table>
<thead>
<tr>
<th></th>
<th>Change</th>
<th>CI</th>
<th>P-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent SDQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Problem Score</td>
<td>-1.95</td>
<td>-4.0 to 0.10</td>
<td>0.062</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Parent SDQ Conduct</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem Score</td>
<td>-0.87</td>
<td>-1.57 to -0.17</td>
<td><strong>0.015</strong></td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Teacher SDQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Problem Score</td>
<td>-1.78</td>
<td>-3.88 to 0.32</td>
<td>0.064</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Teacher SDQ Conduct</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem Score</td>
<td>-0.86</td>
<td>-1.74 to 0.18</td>
<td>0.055</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Teacher BRIEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral Reg. Index</td>
<td>-4.31</td>
<td>-8.68 to 0.07</td>
<td>0.053</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Teacher BRIEF Emotional Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscale</td>
<td>-2.15</td>
<td>-3.74 to -0.60</td>
<td><strong>0.009</strong></td>
<td>0.66</td>
</tr>
</tbody>
</table>

\[ n = 56 \]

Rucklidge et al. (In Press). JCPP
Re-Classifying ADHD Subtypes

Original Investigation

Subtyping Attention-Deficit/Hyperactivity Disorder Using Temperament Dimensions Toward Biologically Based Nosologic Criteria

Sarah L. Karalunas, PhD; Damien Fair, PhD; Erica D. Musser, PhD; Kamari Aykes, BS; Swathi P. Iyer, MS; Joel T. Nigg, PhD

Importance: Psychiatric nosology is limited by behavioral and biological heterogeneity within existing disorder categories. The imprecise nature of current nosologic distinctions limits both mechanistic understanding and clinical prediction. We demonstrate an approach consistent with the National Institute of Mental Health Research Domain Criteria initiative to identify superior, neurobiologically valid subgroups with better predictive capacity than existing psychiatric categories for childhood attention-deficit/hyperactivity disorder (ADHD).

Objective: To refine subtyping of childhood ADHD by using biologically based behavioral dimensions (i.e., temperament), novel classification algorithms, and multiple external validators.

Design, Setting, and Participants: A total of 437 clinically well-characterized, community-recruited children, with and without ADHD, participated in an ongoing longitudinal study. Baseline data were used to classify children into subgroups based on temperament dimensions and examine external validators including physiological and magnetic resonance imaging measures. One-year longitudinal follow-up data are reported for a subgroup of the ADHD sample to address stability and clinical prediction.

Main Outcomes and Measures: Parent/guardian ratings of children on a measure of temperament were used as input features in novel community detection analyses to identify subgroups within the sample. Groups were validated using 3 widely accepted external validators: peripheral physiological characteristics (cardiac measures of respiratory sinus arrhythmia and pre-ejection period), central nervous system functioning (via resting-state functional connectivity magnetic resonance imaging), and clinical outcomes (at 1-year longitudinal follow-up).

Results: The community detection algorithm suggested 3 novel types of ADHD, labeled as mild (normative emotion regulation), surgent (extreme levels of positive approach-motivation), and irritable (extreme levels of negative emotionality, anger, and poor soothability). Types were independent of existing clinical demarcations including DSM-5 presentations or symptom severity. These types showed stability over time and were distinguished by unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes 1 year later.

Conclusions and Relevance: Results suggest that a biologically informed temperament-based typology, developed with a discovery-based community detection algorithm, provides a superior description of heterogeneity in the ADHD population than does any current clinical nosologic criteria. This demonstration sets the stage for more aggressive attempts at a tractable, biologically based nosology.
RCT Take Away Points

- Beneficial treatment for moody, angry, irritable kids: ES range 0.35-0.66)
- Hyperactivity still present
- Better attention reported across raters
- Safe, no adverse effects
- Good retention
- It’s time to do a US-based study…
Micronutrients in ADHD Youth: The “MADDY” Study
The “MADDY” Study
IRB # 06870

Micronutrients for ADHD Youth
Seeking participants, 6-12 years old, for an ADHD treatment study

OHSU researchers are conducting an 8-week randomized controlled trial of vitamins and minerals to treat symptoms of ADHD and emotional dysregulation. Participants will be randomly assigned to receive either the vitamins and minerals or a placebo for 8 weeks. At the end of the 8 weeks, all participants will be eligible to take the vitamins and minerals for the last 8 weeks.

Your child may be eligible if:
• 6-12 years old at enrollment
• Not taking ADHD medication (or at least 2 weeks)
• Able to/willing to swallow up to 12 pills per day - pill swallowing training is available

What is involved?
• 5 visits to OHSU to answer questions and receive study product
• Biological samples requested (urine, saliva, stool)
• Take pills daily for duration of study

For more information, please contact us at 503-494-3700 or healthykids@ohsu.edu.
Biological Samples
What You Can Do

• Start a conversation:
  “....What we eat influences how we feel. Let’s talk about your diet.”
• Send referrals for the MADDY study
• In Oregon: Anonymous Donor, Foundation for Excellence in Mental Health Care, T32

• In New Zealand: GRAVIDA, Vic Davis Memorial Trust, GAMA Foundation, University of Canterbury, UC Foundation
For More Information

• jojeanet@ohsu.edu

• kaplan@ucalgary.ca – if you are interested in getting on Bonnie’s email update list

• International Society for Nutritional Psychiatry Research (ISNPR)
Questions and Answers

• Remote Sites: Please send email to sandovmi@ohsu.edu or reply to the announcement email if you have questions and it will be asked on your behalf.

• Please limit your questions to 30 seconds or less to allow everyone to participate. If you have general comments or appreciation for the speaker, they will be available after the program to speak with individuals.