Broad-spectrum micronutrient supplements as psychiatric disorder treatments: rationale, background, and safety

Barbara L. Gracious MD, Jeffrey Research Fellow
Center for Innovation in Pediatric Practice
The Research Institute at Nationwide Children’s Hospital
Associate Professor of Clinical Psychiatry and Nutrition
The Ohio State University
Barbara L. Gracious MD has no related conflicts to disclose
She will be discussing “off-label” use of micronutrients
Credits and Disclaimers

• Thank you to Charlie Popper MD, Julia Rucklidge PhD, and Bonnie Kaplan MD for allowing use of their slides

• Similar material is presented from the 2015 APA symposium “Mineral-vitamin Combinations as Primary Treatment of Psychiatric Disorders”, sponsored by the Caucus on Integrative Medicine

• No BSMN treatment has yet been approved by the U.S. FDA or by Health Canada
What is a micronutrient?

• an essential nutrient, as a trace mineral or vitamin, that is required by an organism in minute amounts, for the normal growth and development of living organisms.
• Scientific Rationale for BSMN treatments
1) The brain is a micronutrient-based organ

- Vitamins and minerals cross the blood brain barrier to:
  - operate as CNS cofactors of enzymatic reactions and transcription factor conversions
  - serve as structural components of enzymes involved in neurotransmitter synthesis and metabolism (minerals)
  - help with receptor transformation, transport systems, ion channels, and pump mechanisms;
  - alter membrane fluidity;
  - affect second and third messenger systems, leading to neuron growth and repair, preventing apoptosis
One small portion of serotonin pathway

- 6-Hydroxy-kynurenate
- 5-Hydroxy-N-formylkyunrenine
- 5-Hydroxyindole-acetyaldehyde
- 5-Hydroxy-L-tryptophan
- Serotonin

Vit. B₆, Molybdenum, Iron, Copper

3-Formyl-aminobenzaldehyde
Indole
3-Indole-glycolaldehyde
Tryptophan

Vit. B₆, Copper, Iron

Coca-Cola, Oreo, Doritos, Ruffles, Chips Ahoy
2) Optimized micronutrients may reverse or prevent oxidative damage in the CNS

- Nutrient deficiencies and genetic variants in cofactors and enzymes can cause oxidative damage to nuclear DNA and mitochondria, leading to:
  - Inflammation
  - Endothelial dysfunction
  - Neuronal apoptosis
  - Accelerated aging
3) American diet quality is poor

- Modern agricultural and food supply practices have reduced micronutrient concentrations

- Naming just the top 4, 92% of Americans do not get enough potassium, 86% not enough vitamin E, 69% not enough calcium, and 57% not enough Mg++, as per the IOM estimated average dietary requirements
Population Health Studies:
12-15 nutritional epidemiology studies from Australia, Spain, UK, Japan, Canada

- People who eat ‘traditional’ ‘unprocessed’ ‘Mediterranean’ ‘prudent’ diets have lower rates of mood and anxiety symptoms

- People who eat ‘Western’ ‘processed’ diets have higher rates of mood and anxiety symptoms
1 litre of blood enters your brain every minute

• That’s 60 litres of blood every hour

• What is it carrying to your tissues?
Risk of depression within 6.2 years in ~9000 people

Based on fast food (hamburgers, pizza)

Sanchez-Villegas et al., *Public Health and Nutrition*, 2012
Questions

• 1. How many of you are psychiatrists?..... clinicians of any type?

• 3. How many of you have personal experience with mental disorders (you, close relative, friend).

• *Think about how hard it is to change someone’s diet and exercise habits.............*
Should we then consider ‘supplementing’ for some and if so…

• Single or multiple nutrients?
4) Single nutrient effect sizes for mental disorders are generally small

- Nutrient insufficiencies, deficiencies, and nutrient-based pathway genetic variants are broad and ubiquitous across the population

- BSMNs are more likely to be more efficacious in more individuals than single nutrients
Nutrients work most effectively together

So treating with only ONE doesn’t *usually* make physiological sense…
• What evidence supports BSMN treatments for mental disorders?
Safety and preliminary support for efficacy published since 2001

- Anxiety
- Aggression
- ADHD
- OCD
- Mood disorders/bipolar spectrum disorders (BPSD)
- Behavioral symptoms associated with autism
- Substance abuse
- Acute stress following natural disasters
Aggression and behavioral problems
Aggression: Schoenthaler’s studies

1997: 62 imprisoned juveniles using DBPCT over 3 months:
Supplement contained 11 minerals and 7 vitamins ≥ RDA:

Active supplement  →  28% less violence

2000: 80 children (6-12) disciplined at least once:
DBPCT over 4 months of 13 vitamins and 10 minerals mostly below RDA:
Active supplement  →  47% fewer rule infractions
threats and fights, vandalism, defiance, disrespect, obscenities
BSMN supplementation in young adult prisoners
Gesch et al., 2002, Brit J Psychiatry

RCT in 231 young offenders:

- Supplement with a broad array of minerals, vitamins, and some EFAs (26 ingredients at RDA levels)

Active supplement

26.3% fewer rule infractions
35.1% fewer violent acts
Replication in Dutch prisoners (n=221) 1-3 months; Zaalberg et al., 2010, Aggressive Behavior

- **Active**
- **Placebo**

*no significant reductions in rating scales of self- or staff-reported aggressivity or psychiatric symptoms, trend toward improved subjective sense of well-being*
ADHD and micronutrients

• Two (-) early studies (Arnold et al., 1978; Haslam et al., 1984)
  – used megadoses and short trials

• Evidence in last decade growing
  – Two RCTs
    • one negative: used low dose micronutrients (< RDA)
      -not compared directly to placebo
    • one positive with BSMNs; ES range 0.33-2.2

Rucklidge et al., 2010, 2011, 2014; Harding et al, 2003; Rucklidge & Harrison, 2010; Sinn & Bryan, 2010; Gordon et al., in prep
Rucklidge et al. RCT: Micronutrients for Adults with ADHD (2014, Br J Psychiatry):

- 80 participants with ADHD (med free)
  - Mean age: 35 years
  - Diagnosis: SCID-I, CAADID, and >70 on a CAARS scale (self/observer)
- 35% ADHD Inattentive type; 57% ADHD combined
- Co-occurring current diagnoses:
  - 23% mood disorder; 35% an anxiety disorder; 14% drug/alcohol abuse/dependency; 19% LD
  - Mean GAF at baseline = 59
- 8 week RCT: 42 micronutrients (n=42) vs. placebo (n=38)
End of study CGI-I-ADHD; % in each category

- Very much improved
- much improved
- mild improvement
- no change
- a little worse
- much worse
- very much worse

\[ p < .02, ES = 0.53 \]
Improvement in self rated ADHD symptoms; Rucklidge et al., 2014, BJP

\[ p = 0.041, \text{ES} = .47 \]
\[ p = 0.007, \text{ES} = .62 \]
Naturalistic 1-year follow-up: ADHD symptoms
Rucklidge et al., 2014; J Attention Disorders

![Graph showing T score changes over time (Baseline, end of open-label (16 weeks), Follow-up 52 weeks) for different groups: Stayed on micronutrients (n=14), Switched to medications (n=17), Not taking medications or micronutrients (n=41).]
BSMNs for children with ADHD

• 14 Participants (14% Female) aged 8-12 years old (mean age 10.18) medication free
  – 6 Inattentive type, 8 Combined type
  – Co-occurring disorders (reflect usual population)
    • 14% Mood disorder
    • 21% Elimination disorder
    • 42% Oppositional defiant disorder
    • 14% Dyspraxia
    • 7% Autism spectrum disorder
  – 64% previously tried medication

• Reversal design, weeks: 8 on/4 off/8 on/4 off
Combined ADHD symptoms; Gordon et al., under revision

**sig different from baseline ($p < .001$)
Evidence to date for BSMNs in mood disorders
Depression and depressive symptoms

• **Very few good** trials on samples specifically recruited for depression –
  – RCTs with normal populations:
    • 5 positive, 5 negative
  – A few other RCTs for those with other health conditions (3 positive, 1 negative)

• **Only two RCTs** have studied participants with depression
Methylated Vitamin B complex for depression & anxiety in depressed adults; Lewis et al., 2013, ISRN Psychiatry

- 2-month DB-RCT vit B complex vs. placebo
- 60 adults with MDD; 30 and 60 day follow up
- Modest improvement with group differences; unable to verify ES with statistics
Change in depression in ADHD adults: for those *clinically depressed* at baseline; Rucklidge et al., 2014, BJP

![Bar chart showing the change in MADRS pre to post with p = 0.039, ES = .64]
Naturalistic follow-up one year post-baseline: Mood symptoms (MADRS) Rucklidge et al., 2014; J Attention Disorders

- Stayed on micronutrients (n=14)
- Switched to medications (n=17)
- Not taking medications or micronutrients (n=41)
Bipolar Disorder treatment with BSMNs

• 5 open label trials; 2 database analyses

  – Significant reductions in all psychiatric symptoms
  – Significant reduction in medications
  – Response rates range from 50-80%

  – Simmons, 2003; JCP; Kaplan et al., 2001; JCP, Kaplan et al., 2004, JCAP; Popper, 2001, JCP; Frazier et al., 2012, JACM; Rucklidge et al., 2010, BMC Psychiatry; Gately & Kaplan, 2009, Clin Med
Case series (open label), 11 adults
Kaplan et al., 2001, J Clin Psychiatry

**p<.01  *p<.05

**ES=1.97  ES=1.07  ES=1.22

Ham-D (Depression)  YMRS (mania)  BPRS (psychosis)
Database analysis of 358 adults with Bipolar Disorder
Gately and Kaplan, 2009; Clinical Medicine: Psychiatry

• Symptom severity
  – ↓ 41% after 3 months (ES = 0.78)
  – ↓ 45% after 6 months (ES = 0.76) ($p < 0.001$)
• Responder status:
  – 53% showed $\geq 50\%$ improvement at 6 months
• Regressions: ↓ symptom severity over 6 m sig associated with
  – ↑ micronutrient dosage
  – ↓ medication
• Symptom improvements sustained at 6 months, suggesting not due to placebo/expectancy effects
Database analysis (6 months) of 120 Youth with Parent-Reported Bipolar Disorder: % improving using BSMNs

Rucklidge et al., 2009, BMC Psychiatry

ES = 0.78
p < 0.001
Evidence to date for BSMNs for addictions
Application to addictions...

- Alcohol and other drugs affect the gut lining:
  - Decrease uptake of nutrients consumed, and of gut flora
- Blum and colleagues developed “neuro-adaptogens”
  - Mix of amino acids, minerals, vitamins
  - One RCT, 3 Open-label studies
  - Decrease drug hunger and withdrawal (alcohol, cocaine)
  - Reduce relapse rates
  - Improve psychological functioning
  - Research quite old and no stats provided
    - Poulos, 1981; Guenther, 1983; Blum et al., 1988; Brown et al., 1990
20 year old male;
Harrison et al., 2013, J Psychoactive Drugs

- ADHD, MDD, Panic Disorder, Substance Abuse (cannabis and nicotine)
- Past history of treatment with methylphenidate, imipramine, fluoxetine, clonidine, amitriptyline, lorazepam and clonazepam
- On (8 weeks)-off (8 weeks)-on (4 months)-”natural” off (5 months) using vitamin-minerals
Pilot RCT: Micronutrients for smoking cessation; Newton et al., under review

• 24 current smokers (>2 cigarettes/day for 12 months) randomized 1:1 placebo or micronutrients
• 3 weeks multiple baseline
• 4 weeks capsules
• NZ Quitline plus 3 months capsules
• Exit study if resume smoking
• Monthly check in, daily diaries
• Categorical outcome: quit/not quit
% successful quit defined as 3 days no smoking

\[ X^2 = 6.171, \ p < .05, \ \text{Odds ratio} = 10 \ (CI \ 1.4-69.3) \]
Per cent quit at 4 weeks

- Micronutrients: +15%
- Placebo: -18%
- Quitline
Evidence to date for BSMNs for stress and natural disasters
Natural disasters

- ~20-30% of those in a natural disaster develop symptoms of psychological stress including PTSD, depression, and anxiety
- Hard to implement efficacious tx (e.g. CBT, medications)
- 4 RCTs of MNs (mostly B complex formulas) decrease stress/anxiety in both acutely stressed & acutely nonstressed populations
  - Carroll et al., 2000; Schlebusch et al., 2000; Kennedy et al., 2010; Stough et al., 2011
RCT: Oral MVI effects on well-being in healthy young males

The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial

David O. Kennedy · Rachel Veasey · Anthony Watson · Fiona Dodd · Emma Jones · Silvia Maggini · Crystal F. Haskell


day 1
day 28

Placebo B Complex

Rated Anxiety

Perceived Stress Scale

Score

Day 33

F(1, 205) = 4.25, p < 0.05

Placebo

B complex

Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males

Douglas Carroll · Christopher Ring · Martin Suter
Gonneke Willemsen
September 4, 2010 4:35 am:

A 7.1 earthquake occurred in Christchurch, NZ during active trials of multinutrient treatment
In the three weeks following the earthquake there were about 1000 aftershocks.
A “natural experiment”:

Sept 2010: The ADHD Diagnostic Assessment & Research Group at UC conducting trials on ADHD using a broad-spectrum formula (OL and RCT)

- **T0**: participants assessed prior to the quake
- Some taking the formula, some not
- **T1, T2**: Surveyed by phone 1 and 2 weeks post-quake
- Used Depression, Anxiety, Stress Scale (DASS, + EQ impact questions)
Outcomes for BSMNs vs. controls

Earthquake

Rucklidge et al., *Psychiatry Res* 2011;
Rucklidge and Blampied, 2011, *NZ J Psychology*
Implications for disaster intervention

• Could these positive changes generalize to the wider “nonclinical” population?

• In a *randomized* trial?
425 Kilometers Perimeter
11,200 Square Kilometers Area

8203 Earthquakes 4th Sept 2010 - 3rd Sept 2011
in the field of view

Christchurch
Ashburton
Impact of micronutrients on stress, anxiety and PTSD symptoms in general population

- Recruited on-line via Trade Me, Facebook, Community Websites
- 91 randomized
  - 30 to B complex (29 completed)
  - 31 to multinutrient low dose (30 completed)
  - 30 to multinutrient high dose (27 completed)
- 4 week trial with 1 month natural follow up – data collection May to July 2011
- Monitored weekly with on-line Q assessing stress, mood, anxiety and PTSD symptoms
RCT Results

- No grp diff in exercise, hx of mental illness, zoning, counselling, SES, age, sex, leaving town, diet
- All 3 tx groups showed large (B complex) or very large (multinutrient both doses) changes from baseline ---- all better than controls
- Multinutrient gps (both doses) showed superiority to B complex for intrusions, and higher dose gp on CGI (clinical global impressions) for stress, anxiety, energy, mood
At one month follow-up

- Those who stayed on nutrients continued to improve
- Those who didn’t, remained the same
- Clear preference: *five times* more of the ‘high multinutrient dose’ participants stayed on micronutrients compared with those in the B complex group
% change from baseline to 4 weeks

* sig different from control
% with significant PTSD symptoms baseline and 4 weeks

Control  Berocca  EMP4  EMP8

B Complex  Multi-low  Multi-high

Baseline  4 weeks
Reduction in trauma after earthquakes

Rucklidge et al., Hum Psychopharmacol 2012, 2014
Change in depression over time based on treatment at 52 weeks

Depression

Rucklidge et al., 2014, Human Psychopharmacology
Replication: The 2013 Southern Alberta flood
Alberta Flood Study

- Sample: 56 adults aged 23 – 66
- Med-free, evidence of moderate depression and/or anxiety on the Depression, Anxiety and Stress Scale (DASS)
- Placebo: unethical
- Randomized to 3 groups – 6 week blinded RCT:
  - Single nutrient (vitamin D 1000 IU): n=17
  - Few nutrients (B complex): n=21
  - Broad spectrum (~30 minerals and vitamins): n=18
AB-NZ collaboration
Kaplan et al., Psychiatry Res. 2015 Jun 27 epub first

F(2, 52) = 3.81, p < .05; ES = 0.76-0.88
Societal implications of multinutrient treatments
An Example of Cost Projections: Canadian Costs for Mental Disorders
Comparison of costs for one 10 y/o boy with severe OCD, hallucinations

Costs of 6 months of conventional inpatient treatment compared to 6 months of outpatient follow-up with micronutrient treatment

Alberta Healthcare costs for an 11-year-old boy with OCD and Anxiety

Cost Breakdowns

6 months medication

6 months micronutrients

Vit/min

NATIONWIDE CHILDREN’S
When your child needs a hospital, everything matters.

THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE
6 months of micronutrient treatment

<2% of the cost of his previous 6 months conventional treatment
An overview of safety of BSMN treatments
One example: suggested “therapeutic doses” vs. Tolerable Upper Intake Levels (ULs)

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Amount in a typical therapeutic dose, 15 capsules daily</th>
<th>UL for adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>5,760 IU</td>
<td>10,000 IU</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>600 mg</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1,440 IU</td>
<td>2,000 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>360 IU</td>
<td>1,500 IU</td>
</tr>
<tr>
<td>Vitamin B1</td>
<td>18 mg</td>
<td>none set</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>13.5 mg</td>
<td>none set</td>
</tr>
<tr>
<td><strong>Vitamin B3</strong></td>
<td><strong>90 mg</strong></td>
<td><strong>35 mg</strong></td>
</tr>
<tr>
<td>Vitamin B5</td>
<td>21.6 mg</td>
<td>none set</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>36 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Folate</strong></td>
<td><strong>1,440 mcg</strong></td>
<td><strong>1,000 mcg</strong></td>
</tr>
<tr>
<td>Vitamin B-12</td>
<td>900 mcg</td>
<td>none set</td>
</tr>
<tr>
<td>Vitamin H</td>
<td>1,080 mcg</td>
<td>none set</td>
</tr>
<tr>
<td>Calcium</td>
<td>1,320 mg</td>
<td>2,500 mg</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>840 mg</td>
<td>4,000 mg</td>
</tr>
<tr>
<td><strong>Magnesium</strong></td>
<td><strong>600 mg</strong></td>
<td><strong>350 mg</strong></td>
</tr>
<tr>
<td>Potassium</td>
<td>240 mg</td>
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<tr>
<td>Iodine</td>
<td>204 mcg</td>
<td>1,100 mcg</td>
</tr>
<tr>
<td><strong>Zinc</strong></td>
<td><strong>48 mg</strong></td>
<td><strong>40 mg</strong></td>
</tr>
<tr>
<td>Selenium</td>
<td>204 mcg</td>
<td>400 mcg</td>
</tr>
<tr>
<td>Copper</td>
<td>7.2 mg</td>
<td>10 mg</td>
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<tr>
<td>Manganese</td>
<td>9.6 mg</td>
<td>11 mg</td>
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<td>Chromium</td>
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<tr>
<td>Molybdenum</td>
<td>144 mcg</td>
<td>2,000 mcg</td>
</tr>
<tr>
<td>Iron</td>
<td>13.74 mg</td>
<td>45 mg</td>
</tr>
</tbody>
</table>

Table 1, Simpson et al. BMC Psychiatry, 2011
Another product example: suggested therapeutic dose vs. UL, LOAEL for 9-13 y/o

<table>
<thead>
<tr>
<th>Amount in 15 capsules</th>
<th>% DV</th>
<th>Unit</th>
<th>M</th>
<th>F</th>
<th>UL</th>
<th>LOAEL</th>
<th>Adult</th>
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<tbody>
<tr>
<td>Vitamin A</td>
<td>5,760 IU</td>
<td>114%</td>
<td>IU</td>
<td>2,000</td>
<td>2,000</td>
<td>5,666.7</td>
<td>46,667</td>
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<tr>
<td>Vitamin C</td>
<td>600 mg</td>
<td>999%</td>
<td>mg</td>
<td>45</td>
<td>45</td>
<td>1,200</td>
<td>3,000</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>3,000 IU</td>
<td>750%</td>
<td>IU</td>
<td>600</td>
<td>600</td>
<td>4,000</td>
<td>3,800</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>360 IU</td>
<td>1200%</td>
<td>IU</td>
<td>16.5</td>
<td>16.5</td>
<td>900</td>
<td>750</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>120 mcg</td>
<td>150%</td>
<td>mcg</td>
<td>60</td>
<td>60</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Thiamin</td>
<td>60 mg</td>
<td>3999%</td>
<td>mg</td>
<td>0.9</td>
<td>0.9</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Riboflavin</td>
<td>18 mg</td>
<td>1059%</td>
<td>mg</td>
<td>0.9</td>
<td>0.9</td>
<td>*</td>
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<tr>
<td>Niacin</td>
<td>90mg</td>
<td>450%</td>
<td>mg</td>
<td>12</td>
<td>12</td>
<td>20</td>
<td>50</td>
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<td>Vitamin B₆</td>
<td>69.9mg</td>
<td>3501%</td>
<td>mg</td>
<td>1</td>
<td>1</td>
<td>60</td>
<td>500</td>
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<tr>
<td>Folate</td>
<td>801mcg</td>
<td>201%</td>
<td>mcg</td>
<td>300</td>
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<td>5000</td>
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<tr>
<td>Vitamin B₁₂</td>
<td>900 mcg</td>
<td>15000%</td>
<td>mcg</td>
<td>1.8</td>
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<td>mcg</td>
<td>20</td>
<td>20</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Pantothentic Acid</td>
<td>30 mg</td>
<td>300%</td>
<td>mg</td>
<td>4</td>
<td>4</td>
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<td>*</td>
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<td>Calcium</td>
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<td>mg</td>
<td>700</td>
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<td>75%</td>
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<td>8</td>
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<td>84%</td>
<td>mg</td>
<td>1,250</td>
<td>1,250</td>
<td>4,000</td>
<td>10,200</td>
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<tr>
<td>Iodine</td>
<td>204 mcg</td>
<td>135%</td>
<td>mcg</td>
<td>700</td>
<td>1,300</td>
<td>3,000</td>
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<td>Zinc</td>
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<td>40</td>
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<td>Copper</td>
<td>7.2 mg</td>
<td>360%</td>
<td>mg</td>
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<td>5</td>
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<td>Manganese</td>
<td>9.6mg</td>
<td>480%</td>
<td>mg</td>
<td>1.9</td>
<td>1.6</td>
<td>6</td>
<td>15</td>
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<tr>
<td>Chromium</td>
<td>624 mcg</td>
<td>519%</td>
<td>mcg</td>
<td>25</td>
<td>21</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>144 mcg</td>
<td>192%</td>
<td>mcg</td>
<td>34</td>
<td>34</td>
<td>1,100</td>
<td>1,500</td>
</tr>
<tr>
<td>Potassium</td>
<td>240 mg</td>
<td>6%</td>
<td>mg</td>
<td>4,500</td>
<td>4,500</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* Value not established
Also consider proprietary blends when thinking about safety and tolerability

A variety of antioxidants/botanicals:
  - Ginkgo biloba (from leaf), grape seed extract, citrus bioflavonoids

Differing amino acids:
  - Glutamine, DL-Phenylalanine, L-Methionine
  - Alpha-lipoic acid, N-acetyl cysteine,
  - Acetyl-L-carnitine

Choline and inositol

Other trace minerals

Organic lithium
Safety and tolerability data from clinical studies
Adverse effects- MCN vs. usual tx. in ASD

Case-control study: N=44 for each group
  • retrospective chart review
    • Matched by age, sex, parental education, income, IQ category, CGI symptom severity.
  • Family chose treatment; 3 differing MCN products
  • Single prescriber, 2 sites
  • Sample largely urban, Caucasian, male, young (<12 y/o)
  • Over 65% on rx medications at referral; goal to use lowest minimum dose for traditional medications

### Number of AEs: MCN 33, medication 214

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Micronutrient group (n)</th>
<th>Medication group (n)</th>
<th>Group difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased appetite</td>
<td>1</td>
<td>32</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>29</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>Drowsiness</td>
<td>1</td>
<td>31</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>9</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>19</td>
<td></td>
<td>0.004</td>
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<tr>
<td>Diarrhea</td>
<td>4</td>
<td>5</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>6</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>1</td>
<td>4</td>
<td></td>
<td>0.360</td>
</tr>
<tr>
<td>Drooling</td>
<td>0</td>
<td>4</td>
<td></td>
<td>0.116</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>8</td>
<td></td>
<td>0.089</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>9</td>
<td>9</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>6</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>Increased thirst</td>
<td>0</td>
<td>5</td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>5</td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>0</td>
<td>7</td>
<td></td>
<td>0.012</td>
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<tr>
<td>Nausea</td>
<td>3</td>
<td>5</td>
<td></td>
<td>0.713</td>
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<tr>
<td>Decreased appetite</td>
<td>2</td>
<td>5</td>
<td></td>
<td>0.434</td>
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<tr>
<td>Tremor</td>
<td>2</td>
<td>8</td>
<td></td>
<td>0.089</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>4</td>
<td></td>
<td>0.116</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>0</td>
<td>4</td>
<td></td>
<td>0.116</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0</td>
<td>3</td>
<td></td>
<td>0.241</td>
</tr>
<tr>
<td>Akathesia</td>
<td>0</td>
<td>6</td>
<td></td>
<td>0.026</td>
</tr>
</tbody>
</table>

*p values obtained from Fisher exact test

Safety, tolerability, and serum micronutrient levels in children with BPSD

10 youth ages 6-12 took up to 15 capsules/day for 8 weeks
7 completed; 3 dropped out due to swallowing issues
All AEs were mild and transient
  • GI upset, resolved with taking product with food
  • Initial insomnia, resolved with taking product earlier
One child started a stimulant without difficulty
4/10 serum levels increased:
  • Vitamin A (retinol), vit B6, vit E-alpha tocopherol, folate

### Mean Serum Concentrations of Vitamins and Minerals Pre- and Supplementation

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Reference range</th>
<th>Average pre-level Mean (SD)</th>
<th>Average post-level Mean (SD)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTfR</td>
<td>2.9–8.3 μg/mL</td>
<td>3.9 (0.82)</td>
<td>3.6 (0.46)</td>
<td>0.600</td>
</tr>
<tr>
<td>Ferritin</td>
<td>20.0–400.0 ng/mL</td>
<td>138.3 (104.31)</td>
<td>90.5 (69.97)</td>
<td>0.091</td>
</tr>
<tr>
<td>Mg</td>
<td>15.0–30.0 μg/mL</td>
<td>17.3 (1.02)</td>
<td>17.7 (0.49)</td>
<td>0.176</td>
</tr>
<tr>
<td>Zinc</td>
<td>&gt;0.8 μg/mL</td>
<td>1.7 (0.42)</td>
<td>1.8 (0.47)</td>
<td>0.612</td>
</tr>
<tr>
<td>Vit A: Retinol</td>
<td>&gt;0.70 μmol/L</td>
<td>3.3 (1.16)</td>
<td>5.0 (1.58)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Vit B₆: PLP</td>
<td>20.0–120.0 nmol/L</td>
<td>54.3 (16.61)</td>
<td>104.0 (41.24)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Vit D</td>
<td>&gt;20.0 ng/L</td>
<td>26.3 (3.93)</td>
<td>38.7 (22.22)</td>
<td>0.063</td>
</tr>
<tr>
<td>Vit E: α-TC</td>
<td>6–12 μg/mL</td>
<td>6.6 (2.07)</td>
<td>10.6 (3.00)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Vit E: γ-TC</td>
<td>——</td>
<td>1.3 (0.59)</td>
<td>0.92 (0.35)</td>
<td>0.063</td>
</tr>
<tr>
<td>Folate</td>
<td>3.8–23.2 μg/mL</td>
<td>3.9 (1.72)</td>
<td>5.9 (0.75)</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

*significant, p<0.05
Rucklidge ADHD in adults study

Adverse effects: NSD between groups

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Micronutrient formula group (n = 42)</th>
<th>Placebo group (n = 38)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16</td>
<td>15</td>
<td>1.00</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13</td>
<td>15</td>
<td>0.49</td>
</tr>
<tr>
<td>Sleep disruptions</td>
<td>16</td>
<td>8</td>
<td>0.14</td>
</tr>
<tr>
<td>Gastrointestinal disturbances/diarrhoea</td>
<td>13</td>
<td>9</td>
<td>0.62</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>8</td>
<td>0.61</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>8</td>
<td>0.37</td>
</tr>
<tr>
<td>Agitation</td>
<td>8</td>
<td>5</td>
<td>0.55</td>
</tr>
<tr>
<td>Sedation</td>
<td>4</td>
<td>7</td>
<td>0.33</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>8</td>
<td>0.37</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>5</td>
<td>0.47</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2</td>
<td>4</td>
<td>0.42</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>2</td>
<td>3</td>
<td>0.66</td>
</tr>
</tbody>
</table>
# Nutrient level changes, MCN vs. placebo

<table>
<thead>
<tr>
<th>Nutrient levels</th>
<th>MCN Baseline mean, (s.e.)</th>
<th>MCN Change, mean, (s.e.)</th>
<th>Placebo Baseline mean, (s.e.)</th>
<th>Placebo Change, mean, (s.e.)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D, nmol/l</td>
<td>62.4 (4.4)</td>
<td>15.6 (3.1)</td>
<td>68.5 (3.8)</td>
<td>0.4 (3.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vitamin B$_{12}$, pmol/l</td>
<td>353.3 (18.3)</td>
<td>383.1 (30.2)</td>
<td>374.9 (22.7)</td>
<td>1.1 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Folate, nmol/l</td>
<td>21.1 (1.5)</td>
<td>24.3 (2.2)</td>
<td>22.4 (1.4)</td>
<td>–1.6 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Magnesium, mmol/l</td>
<td>0.89 (0.01)</td>
<td>–0.00 (0.01)</td>
<td>0.92 (0.01)</td>
<td>–0.01 (0.01)</td>
<td>0.724</td>
</tr>
<tr>
<td>Ferritin, μg/l</td>
<td>116.9 (13.1)</td>
<td>–2.44 (5.57)</td>
<td>105.6 (11.8)</td>
<td>–6.83 (5.49)</td>
<td>0.577</td>
</tr>
<tr>
<td>Iron, μmol/l</td>
<td>18.3 (0.9)</td>
<td>–0.4 (1.0)</td>
<td>19.3 (1.2)</td>
<td>0.4 (1.0)</td>
<td>0.568</td>
</tr>
<tr>
<td>Calcium, mmol/l</td>
<td>2.39 (0.02)</td>
<td>0.03 (0.02)</td>
<td>2.39 (0.02)</td>
<td>0.01 (0.02)</td>
<td>0.286</td>
</tr>
<tr>
<td>Zinc, μmol/l</td>
<td>12.1 (0.2)</td>
<td>0.4 (0.3)</td>
<td>12.5 (0.2)</td>
<td>0.1 (0.3)</td>
<td>0.423</td>
</tr>
<tr>
<td>Copper, μmol/l</td>
<td>15.4 (0.6)</td>
<td>0.4 (0.4)</td>
<td>13.5 (0.4)</td>
<td>–0.4 (0.4)</td>
<td>0.171</td>
</tr>
</tbody>
</table>
1-year naturalistic follow up, ADHD in adults

72/80 were followed up at a mean of 11 mo.
19% continued the broad-spectrum MCN after 10 weeks
24% switched to medications/stopped MCN

57% stopped MCN and were not taking medications
Reasons for cessation:
   1) cost; 2) number of pills; 3) lack of benefit; 4) AEs.

*No participant continuing MCN reported any ongoing AEs.*

Example of labeling information for clinicians

“Because interactions … with psychiatric medications have not been systematically evaluated, caution is warranted. Any agent with CNS activity has the potential to interact with broad spectrum micronutrients and complicate the management of micronutrient treatments.”

“These include psychiatric medications, medical drugs with CNS actions (antihistamines, medications for ‘colds’, theophylline, etc.), recreational agents (alcohol, marijuana, heroin, etc.), other commonly used substances that are not necessarily thought of as recreational agents (caffeine, nicotine), and certain hormones (e.g., glucocorticoids).”
Common side effects of broad spectrum MCNs

Renal:
Common: “Neon” yellow urine (due to riboflavin excretion; not harmful)

GI:
Dyspepsia, nausea, or rarely vomiting, if not taken with food
Loose stools, flatulence, watery diarrhea

CNS:
Insomnia
Headache

Anxiety, agitation, or impulsivity if dose too high/sensitivity
Other important nutrient product-drug interactions

Antibiotics:
- Change gut flora, decrease breakdown and absorption
  - symptoms may worsen; can raise dose temporarily

Antacids (e.g. Zantac, Prilosec, Tagamet):
- neutralize or inhibit the production of stomach acid,
  reduce the breakdown and absorption of nutrients

Caffeine, chocolate, marijuana:
- decreased effectiveness
Patient selection factors

Strict contraindications:
Wilson’s disease (copper overload)
- what about carriers?
Hemochromatosis and hemosiderosis
  what about carriers/early expression?
Phenylketonuria
  only for the supplement with phenylalanine?
Trimethylaminuria (risk of choline overload)
Immunosuppressed
Active or remitted cancer
Active infectious disease
Acute or chronic liver, renal disease
Summary I

There are no formal product development phase I, II, III bioavailability, pharmacokinetic or dosing safety trials

Therefore, check the MCN preparation to ensure doses under the LOAEL
  • Pay attention to individual patient factors as key to safe use
  • Added proprietary blend ingredients are often without sufficient study and require screening for contraindications for any specific patient

Products have government product licenses; manufacturing processes may be monitored and regulated for quality control, and several products have had FDA Investigational New Drug (IND) approvals for study

Short-term profile of side effects in clinical studies to date show adequate safety and tolerability
Only one RCT to date of short-term use
No prospective RCTs of long-term use
Summary II

Independent, foundation and/or federal funding is critically needed to provide research data on safety, tolerability, and confirm dosing for different populations and uses.

Practitioners desiring to use MCN treatments should:

- educate themselves sufficiently about products, studies to date
- obtain experienced consultation around their use
- update regularly on nutritional safety data—
  - a constantly changing field!
Perhaps our ancestors had it right

- 1910 People’s Home Library
- guided families; health care providers were not easily accessed
- The number one cause of acquired insanity was:

“imperfect nutrition”
Commercial vs research products: are they the same?
Rucklidge, Harris & Shaw, 2014, NZMJ
Which BSMNs have evidence of benefit with mental symptoms?
Summary

• **Offending:** Four RCTs showed superiority of nutrients over placebo in reducing offending behaviours (28-47% reduction) in incarcerated adults and antisocial youth

• **ADHD:** most trials, including 1 RTC, showed benefits of micronutrients (ES=0.33-2.18)

• **Depression:** Two RCTs showed superiority of nutrients over placebo for reducing clinical depression (ES=0.64)
  
  – Other RCTs examined mood changes in healthy or medically ill populations (8 positive, 6 negative), making generalization to psychiatric samples difficult

• **Bipolar disorder:** 5 OL trials showed benefit with large effect sizes (>0.8)
Summary

- **Addictions**: very old studies documenting some benefit of nutrients in diminishing alcohol and opiate withdrawal symptoms
  - A pilot RCT showed benefits of multinutrients in assisting people with quitting smoking
- Most consistent results obtained from formulas with broad range of nutrients higher than RDA
- **Challenges**: doses, sample sizes, generalizability, variable nutrients used, lack of controlled studies, replication, *urgent research is required*
Useful References


Acknowledgements

• **Current Graduate students working on nutrient studies**
  - Heather Gordon
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  - Kathryn Darling
  - Hahna Retallick-Brown

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  - Rachel Harrison
  - Sarah Anticich
  - Kathryn Whitehead
  - Dr Nicola Ward
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  - Dr Petra Hoggarth

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  - Prof Neville Blampied
  - Prof Chris Frampton
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  - Summer studentships
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julia.rucklidge@canterbury.ac.nz