Micronutrients as a treatment for psychiatric disorders: The evidence to date

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Disclosure

• No commercial interest in any company or sale of any product
Overview

- Within framework of nutrients as being essential for optimal brain functioning
  - Review evidence across a broad range of psychiatric conditions using micronutrients
  - Focus only on *broad spectrum* supplementation
  - Select examples from mood, forensics, autism, stress, anxiety, trauma, ADHD
Our current approach to psychiatric problems

- Nonresponders can range from 20-50% with greater complexity of problems associated with worse outcomes
- Side effects ongoing concern for many
What’s the evidence for broad spectrum micronutrients?
Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
- Case series
- Case controls
- RCTs

Why is this level of evidence important?

Evidence-based medicine

Rollout into clinical practice
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20 year old male

ADHD, MDD, Panic Disorder, Substance Abuse (cannabis and nicotine)

Past hx of tx 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
On-off control of ADHD symptoms

Harrison et al., 2013, J of Psychoactive Drugs
Progression of Evidence on Micronutrients & Psychiatric Symptoms

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Tx of Bipolar Disorder with nutrients

- All studies to date on one formula, EMPowerplus
- 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

Improvement in Bipolar Disorder in 120 children over a 6-month period

Rucklidge JJ, Gately D, Kaplan BJ; BMC Psychiatry 2010
Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
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- RCTs
- Roll out into clinical practice
No grp differences on the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale

Case-control study of 88 children with autism
Yale-Paris Self-injurious Behaviour

CGI Ratings also sig better in micronutrient group
Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
- Case series
- Case controls
- Randomized controlled trials (RCTs)
- Roll out into clinical practice
Depression
Anxiety
ADHD

Over 20 positive RCTs to date
All negative trials (6) done on people WITHOUT psychiatric symptoms
Forensics: 4 RCTs

All four studies show benefit for reducing violence acts and rule infractions
Schoenthaler et al., 1997, 2000; Gesch et al., 2002; Zaalberg et al., 2010
Micronutrient supplementation (Forceval) in 231 young adult prisoners, Gesch et al. 2002, *Brit J Psychiatry*

![Graph showing the ratio of rate of disciplinary incidents before and during supplementation.](image)

**Before Supplementation**
- Active: 1.0
- Placebo: 0.8

**During Supplementation**
- Active: 0.7
- Placebo: 0.3

↓35% for Active
↓6.7% for Placebo
Replication in a Dutch sample, Zaalberg et al., 2010, *Aggressive Behavior*
Stress, Natural disasters and nutrients
Micronutrients for stress

- 5 RCTs have shown that over-the-counter micronutrients (Berocca or Blackmore’s):
  - decrease stress/anxiety, improve energy and mood in both stressed and nonstressed populations
  - Carroll et al., 2000; Gruenwald et al., 2002; Schlebusch et al., 2000; Kennedy et al., 2010, 2011; Stough et al., 2011
Can this effect generalize to stress following an earthquake?
February 22\textsuperscript{nd} 2011 12:51 pm

185 people died, 6659 injured, 30,000 homes destroyed, cost to NZ: 12.9 billion dollars
425 Kilometers Perimeter
11,200 Square Kilometers Area

8203 Earthquakes 4th Sept 2010 - 3rd Sept 2011
in the field of view
Micronutrients on PTSD symptoms in general population experiencing stress following earthquake
Rucklidge et al., 2012, Human Psychopharmacology

- Recruited on-line
  - 201 completed survey: 127 eligible

- 91 randomized
  - 30 to Berocca (29 completed)
  - 31 to EMP4 (30 completed)
  - 30 to EMP8 (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

- 25 of original pool served as controls (7 medicated)
Reduction in trauma after earthquakes

Rucklidge et al., Hum Psychopharmacol 2012, 2014
Protective in the Long term? Change in stress over time between those treated acutely with micronutrients and control group

Rucklidge et al., 2014, Human Psychopharmacology
Change in depression over time based on treatment at 52 weeks

Rucklidge et al., 2014, Human Psychopharmacology
“The triage theory posits that when the availability of a micronutrient is inadequate, nature ensures that micro-nutrient-dependent functions required for short-term survival are protected at the expense of functions whose lack has only longer-term consequences…”

- McCann and Ames 2009
ADHD
Micronutrients with adults with ADHD: RCT evidence
Rucklidge et al., 2014, British Journal of Psychiatry

- 80 participants: 42 micronutrients, 38 placebo
- Mean age: 35 years
- Diagnosis:
  - SCID-I and CAADID and
  - >70 on one of the DSM based scales of CAARS (self/observer)
- 35% ADHD Pred Inatt; 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
Change in self-rated ADHD symptoms

Rucklidge et al; *British Journal of Psychiatry, 2014*

\[ p = 0.041, \ ES = .47 \]

\[ p = 0.007, \ ES = .62 \]
CGI – I – ADHD post RCT

\[ p < .02, ES = 0.53 \]
Change in depression: only those *clinically depressed* at baseline

\[ p = 0.039, \text{ ES} = 0.64 \]

**Active (n=11)** vs **Placebo (n=10)**

*change in MADRS pre to post*
Naturalistic follow-up one year post-baseline: ADHD symptoms
Rucklidge et al., 2014; Journal of Attention Disorders

![Graph showing symptom changes over time for different treatment groups.]

- **Stayed on micronutrients** (n=14)
- **Switched to medications** (n=17)
- **Not taking medications or micronutrients** (n=41)
Can we predict who will respond to micronutrients?

Not really, not yet
Percentage falling within or outside normal reference ranges for serum nutrients
Baseline nutrient levels converted to tertiles and compared with per cent ADHD responders

Per cent classified as ADHD responders

* \( p < 0.05 \)
Side effects?

- minor and transitory

Compliance?

- No difficulties with the regimen†

Impact on blood results?

- None to date…*

Long-term effects?

- Needs to be studied properly

* *lack* of difference in fasting glucose, lipids, white blood cell count, and neutrophils, slight elevation on prolactin but still within normal range

† some find taking the pills tedious and stop for that reason

"The tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the specified life stage group."

Progression of Evidence on Micronutrients & Psychiatric Symptoms

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- Case series
- Case controls
- Randomized controlled trials (RCTs)
- Roll out into clinical practice....
Rodway et al., BMJ Case Reports, 2012

Cost of conventional inpatient treatment

Cost of micronutrient outpatient treatment
None of them have been developed specifically for mental health symptoms...
Commercial vs research products: Are they the same? Rucklidge, Harris & Shaw, 2014, NZMJ
Vitamin B₆ Daily Dose (mg)

Research supplements

Over-the-counter supplements
Research supplements

Over-the-counter supplements

Vitamin B₁₂ Daily Dose (mcg)
Which ones have any evidence to help with mental illness?
Do these data challenge our conceptualization of mental illness?
Could some forms of mental illness reflect metabolic reactions going wrong?

AKA Inborn errors of metabolism
Could some cases of mental disorders reflect inborn errors of metabolism?

- People inherit a *genetic defect* that results in decreased binding ability of an enzyme(s).
- Results in slowed metabolic reactions.
- Less efficiency in making chemicals for optimal functioning.
- Resulting in psychiatric symptoms.
- Can be corrected at endpoint by:
  - Administration of high doses of the vitamin component of corresponding coenzyme, restoring enzymatic activity.

  - Ames et al., 2002; Kaplan et al., 2007
One small portion of serotonin pathways

6-Hydroxykynurenone → 5-Hydroxy-N-formylkynurenone (Vit. B₆) → 5-Hydroxy-L-tryptophan (Vit. B₆) → Serotonin (Iron)

5-Hydroxyindoleacetyaldehyde → 5-Hydroxyindolepyruvate → 3-Formylaminobenzaldehyde (Copper) → Indole (Vit. B₆) → Copper → Tryptophan (Iron)

3-Indole-glycolaldehyde → Copper → Tryptophan
Krebs (Citric Acid) Cycle

Pyruvate

\[ \text{Pyruvate dehydrogenase - Thiamine} \]

\[ \text{NAD} \]

\[ \text{NADH + H} \]

\[ \text{Acetyl-CoA} \]

\[ \text{Citrate} \]

\[ \text{Aconitate hydratase - [4Fe-4S]} \]

\[ \text{Isocitrate} \]

\[ \text{Isocitrate dehydrogenase - Mn}^{2+} \text{ or Mg}^{2+}, \text{Nicotinamide} \]

\[ \text{Oxaloacetate} \]

\[ \text{Fumarate} \]

\[ \text{Succinate dehydrogenase - Fe, S, Riboflavin} \]

\[ \text{Succinate} \]

\[ \text{Succinyl-CoA} \]

\[ \text{NAD} \]

\[ \text{NADH + H} \]

\[ \text{GTP} \]

\[ \text{GDP} \]

\[ \text{P}_i \]

oxoglutarate dehydrogenase - Thiamine

2-oxoglutarate synthase - Thiamine and 2 [4Fe-4S] clusters
dihydrolipoyl dehydrogenase - Riboflavin

\[ \text{NAD} \]

\[ \text{NADH + H} \]

\[ \text{Oxalosuccinate} \]

\[ \text{isocitrate dehydrogenase - Mn}^{2+} \text{ or Mg}^{2+}, \text{Nicotinamide} \]

\[ \text{NAD} \]

\[ \text{NADH + H} \]

http://www.genome.jp/kegg/pathway/map/map00020.html
Growth is controlled not by the total amount of resources available, but by the scarcest resource (limiting factor).
Future research

Photo credits: Greg Emmerich; Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine; Taki Steve
Considerations and challenges

- Which nutrient(s) is necessary? Could we get away with a smaller set of key nutrients?
- Dietary changes versus supplementation?
- Other medications (particularly psychiatric ones)
- Short and long-term compliance – many people stop them, even if working...
- Cost to patients
Conventional medicine

therapy

medication

other
Concluding messages...

- Physiologically, makes sense to provide body/brain with nutrients to optimize functioning for those with psychiatric symptoms.

- If can’t be achieved through diet or diet manipulation alone, then additional nutrients may be required.

- After a decade of research, most studies on broad spectrum nutrients positive across different countries, different formulas, different conditions.
  - But we need replication, consideration of the role of specific nutrients and optimal doses.
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The most studied micronutrient formula: EMPowerplus

- Vitamins A, C, D, E, B₁, B₂, B₃, B₅, B₆, B₉, B₁₂
- Biotin, Pantothenic acid, Calcium
- Iron, Phosphorous, Iodine, Magnesium
- Chromium, Molybdenum, Potassium
- Zinc, Selenium, Copper, Manganese
- dl-Phenylalanine, Glutamine, Citrus bioflavonoids, Grape seed, Ginkgo biloba
- Vanadium, Boron, Methionine, Germanium, Inositol, Nickel
For further info on the formulas mentioned here today....... 

- **EMPowerplus/CNE/Q96**: [www.truehope.com](http://www.truehope.com)  
- **Brain Child Spectrum Support**:  
- **Forceval**: [http://www.forceval.co.uk/](http://www.forceval.co.uk/)  
- **Blackmores Executive B**:  
- **Max Stress B**  
  [http://www.healthproductsusa.net/30_max_stress_b_health.html](http://www.healthproductsusa.net/30_max_stress_b_health.html)  