Micronutrients in mental illness: What is the evidence?

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Invited talk, April 13th 2014
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 based* supplementation
  - Select examples from mood, forensics, autism, stress, anxiety, trauma, ADHD
Nonresponders can range from 20-50% with greater complexity of problems associated with worse outcomes. And side effects an ongoing concern for many.
What’s the evidence for broad based micronutrients?
Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
- Case series
- Case series of hundreds
- Case controls
- RCTs
- Roll out into clinical practice

**WHY IS THIS LEVEL OF EVIDENCE IMPORTANT?**
Progression of Evidence on Micronutrients & Psychiatric Symptoms

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Case study: 18-yr-old boy with OCD

Rucklidge, 2009
Journal of Anxiety Disorders

• Hand washing, religiosity, etc.
• CBT for 1 yr with modest response
  – OCD had shifted from severe to moderate
• Within a year, anxiety deteriorated back to severe range and now had major depression
• Entered ABAB design trial using EMPowerplus
• After 8 wks on formula, his mood stabilized, anxiety reduced, and obsessions in remission
• Treatment discontinued for 8 wks, during which time obsessions and anxiety worsened and mood dropped. {Note: he did not believe formula was responsible for improvement.}
• Reintroduction of formula again improved the symptoms
Case study: Natural ABAB

- Y-BOCS- Total
  - Baseline
  - CBT
  - Baseline (1 yr post termination of CBT)
  - Supplement
  - No supplement
  - Supplement

- Y-BOCS - Obsessions
  - Baseline
  - CBT
  - Baseline (1 yr post termination of CBT)
  - Supplement
  - No supplement
  - Supplement
“Brian”

- 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
- Monitored with CGI, Conners, MADRS, YMRS, GAF
- On (8 weeks)-off (8 weeks)-on (4 months)-”natural” off (5 months) using EMP
On-off control of ADHD symptoms

Harrison et al., 2013, J of Psychoactive Drugs
Can micronutrients help with reducing substance abuse?
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Tx of Bipolar Disorder with nutrients

- All studies to date on one formula, EMP
- 3 case studies with reversals
  - Kaplan et al., 2002; Rucklidge & Harrison, 2010
- 5 open label trials
  - Significant reductions in all psychiatric symptoms
  - Significant reduction in medications
  - Response rates approx 80%
    - Simmons, 2003; JCP; Kaplan et al., 2001; JCP, Kaplan et al., 2004, JCAP; Popper, 2001, JCP; Frazier et al., 2012, JACM
Case series (open label), 11 adults

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Database analysis of 120 children with bipolar: percent improving using EMP
Rucklidge et al., 2009, BMC Psychiatry

% of 120 clients
(ordered by greatest % reduction from Baseline)

% change in bipolar symptom severity from Baseline to Last Observation Carried Forward

-100%  -75%  -50%  -25%  0%  25%  50%  75%  100%

10%  20%  30%  40%  50%  60%  70%  80%  90%  100%

20% of clients
21% of clients
21% of clients
14% of clients
19% of clients
5% of clients
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Micronutrients and autism
Mehl-Madrona et al., 2010, JCAP

- 88 children in private practice – 44 taking micronutrients and 44 matched children taking medications
  - Micronutrient Group improved as much as Medication Group on both the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale
  - Both groups exhibited significant decreases in total Aberrant Behavior Checklist scores, but the Micronutrient Group’s improvement was greater, p < 0.0001.
  - Improvements in Micronutrient Group were also greater for Self Injurious Behaviour Intensity (p = 0.005), Clinical Global Impressions (p = 0.0029)
  - Adverse events and average weight gain were less in the Micronutrient Group
Case-control study of 88 children with autism

No grp differences on the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale
Yale-Paris Self-injurious Behaviour

CGI Ratings also sig better in micronutrient group
Case studies

Case series

Case series of hundreds

Case controls

Randomized controlled trials (RCTs)

Roll out into clinical practice
Natural disasters and nutrients
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?
Poor food choices after a disaster + growing research showing micronutrients can have a positive effect on a wealth of psychological symptoms suggests supplementation following a natural disaster could be beneficial
February 22nd 2011 12:51pm

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)
Results

- No grp diff in exercise, hx of mental illness, zoning, counselling, SES, age, sex, leaving town, diet

- All 3 tx groups showed large (Berocca) or very large (EMP both doses) changes from baseline
  - All 3 significantly better than controls

- EMP (both doses) showed superiority to Berocca for intrusions, and higher dose for CGIs of stress, anxiety, energy, mood
  - no tx differences on other measures

- 1 mnth follow up:
  - those who stayed on continued to improve, those who didn’t, stayed same
  - preference for higher dose of EMP: 5x more of these participants stayed on EMP micronutrients compared with those in the Berocca™ group
% with significant PTSD symptoms baseline and 4 weeks

- Baseline
- 4 weeks

Control | Berocca | EMP4 | EMP8

0% | 20% | 40% | 60% | 80%
Maybe nutrients feed the brain and replete the system under chronic stress

“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
Change in stress over time between 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
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*
Replication in a Dutch sample, Zaalberg et al., 2010, Aggressive Behavior

Incident ratios

Before Supplementation: Active (11) vs. Placebo (10)
During Supplementation: Active (7) vs. Placebo (11)

- Active: ↓34% (Before) vs. ↑14% (During)
- Placebo: ↑14% (Before) vs. ↓34% (During)
Autism
Micronutrients and autism: 2 RCTs; Adams et al., 2004, 2011

- First pilot trial = 20 children – 10 micronutrients (Spectrum Support) and 10 placebo
  - Improved sleep and GI problems

- Second trial: 141 children and adults with ASD treated with micronutrients (29 ingredients) – 3 month treatment
  - Vitamins/minerals used adjunctively (Syndion)
  - Those taking micronutrients showed improved sleep, reductions of tantrums, hyperactivity, and improved verbal language as well as GI problems compared with placebo
Change in functioning after 3 months micronutrients versus placebo

Small to medium effects in group differences
ADHD
ADHD and micronutrients

- Early studies negative
  - used megadoses and short trials
- Evidence in last decade growing based on:
  - open-label
  - retrospective database analyses
  - case reports
  - patient preference studies
  - One RCT on micronutrients
    - Rucklidge et al., 2010, 2011, 2014; Harding et al, 2003; Rucklidge & Harrison, 2010
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 Inattention across raters

- Change in CAARS Inattention Self: $p = 0.007, ES = .62$
- Change in CAARS Inattention Observer: $p = 0.215, ES = .33$
- Change in CAARS Inattention Clinician: $p = 0.919, ES = .02$
Change in Hyperactivity/Impulsivity across raters

\[ p = 0.041, \text{ ES } = 0.47 \]

\[ p = 0.013, \text{ ES } = 0.67 \]

\[ p = 0.081, \text{ ES } = 0.40 \]
CGI – I – ADHD post RCT

\[ p < .02, \ ES = 0.53 \]
Naturalistic follow-up one year post-baseline: ADHD symptoms

- Stayed on micronutrients (n=14)
- Switched to medications (n=17)
- Not taking medications or micronutrients (n=41)
Naturalistic follow-up one year post-baseline: Mood symptoms

- Stayed on micronutrients (n=14)
- Switched to medications (n=17)
- Not taking medications or micronutrients (n=41)
Mood
Depression: No good trials on samples specifically recruited for depression –

- lots of RCTs with normal populations (5 +ve RCT, 5 –ve RCTs) and others with health conditions (3 +ve RCTs, 1 – ve RCT)
- Our RCT using EMP with ADHD showed benefit for a small subgroup who entered trial moderately to severely depressed
MADRS: only those clinically depressed at baseline

- Active (n=11)
- Placebo (n=10)

$p = 0.039$, $ES = .64$
Does any of this amount to evidence?

- Depends how we conceptualize mental illness
  - DSM based categories suggest each category may have a separate etiology
  - But are they that separate? – can we lump all of the studies together?
- Bradford Hill, 1952: Created the basis for modern RCTs
- 1965: Recognized limitations – defined Bradford Hill criteria for establishing causation – *5 are relevant here*
  - Biologic rationale
  - Strength of association (clinical significance)
  - Consistency of the evidence (across sites, studies)
  - Temporal sequence (A must precede B)
  - Experimental evidence (RCTs and others – such as studies where the effect is manipulated like ABAB)
But could vitamins be... killing you...?
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

Micronutrient safety

“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.”

Societal vs Individual Risk in Australia

Bubble size represents risk relative to 1: million individual risk or equivalent to the risk of a single flight on a Boeing 747 anywhere in the world. Note: Log scales

Sources: Variety of Australian government and NGO databases and reports.

© 2004, Juderon Associates
We need to do a cost-benefit analysis for each individual...because there are some people who will not tolerate nutrients
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Interestingly, risk factors associated with nutrition are typically *HIGHER* than any odds ratio ever reported for genetics

*Why do we not give this more weight when explaining aetiology to patients?*
Table 1: Average odds ratios and 95% confidence (CI) from the pooled analysis of genetic variants in more than one study (Faraone et al., 2005) [1]. Quantitative trait effects are estimated for these components 2 relative risk calculator [http://pngu.mgh.harvard.edu/~purcell/gpc/vc2rr.html](http://pngu.mgh.harvard.edu/~purcell/gpc/vc2rr.html). This paper assumes a standard normal trait distribution, such that the QTL variance for the discrete category be the same as the QTL variance for the continuous measure. Assuming an additive genetic model, variance explained by the associated genes is around 3.2%. The number of families needed to replicate alpha of 0.05 and 80% is listed, in addition to the power from a sample of 200 families for the same.

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR</th>
<th>95% CI</th>
<th>Allele frequency</th>
<th>QTL</th>
<th>Number of families to replicate with 80% power</th>
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<td>1.03</td>
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<td>SERT (HTTLPR)</td>
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<td>1.09</td>
<td>1.59</td>
<td>0.6</td>
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<td>HTR1B</td>
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<td>1.14</td>
<td>1.83</td>
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<td>0.010</td>
</tr>
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</table>
Adolescents with a high score for the “Western” dietary pattern more likely to have ADHD, OR=2.21 even after adjusting for potential confounding factors.
WHICH FORMULA DOES ONE CHOOSE????

None of them have been developed specifically for mental health symptoms...
Commercial vs research products: are they the same? Rucklidge, Harris & Shaw, 2014, NZMJ
Research supplements  Over-the-counter supplements

Vitamin B₁₂ Daily Dose (mcg)
Which ones have any evidence to help with mental illness?
Other considerations

- Which nutrient(s) is necessary? Could we get away with a smaller set of key nutrients?
- Dietary changes versus supplementation?
- Antibiotic use/inflammation/food allergies
- Other medications (particularly psychiatric ones)
- Short and long-term compliance – many people stop them, even if working...
- Yeast infections and illness – do they impact on response?
- Cost to patients

**Not everyone improves** – one size doesn’t fit all
- An example – those with a mutation to the MTHFR gene affects metabolism of folic acid
Physiologically, makes sense to provide body/brain with a broad spectrum of nutrients to correct possible metabolic deficiencies/inflammation to optimize functioning.

After a decade of research, most studies positive across different countries, different formulas.

- And depending on how we conceptualize mental illness, the evidence is pretty strong.
- Over 20 DBRCTs showing benefit for psychological/psychiatric symptoms.

How long can we ignore these data?
For further info on the formulas mentioned here today.......