Evaluation of current evidence on multi-nutrient treatment of mental health symptoms

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- No commercial interest in any company or sale of any product

and a Disclaimer

- There are many causes of mental disorders

NUTRITION AND MENTAL HEALTH
A multi-part webinar series

- Bonnie J. Kaplan, PhD
  - 2600 years of folklore and modern science: from population health to supplementation
- Julia J. Rucklidge, PhD
  - Evaluation of current evidence on multi-nutrient treatment of mental health symptoms

- These talks are sponsored by the Mad in America Continuing Education Fund, which is a fund of the Foundation for Excellence in Mental Health Care (FEMHC).
- My connection:
  - Nutrition blog on www.madinamerica.com

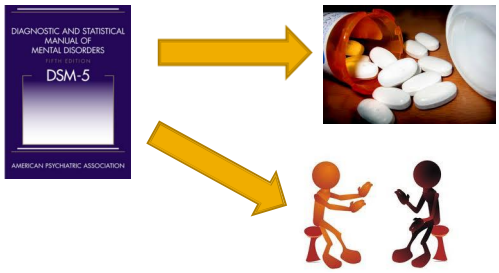
What was covered in Parts 1 & 2

1. Historically, what did humanity know about nutrition?
   From 2600 years ago until ~1950
2. Why increasing interest in nutrition now?
3. Population health research: both correlational and prospective studies
4. What we know about dietary patterns and relationship to mental health
5. Why dietary manipulation alone probably won't help everyone (e.g., depletion of nutrients in food, genetic differences, gut health)
6. A discussion of ~100 years of studies using single nutrients and why this approach has been so modest
7. Exploring treatment with nutrients and why it makes sense physiologically to use a broad spectrum of nutrients

Overview of Part 3

- 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: mood, forensics, autism, stress, anxiety, trauma, ADHD

Our current approach to psychiatric problems



Our gold standard is

resulting in only

"…modest benefits…"

- Sarris et al. (2015). Nutritional medicine as mainstream in Psychiatry. The Lancet Psychiatry.

What's the evidence for broad spectrum micronutrients?

Progression of Evidence on Micronutrients & Psychiatric Symptoms

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

WHY IS THIS LEVEL OF EVIDENCE IMPORTANT?

Evidence-based medicine

Progression of Evidence on Micronutrients & Psychiatric Symptoms

- **Case studies**
- Case series
- Case controls
- RCTs
- Roll out into clinical practice

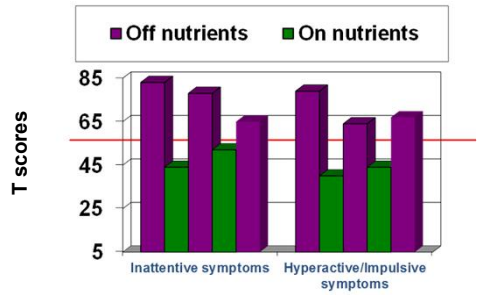
"Brian": one of MANY (e.g., OCD, Psychosis, Bipolar, ADHD)

Harrison et al., 2013, *J Psychoactive Drugs*

- 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 minerals-vitamins

On-off control of ADHD symptoms

Harrison et al., 2013, *J Psychoactive Drugs*



Progression of Evidence on Micronutrients & Psychiatric Symptoms

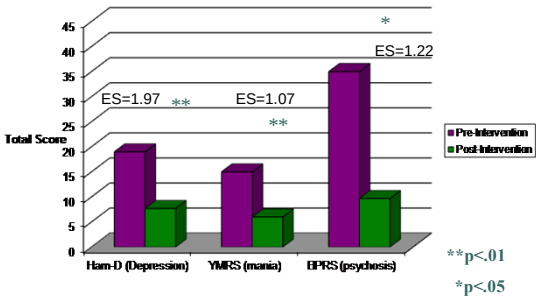
- Case studies
- **Case series**
- Case controls
- RCTs
- Roll out into clinical practice

Summary

- **Many open label trials across anxiety, sleep, Bipolar Disorder and ADHD:**
  - All have shown significant reductions in psychiatric/psychological symptoms
  - Response rates range from 50-80%
    - Kaplan et al., 2001, *JCP*; Popper, 2001, *JCP*; Simmons, 2003, *JCP*; Kaplan et al., 2004, *JCAP*; Gately & Kaplan, 2009, *Clin Med*; Rucklidge et al., 2010, *BMC Psychiatry*; Rucklidge et al., 2011; *JAD*; Frazier et al., 2012, *JACM*; Gordon et al., 2015, *JCAP*; Lothian et al., in press, *Clinical Psychological Science*

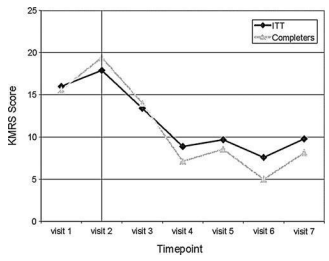
Case series (open label), 11 adults

Kaplan et al., 2001, *J Clin Psychiatry*



Treatment of pediatric bipolar disorder over 8 weeks; 10 children

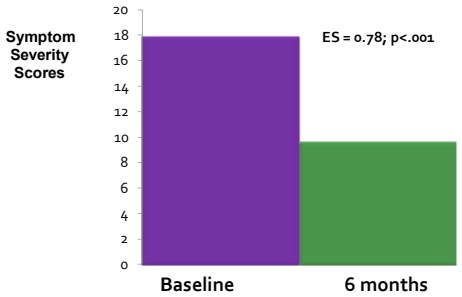
Frazier et al., 2012, *JACM*



58% drop; $p < .05$

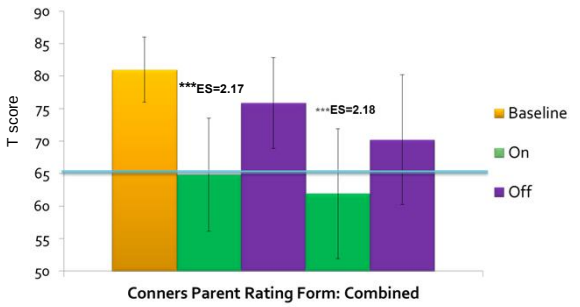
Improvement in Bipolar Disorder in 120 children over a 6-month period

Rucklidge et al., 2010, *BMC Psychiatry*



Significant symptom reduction in 14 children with ADHD treated with micronutrients: An open-label reversal design

Gordon et al., 2015, *J Child Adolesc Psychopharmacology*



Conners Parent Rating Form: Combined

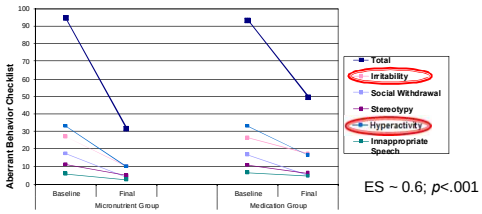
***sig different from baseline ($p < .001$)

Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
- Case series
- **Case controls**
- RCTs
- Roll out into clinical practice

Case-control study of 88 children with autism

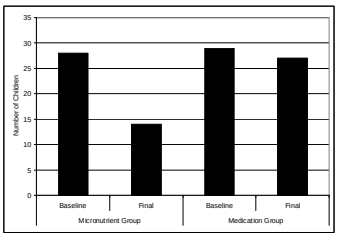
Mehl-Madrona et al., 2010, *J Child Adolesc Psychopharmacology*



ES ~ 0.6; $p<.001$

No grp differences on the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale

Yale-Paris Self-injurious Behaviour

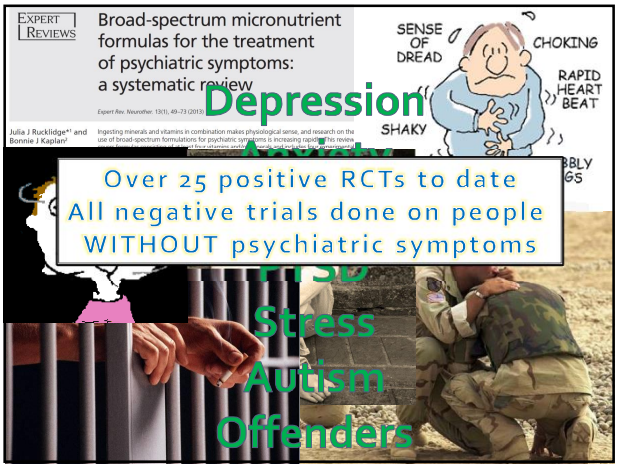


CGI Ratings also sig better in micronutrient group; ES = 0.82, $p < .001$

AE	Micronutr gp (n)	Med gp (n)	Group diff
Increased appetite	1	32	<0.0001
Fatigue	1	29	<0.0001
Drowsiness	1	31	<0.0001
Vomiting	1	9	0.015
Anxiety	6	19	0.004
Diarrhea	4	5	1.000
Constipation	0	6	0.026
Sleep problems	1	4	0.360
Drooling	0	4	0.116
Headache	2	8	0.089
Stomach ache	9	9	1.000
Dry mouth	0	6	0.026
Increased thirst	0	5	0.055
Dizziness	0	5	0.055
Dyskinesia	0	7	0.012
Nausea	3	5	0.713
Decreased appetite	2	5	0.434
Tremor	2	8	0.089
Tachycardia	0	4	0.116
Muscle rigidity	0	4	0.116
Restlessness	0	3	0.241
Akathisia	0	6	0.026
	33	214	

Progression of Evidence on Micronutrients & Psychiatric Symptoms

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



Forensics

Summary

- 5 RCTs
  - All five studies show benefit for reducing aggression, violence acts and rule infractions
    - Schoenthaler et al.,1997, *JMEN,* 2000, *JCAM*; Gesch et al., 2002, *BJP*; Zaalberg et al., 2010, *AB*; Tammam et al., 2015, *BJN*

Schoenthaler's studies

- Schoenthaler et al (1997): 62 imprisoned juveniles using DBPCT over 3 months, showed:
- **Active supplement** → **28% less violence**
- Schoenthaler and Bier (2000): 80 children (6-12) who had been disciplined at least once using DBPCT over 4 months, showed:
- **Active supplement** → **47% fewer rule infractions**
  threats and fights, vandalism, defiance, disrespect, obscenities

Micronutrient supplementation in 231 young adult prisoners

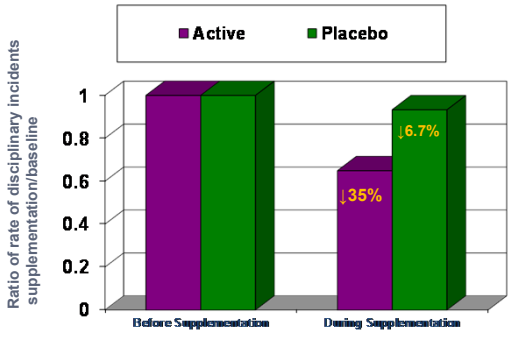
Gesch et al. 2002, *Br J Psychiatry*

- RCT in 231 young offenders –average length in RCT: 142 days
- Supplement with a broad array of minerals, vitamins, and some EFAs (26 ingredients at RDA levels)

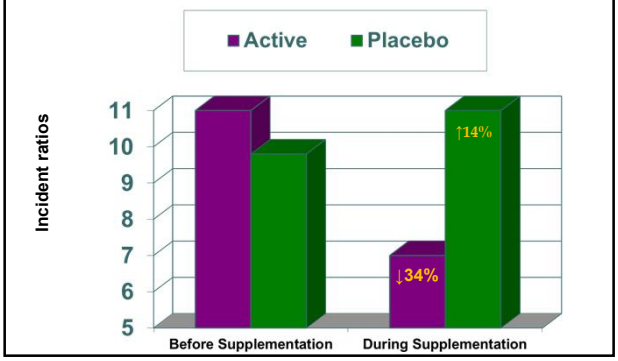
Active supplement → 26.3% fewer rule infractions
35.1% fewer violent acts

Micronutrient supplementation in 231 young adult prisoners

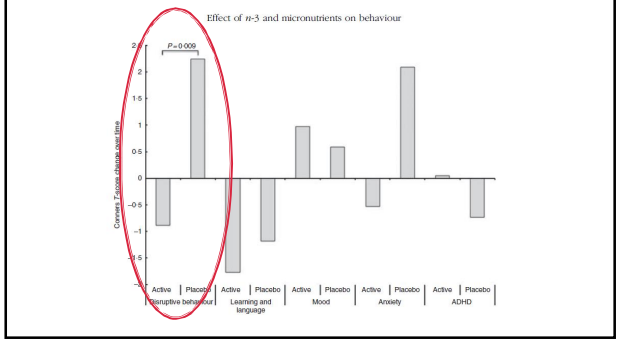
Gesch et al. 2002, *Br J Psychiatry*



Replication in a Dutch sample
Zaalberg et al. 2010, *Aggressive Behavior*



Micronutrients may have a protective effect on worsening behaviour? 196 typically developing UK adolescents
Tammam et al., 2015, *Br J Nutrition*

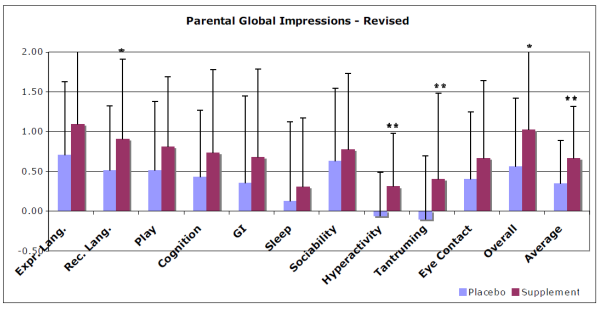


Autism

Summary

- First pilot trial = 20 children – 10 micronutrients and 10 placebo
  - Improved sleep and GI problems
    - Adams et; 2004, *JCAM*
- Second trial: 141 children and adults with ASD treated with micronutrients (29 ingredients) – 3 month treatment
  - Vitamins/minerals used adjunctively
  - Those taking micronutrients showed improved sleep, reductions of tantrums, hyperactivity, and improved verbal language as well as GI problems compared with placebo
    - Adams et al., 2011, *BMC Pediatrics*

Change in functioning after 3 months micronutrients versus placebo (131 children/adults with autism)
Adams et al., 2011, *BMC Pediatrics*

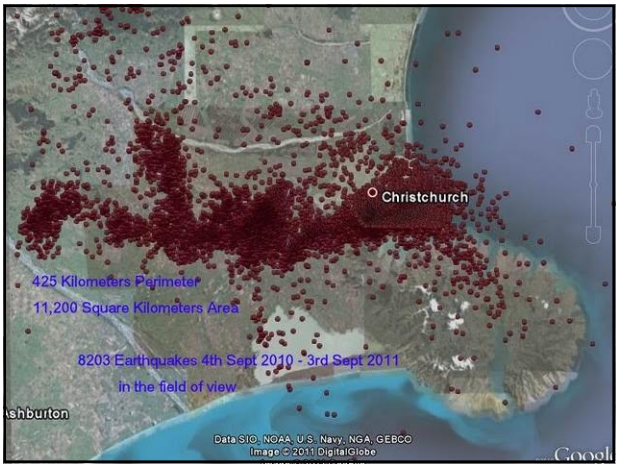


Small to medium effects in group differences

Stress, Natural disasters and nutrients

Summary

- 8 RCTs have shown that micronutrients:
  - decrease stress/anxiety in both stressed and nonstressed populations
    - Carroll et al., 2000, *Psychopharmacology*; Gruenwald et al., 2002, *AT*; Schlebusch et al., 2000, *SAMJ*; Kennedy et al., 2010, *Psychopharmacology*; Stough et al., 2011, *Hum Psychopharmacol* ; Long & Benton, 2013, *Hum Psychopharmacol* ; Rucklidge et al., 2012, *Hum Psychopharmacol* ; Kaplan et al., 2015, *Psychiatry Res*
- 1 RCT found no benefit of micronutrients over placebo in a normal population on anxiety/stress measures
  - Harris et al., 2011, *Hum Psychopharmacol*



Micronutrients on PTSD symptoms in general population experiencing stress following earthquake

Rucklidge et al., 2012, *Hum Psychopharmacol*

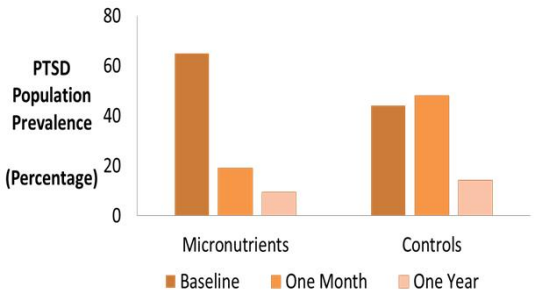
- Recruited on-line
  - 201 completed survey: 127 eligible
- 91 randomized
  - 30 to B complex (29 completed)
  - 31 to low dose broad spectrum micronutrient formula – BSMF (30 completed)
  - 30 to high dose BSMF (27 completed)
- 4 week trial with 1 month natural follow up – data collection May to July 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 (B complex) or very large (BSMF both doses) changes from baseline
  - All 3 significantly better than controls
- BSMF (both doses) showed superiority to B complex 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 BSMF: 5x more of these participants stayed on BSMF micronutrients compared with those in the B complex group

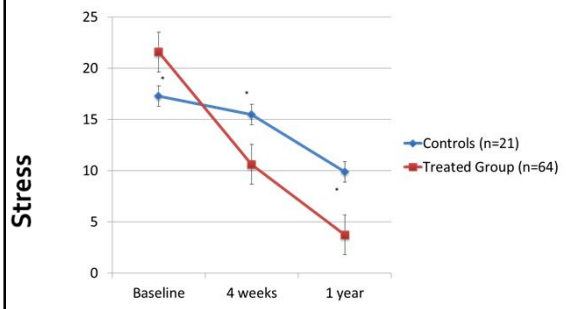
Reduction in trauma after earthquakes

Rucklidge et al., 2012 & 2014, *Hum Psychopharmacol*



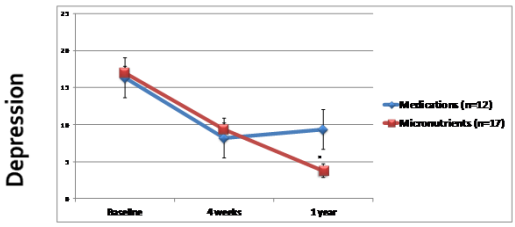
Protective in long term? Change in stress over time between those treated acutely with micronutrients and control group

Rucklidge et al., 2012& 2014, *Hum Psychopharmacol*

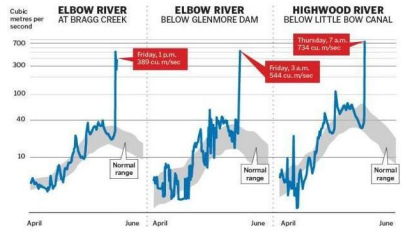


Change in depression over time based on treatment at 52 weeks

Rucklidge et al., 2012& 2014, *Hum Psychopharmacol*



Southern Alberta flood (2013)



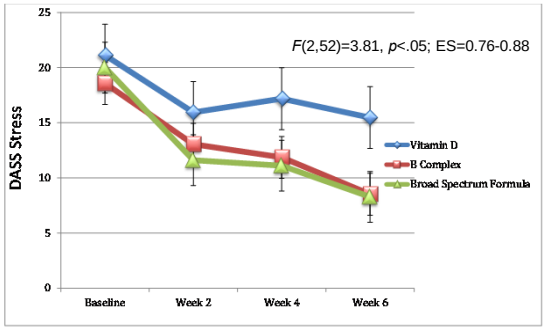
Flood study, Alberta, 2013

Kaplan et al., 2015, *Psychiatry Research*

- 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 RCT:
  - Single nutrient (vitamin D 1000 IU): n=17
  - Few nutrients (B complex): n=21
  - Broad spectrum (~30 minerals and vitamins): n=18

Flood study, Alberta, 2013

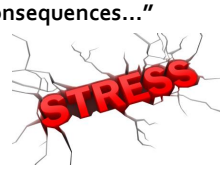
Kaplan et al., 2015, *Psychiatry Research*



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…"

ĭ McCann and Ames 2009



ADHD

Summary

- Two RCTs
  - one showed no additional benefit of nutrients above effect of omega 3s but used low dose (below RDA) of micronutrients
  - one positive with broad spectrum micronutrients
    - Rucklidge et al., 2014, *BJP*; Sinn & Bryan, 2010, *JDBP*

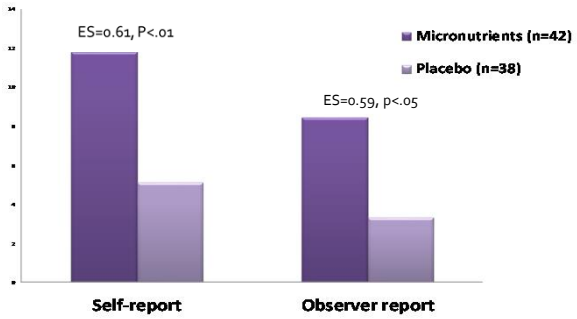
Micronutrients with adults with ADHD: RCT evidence

Rucklidge et al., 2014, *Br J Psychiatry*

- 80 participants with ADHD (med free)
- Mean age: 35 years
- Diagnosis:
  - SCID-I and CAADID *and*
  - >70 on one of the DSM based scales of CAARS (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 weeks RCT: 42 micronutrients, 38 placebo

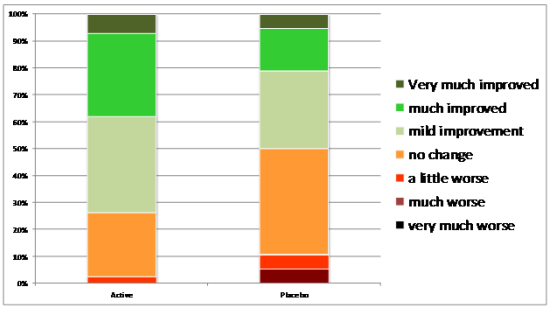
Reduction in ADHD symptoms using micronutrients

Rucklidge et al., 2014, *Br J Psychiatry*



Percent improving micronutrients versus placebo based on clinician rating

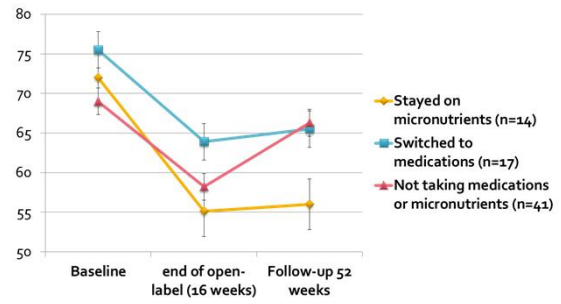
Rucklidge et al., 2014 *Br J Psychiatry*



ES = 0.53, *p*<.02

Naturalistic follow-up one year post-baseline: ADHD symptoms

Rucklidge et al., 2014, *J Attention Disorders*



Mood

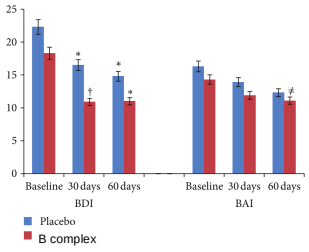
Summary

- *Very few good* trials on samples specifically recruited for depression –
  - lots of RCTs with normal populations (6 positive RCTs, 5 negative RCTs)
  - A few others with health conditions (3 positive RCTs, 1 negative RCT)
- Only two RCTs studied people with mood problems – both positive

Methylated Vitamin B complex on depression & anxiety in depressed adults

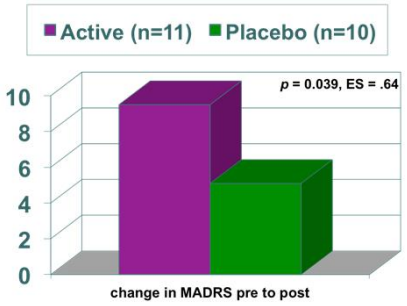
Lewis et al., 2013, *ISRN Psychiatry*

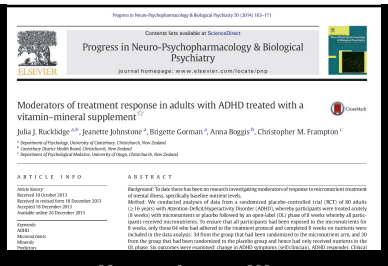
- 60 adults with MDD
- DBRCT: B complex versus placebo
- 30 and 60 days follow up
- Modest improvement
- Sig group differences



Broad-spectrum micronutrients improved depression ratings among ADHD adults with clinical depression

Rucklidge et al., 2014, *BJP*



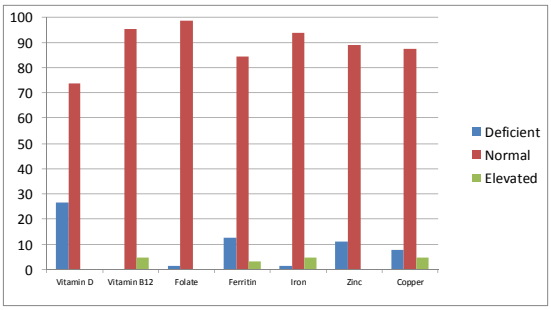


Can we predict who will respond to micronutrients?

Not really, not yet

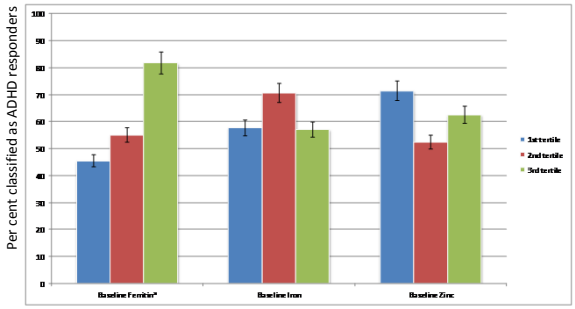
Percentage falling within or outside normal reference ranges for serum nutrients

Rucklidge et al., 2014, *Prog Neuropsychopharmacol Biol Psychiatry*



Baseline nutrient levels converted to tertiles and compared with per cent ADHD responder

Rucklidge et al., 2014, *Prog Neuropsychopharmacol Biol Psychiatry*

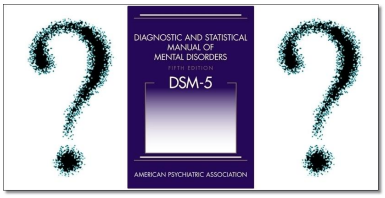


*$p<0.05$

Do these data challenge our conceptualization of mental illness?

Conventional medicine

- DSM based categories suggest each psychiatric category may have a separate etiology
- But are they that separate?



Could some cases of psychiatric illness 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 micronutrient component of corresponding coenzyme, restoring enzymatic activity
    - Ames et al., 2002; Kaplan et al., 2007

Does any of this amount to evidence?

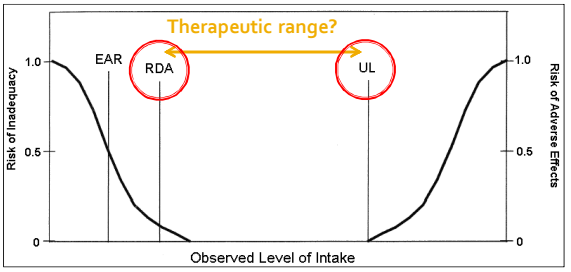
- Bradford Hill, 1952: Created basis for modern RCTs
- 1965: Recognized limitations – defined Bradford Hill criteria for establishing causation – *5 are relevant here*

- ✓ Biologic rationale (covered in Bonnie's lecture)
- ✓ 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*)

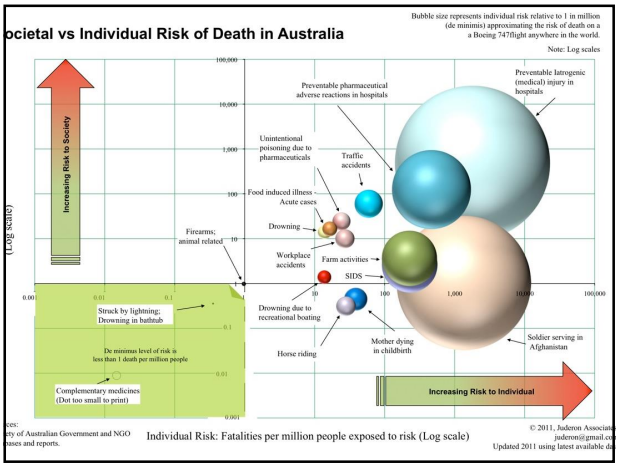
Side effects?	minor and transitory
Compliance?	No difficulties with the regimenÂ
Impact on blood results?	None to dateé *
Long-term effects?	Needs to be studied *properly*

- †some find taking the pills tedious and stop for that reason
- * *lack* of difference in fasting glucose, lipids, white blood cell count, and neutrophils, slight elevation on prolactin but still within normal range
  - Review of safety: Simpson et al., 2011, *BMC Psychiatry*
- Help for pill swallowing: www.research4kids.ucalgary.ca/pillswallowing

How much?

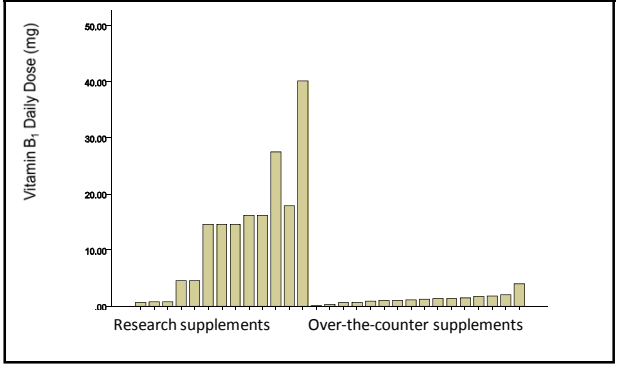


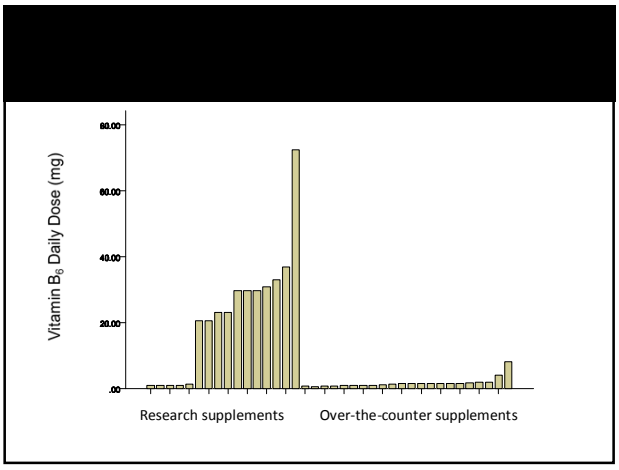
Food and Nutrition Board, Institute of Medicine

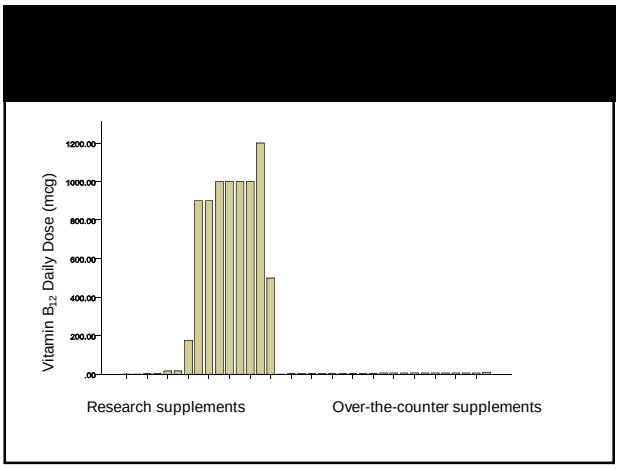


Commercial vs research products: Are they the same?

Rucklidge et al., 2014, *NZMJ*







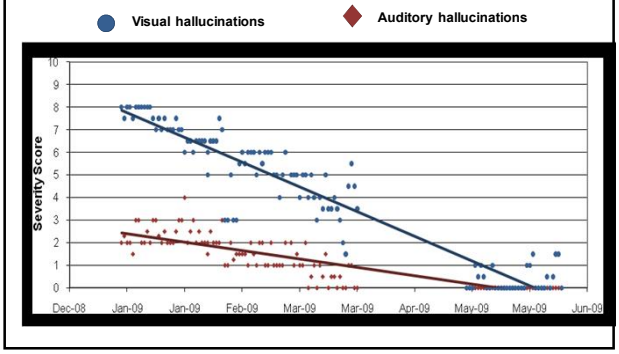
Which commercial broad spectrum formulas have any evidence of benefit with mental symptoms?

Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
- Case series
- Case controls
- Randomized controlled trials (RCTs)
- Roll out into clinical practice….

Self-reported account of hallucinations

Rodway et al., 2012, *BMJ Case Reports*



Cost savings of micronutrients

Cost of conventional inpatient treatment

Micronutrients cost <2% of conventional treatment

Cost of micronutrient outpatient treatment

Concluding messages…

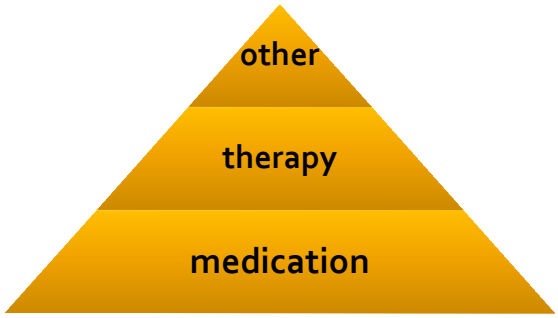
- Physiologically, makes sense to provide body/brain with nutrients to optimize functioning
- If can't be achieved through diet manipulation alone, then additional nutrients may be required
- Most studies on broad spectrum nutrients positive across different countries, different formulas, different conditions
  - But we need replication, more studies investigating optimal doses and understanding mechanisms of action

END OF WEBINAR RECORDING

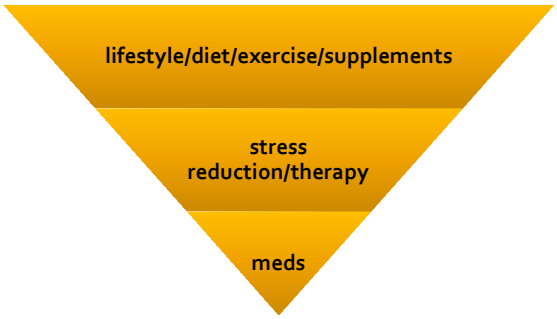
Additional slides for the public talk

Video clip

Conventional medicine



Integrative medicine



On a personal note

For further info on the formulas mentioned here today.....

- **EMPowerplus/CNE/Q96:** www.truehope.com
- **Daily Self Defense:** http://optimusnutraceuticals.com/
- **Daily Essential Nutrients:** http://www.hardynutritionals.com/
- **Brain Child Spectrum Support:** http://www.brainchildnutritionals.com/spectrum-support-vitamins.html/
- **Forceval:** http://www.forceval.co.uk/
- **Blackmores Executive B:** http://www.blackmores.com.au/products/executive-b-stress-formula
- **Max Stress B** http://www.healthproductsusa.net/30_max_stress_b_health.htm
- **Swisse Ultivite:** http://www.swisse.com/au/vitamins-and-supplements/mens-health/73/swisse-mens-ultivite-f1
- **Bayer's Berocca:** http://www.berocca.com/en/home.php

Petitions

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  - Dr Mairin Taylor
  - Rachel Harrison
  - Sarah Anticich
  - Kathryn Whitehead
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  - Dr Brigette Gorman
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- Âprof Neville Blampied
- Âprof Chris Frampton
- Âprof Martin Kennedy
- Âprof Dermot Gately
- Âprof Rob Hughes
- Âdr Jeni Johnstone
- Âdr Amy Romijn
- Âprof Roger Mulder

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- Âdr. David Ritchie
- Âdr. Katharine Shaw

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