

Disclosure

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

Aims

- ▶ Challenge traditional way of thinking
- ▶ Encourage psychologists to consider how poor quality food & deficiencies in nutrients might contribute to psychological problems we see
- ▶ Not promoting a new treatment approach.....not yet anyway
- ▶ *Highlighting need for further research*

Some of the theoretical background

First up – Nutrients are essential for metabolic reactions to occur

Individual micronutrients affect mental health

Individual micronutrients affect mood: some known for centuries

- ▶ *Deficiencies cause psychiatric sx*
 - ❖ thiamine/B1 (Wernicke's encephalopathy)
 - ❖ niacin/B3 (pellagra)
 - ❖ cyanocobalamin/B12 (psychosis of pernicious anemia)
 - ❖ iodine ('myxedema madness')

Nutrient deficiencies: Niacin (vit B3)

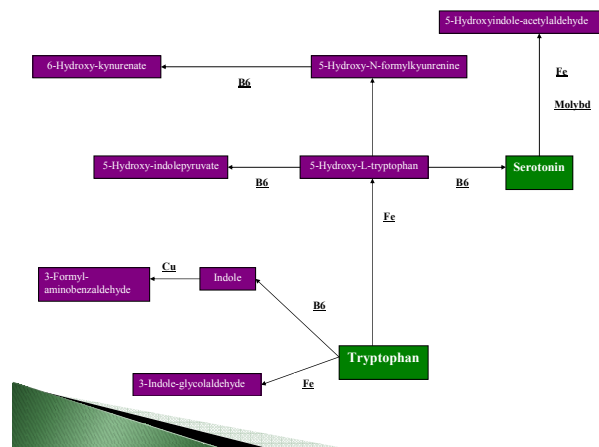
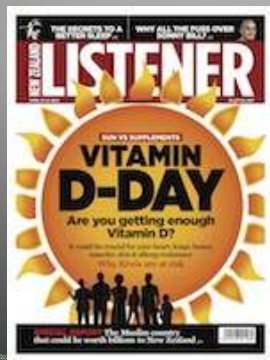
- ▶ Pellagra: means rough skin
 - ▶ First described 1735
 - ▶ In 1914, linked to corn-based diet by Goldberger and determined NOT to be infectious
 - ▶ Linked to niacin in 1937
 - ▶ in 1930–32, 19% of admissions to mental hospitals was due to pellagra due to psychosis
- Fortification cured problem



BUT...for the whole, nutrients work most effectively together, as cofactors!

- ▶ So supplementing with only ONE doesn't *usually* make physiological sense...
- ▶ although that is often how science works
 - e.g. calls for vitamin D increases

Current Issue of Listener: April 27th 2012



Role of nutrients in everyday functioning

thiamine (B_1)	→	Protects adrenal glands from exhaustion
niacinamide (B_3)	→	shunts tryptophan to serotonin
Vitamin B_6	→	cofactor for synthesis of GABA, serotonin, and dopamine
Vitamin B_{12}	→	normalizes cortisol production
Vitamin C	→	given in higher than RDA values, supports adrenal function and decreases high cortisol levels
Mg, Zn & Ca	→	play essential roles as co-enzymes in hundreds of biochemical reactions

Some people have a **higher genetic need** for nutrients

- Mutations in genes can result in enzymes having a decreased binding affinity for a coenzyme, resulting in a **lower rate of reaction**
- **genetic diseases** due to defective enzymes can be remedied or ameliorated by the administration of **high doses of the vitamin** component of the corresponding coenzyme, which at least partially restores enzymatic activity

Ames et al., Am J Clin Nutr. 2002 Apr;75(4):616-58.

Could some forms of mental illness reflect metabolic reactions going wrong?

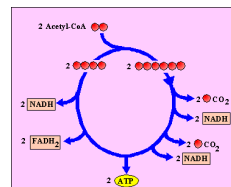


AKA Inborn errors of metabolism

Another idea: Are the mitochondria dysfunctional in people with mental illness?

Mitochondria – What are they?

- ▶ The mitochondria are the 'powerhouse' of the cell, for their ability to form energy in form of adenosine triphosphate (ATP)



Mitochondrial Dysfunction – when they don't work, we need to feed them!

- ▶ There are known mitochondrial disorders, and often associated with psychiatric symptoms
- ▶ In mental illness, mitochondria lack sufficient energy stores
- ▶ Growing evidence from molecular research that some individuals with **bipolar disorder, ADHD and schizophrenia** have **mitochondrial dysfunction** (Konradi et al., 2004; Iwamoto et al., 2005; Gardner & Boles, 2005)
- ▶ Likely due to *decreased* energy production, caused by mtDNA mutations
- ▶ Adding micronutrients helps correct that imbalance

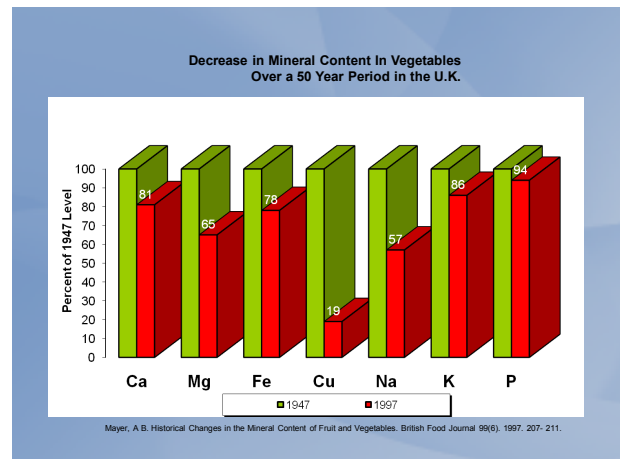
Mitochondrial cocktails include B vitamins, Vit C, Vit E, carnitine, co-enzyme Q10

Drug-Induced Depletion of Micronutrients: Psychiatric Drugs

- | | |
|-------------------|-------------------|
| ▶ Lithium | ▶ Inositol |
| ▶ Valproate | ▶ Carnitine |
| ▶ Carbamazepine | ▶ folate (B9) |
| ▶ Anticonvulsants | ▶ Selenium |
| ▶ Tricyclics | ▶ zinc |
| ▶ Phenothiazines | ▶ Calcium |
| ▶ Haloperidol | ▶ biotin |
| ▶ Beta blockers | ▶ riboflavin (B2) |
| ▶ Clonidine | ▶ thiamine (B1) |
| | ▶ vitamin D |
| | ▶ vitamin K |
| | ▶ CoQ10 |

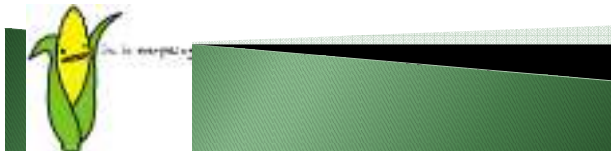
What role does quality of food and 21st century food choices play in all of this?





Michael Pollan The Omnivore's Dilemma:

"Cheap food is an illusion. There is no such thing as cheap food. The real cost of the food is paid somewhere. And if it isn't paid at the cash register, it's charged to the environment or to the public purse in the form of subsidies. And it's charged to your health."



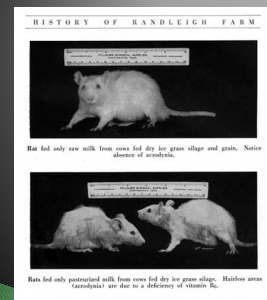
Western vs traditional diets

- An example: Jacka et al 2011
- 23 women with BD and 691 with no psychopathology: 12-month FFQ
- Women with BD
 - higher glycemic load
 - higher scores on a 'western' dietary factor
- For each SD increase in a 'western' and 'modern' dietary pattern and glycemic load, chances of developing bipolar increased ('western' OR=1.88; 'modern' OR=1.72; GL OR=1.56)
- Conversely, a 'traditional' dietary pattern associated with reduced odds for BD (OR=0.53)
- Replicated in ADHD and depression (Oddy et al, 2011; Jacka et al., 2011)

Food supply studies

- ❖ One example: Hoek et al (1996)
 - ❖ Risk of schizoid personality disorder in men at age 18 yrs was compared in birth cohorts conceived at height of Dutch Hunger Winter famine and in unexposed birth cohorts in famine region of Holland
 - ❖ Exposed cohort significantly *greater risk* (relative risk = 2.01) of schizoid personality disorder
 - ❖ More recent studies confirming early malnutrition predicts both depression and attention problems in youth and adulthood (Galler et al., 2010; 2012)

Studies on Raw vs. Pasteurized Milk at Randleigh Farm, 1935-1940



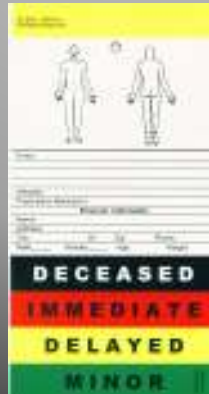
Above: Rat fed only raw milk. Good development, healthy fur.

Below: Rats fed only pasteurized milk. Poor development. Hairless areas (acrodynia) due to vitamin B-6 deficiency.

Triage theory applied to the body



McCann & Ames, 2009



Importance of nutrients during 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



Is it time to revisit a *very* old idea?



586-538 BCE



200 years later...



1910

From the Book of Daniel...

- ▶ Daniel proposed a 10-day clinical trial of (broad spectrum) nutrition
 - Asked that he and his friends consume only pulse and water
 - And then compare them to the royal youth eating royal food
- ▶ "At the end of 10 days their countenances appeared fairer.....than all the youths that did eat of the king's food."
- ▶ "And in all matters of **wisdom and understanding**, that the king inquired of them, he found them ten times better"
- ▶ **Diet affected brain function!!**

Early 20th century

- ▶ 1910 People's Home Library: source of in-depth practical knowledge for North Americans; 500 pages
- ▶ guided families; health care providers not easily accessed; treatments for everything from minor burns up to TB and heart disease
- ▶ *The number one cause of acquired insanity was:*



"imperfect nutrition"

In summary and more...

- ▶ ☒ Inborn errors of metabolism
- ▶ ☒ Mitochondrial dysfunction
- ▶ ☒ Eating nutrient deficient food
- ▶ ☒ Severely stressed
- ▶ Mimicking neurotransmitters
- ▶ Deficient methylation processes (SAM-e)
- ▶ Altered gene expression (epigenetic effects)
- ▶ Anti-inflammatory effects
- ▶ Genetic mutations
- ▶ Gut problems
- ▶ Allergies
- ▶ Viruses and disease

***Some* people with mental illness may not be getting enough nutrients from their diet**



- BUT they may simply need **more** than what they can get out of food...(even it is of good quality)
- Changes in quality of food supply hasn't helped
- broad-based supplementation may correct this problem

In the field of physical illness studying multiple nutrients together *is* more accepted – many RCTs completed

- In infectious diseases
- In sexual disorders
- In cardiovascular diseases
- In Alzheimer's
- In stroke recovery
- In diabetic peripheral neuropathy
- In pregnancy outcomes
- In cognitive function, generally

e.g. Farvid et al., 2011; Remington et al., 2008; Schoenthaler et al., 2000; Barringer et al., 2003; Sato et al., 2005; Liu et al., 2007; Shah et al., 2009;

In field of mental health, studying one nutrient at a time is often the rule, not the exception.... even though evidence of supplementing with one nutrient is generally modest

Forensics: 4 RCTs

What's the evidence for **multiple** ingredients?

Schoenthaler's studies – 1997 and 2000

- ❖ Schoenthaler et al (1997) using 300% RDA for 11 minerals, using DBPCT, showed 28% less violence in 62 imprisoned juveniles who received the supplement than those who received placebo
- ❖ Schoenthaler and Bier (2000): 80 children (6–12) who had been disciplined at least once; randomly assigned to active or placebo 4 months tx
- ❖ Active (18 ingredients): 100% RDA for 8 minerals, 3 fat-soluble vitamins, folate; 300% RDA remaining 7 water-soluble vitamins

Active supplement → 47% fewer rule infractions

Micronutrient supplementation in young adult prisoners, Gesch et al. (Oxford), *Brit J Psychiatr*, 2002, 181:22–28

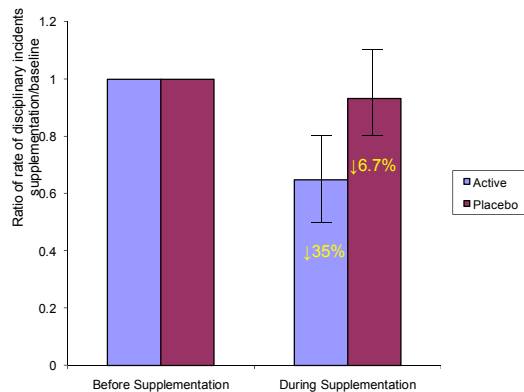
- ❖ **RCT in 231 young offenders**
- ❖ **Supplement (Forcival) with a broad array of minerals, vitamins (most at or below RDA), and some EFAs (26 ingredients)**

Active supplement

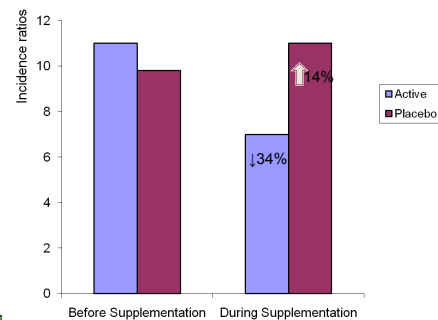


26.3% fewer rule infractions

35.1% fewer violent acts



Replication in a Dutch sample, Zaalberg et al., 2010



Bipolar Disorder

From Alberta: EMPowerplus

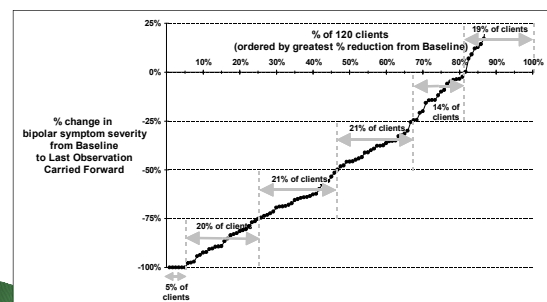
- ▶ Tony Stephan
 - ▶ married into family with genetic predisposition
 - ▶ ~1995 his wife suicided; 8 children, two with Bipolar Disorder
- ▶ David Hardy
 - ▶ Worked for 20 yrs for animal feed company
 - ▶ Did research on feed for pigs, cattle
- ▶ Eventually, they created EMPowerplus
 - ▶ 36 ingredients: *not exotic* - minerals, vitamins, antioxidants, amino acids



Tx of Mood with nutrients

- ▶ Depression: No good trials on samples specifically recruited for depression –
 - lots of RCTs with normal populations (4 +ve RCT, 5 -ve RCTs) and others with health conditions (3 +ve RCTs, 1 -ve RCT)
 - ▶ Bipolar: Only open label trials and all with one formula – EMPowerplus
 - 5 open label trials
 - 3 case studies with reversals
 - 2 database analyses
 - Significant reductions in all psychiatric symptoms
 - Significant reduction in medications
- Response rates approx 80%

Distribution of % change in bipolar symptom severity from Baseline to LOCF

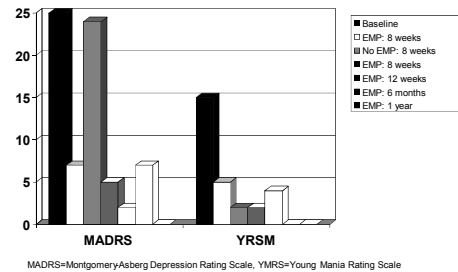


Case study : Bipolar II, ADHD, and anxiety

Rucklidge & Harrison, 2010, CNS Spectrums

- KT 21 year old female
- In 2008, KT diagnosed ADHD Combined Type, Social Anxiety, PTSD, BP II, Panic Disorder
- 8 years of well documented history of on going interventions with conventional treatments with little improvement
- Past meds: fluoxetine and methylphenidate
- CGI: moderately ill range at baseline, GAF = 45
- Followed over 1 year with naturalistic ABAB design

MADRS and YRMS scores across time and EMP use



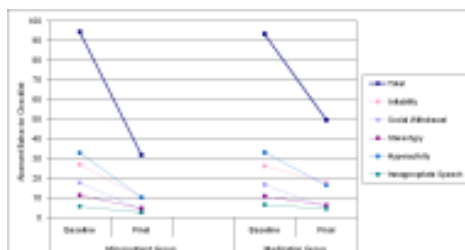
Autism

Micronutrients and autism

- 2 RCTs (Adam et al., 2004, 2011)
 - Used "Spectrum Support" (13 vitamins, 8 minerals plus other herbs + nutrients)
 - Those taking micronutrients showed **improved sleep, reductions of tantrums, hyperactivity, and improved verbal language as well as GI problems compared with placebo**
- Mehl-Madrona et al (2010) – 88 children in private practice – 44 taking EMP and 44 matched children taking medications

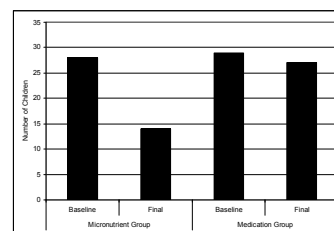
Case-control study of 88 children with autism

--Mehl-Madrona, Leung, Kennedy, Paul, Kaplan (2010, Journal of Child and Adolescent Psychopharmacology)



No group 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

Substance Abuse

Micronutrients and substance abuse

- ▶ Long hx of using nutrients to treat Wernicke-Korsakoff Syndrome (causes thiamine deficiency)
- ▶ A few RCTs in 80s showing “neuronutrients” can assist with withdrawal from both cocaine and alcohol
- ▶ No recent trials
- ▶ Anecdotal reports from our research showing when mood improves, cigarette, cannabis and alcohol use decrease (Harrison, Blampied & Rucklidge, in preparation)

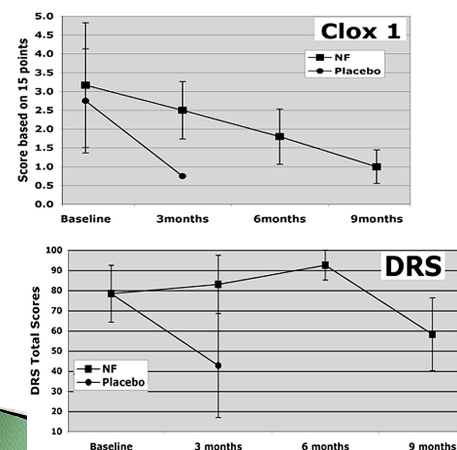
Nutrients and cognition

- ▶ Combination nutrient supplementation improves cognitive functioning in children
 - Benton et al, 1988, 1990, 1991
- ▶ Benton et al (1995) showed improved **attentional processing** in *females* supplemented with broad range of nutrients (10xRDA) compared with a placebo for one year (127 healthy adults)
- ▶ Haskell et al (2011), with 216 females using 3xRDA for water soluble vitamins and RDA for fat soluble vitamins, and 15% RDA for minerals Ca, mg, P and 0.5RDA for other trace elements (Supradyn)
 - Randomized to either nutrients or placebo for 9 weeks
 - **Improved cognitive accuracy, processing speed, and cognitive switching**
- ▶ Dose may be important – one negative trial used lower than RDA dose

Cognitive functioning

Micronutrients and memory in older adults

- ▶ Folic acid, B12, VitE, SAMe, NAC, carnitine (memory XL)
- ▶ Pilot RCT 12 Alzheimer patients:
 - Active grp: **delay in decline on the Dementia Rating Scale and clock drawing**
 - Remington et al., 2009
- ▶ Extended to adults w/o dementia:
 - RCT with 93 adults
 - Those receiving nutrients but not placebo improved on **CVLT-II and Trails**
 - Performance declined with removal of nutrients
 - Chan et al., 2009



ADHD

ADHD and micronutrients

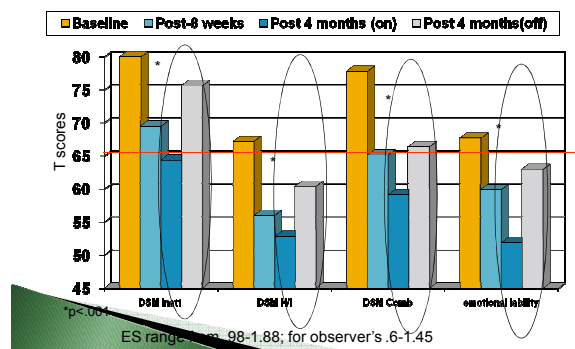
- ▶ Early studies were negative – used megadoses and short trials
 • e.g. Arnold et al., 1978; Haslam et al., 1984
- ▶ Some small open label pilot studies (e.g. Patel et al., 2007) suggest benefit but ecologically challenging
- ▶ 1 RCT confirms nutrients better than placebo at improving functioning on T.O.V.A. (Katz et al., 2010)
- ▶ Sinn and Bryan (2007) used over-the-counter supplement (Blackmore's) + PUFA as a third arm – no additional benefit for supplement+PUFA over PUFA alone
- ▶ More studies on EFAs – 11 RCTs – ES about .4

Open label trial using micronutrients with adults with ADHD and mood instability

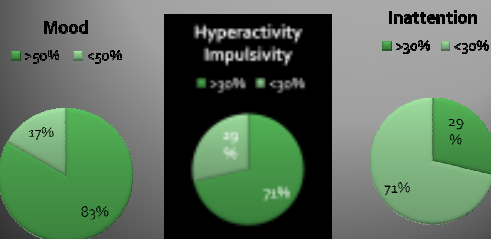
Rucklidge, Taylor, & Wirthwein, 2011, Journal of Attention Disorders

- ▶ 14 participants (5 female), mean age age: 37.53 (9.56)
- ▶ 6 (43%) ADHD Pred Inatt; 8 (57%) ADHD combined
- ▶ Co-occurring diagnoses:
 - 12 Mood Disorder (9 MDD/ 3 BDII 85.7%)
 - 6 Social Phobia (42.9%)
 - 3 GAD (21.4%)
 - 3 drug/alcohol abuse/dependency (21.4%)
- ▶ All given EMP for 8 weeks and monitored with blood work
- ▶ followed up 2 months post trial

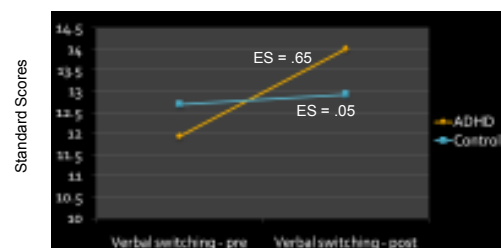
ADHD and emotional lability/anger related measures (self)



Percent showing significant improvement

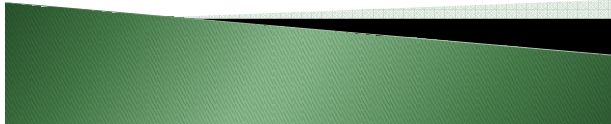


Neurocognitive: Verbal switching

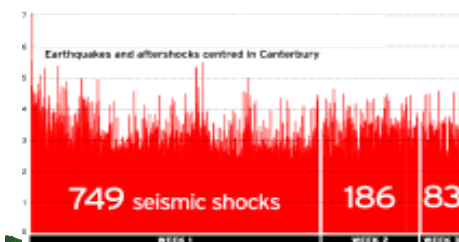


ADHD and Earthquakes? 7.1 earthquake in Christchurch occurred during active trials

September 4th 2010 4:35am



In the three weeks following
the earthquake there were
about 1000 aftershocks



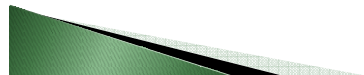
Micronutrients and earthquakes

Rucklidge, Johnstone, Harrison & Boggis, 2011, Psychiatry
Research; Rucklidge & Blampied, 2011, NZ J Psych

► Pooled three studies:

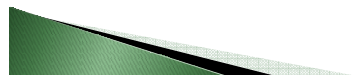
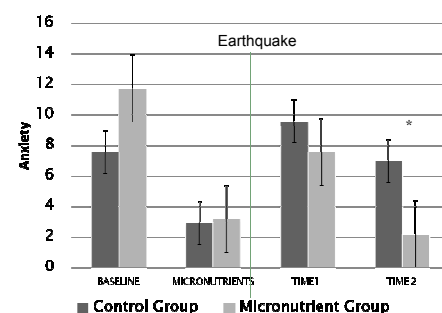
- Found 16 taking & 17 not taking micronutrients at time of earthquake
- All had ADHD diagnosis

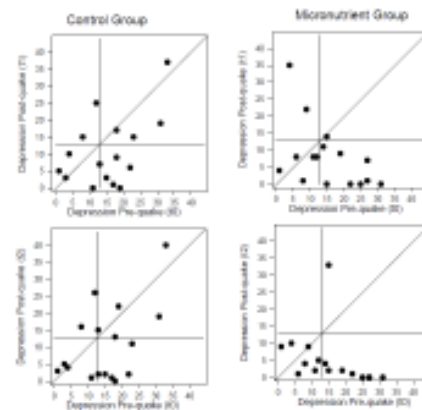
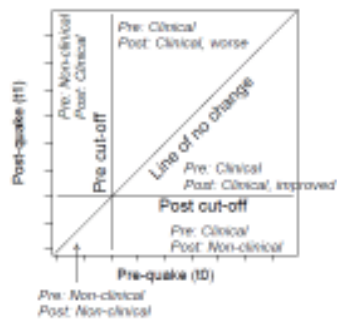
► Measured depression, anxiety, stress one week (Time 1) and two weeks (Time 2) post earthquake



Results

- No differences in baseline functioning, co-occurring diagnoses, ADHD subtype, SES, gender, ethnicity, IQ
- No group differences at Time 1
- At Time 2, those taking micronutrients reported significantly less anxiety and stress (effect size 0.69) than those not taking them
- no change from baseline to Time 2 for control group (effect sizes ranged from 0.11–0.45)
- significant changes in *all areas assessed* for micronutrient group at Time 2 (effect sizes ranged from 0.73–1.01)





Relevance to population health

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

Psychological well being in general population

- ▶ 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; Gruenewald 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?

Current treatments post earthquakes

- ▶ Studies of survivors of natural disasters show about 20–30% of population show immediate or delayed symptoms of stress including PTSD, depression and anxiety
 - (Bonanno et al., 2010; Suhail et al., 2009; Wang et al., 2010)
- ▶ Some evidence that those who eat more poorly show a poorer psychological recovery
 - (Yesilyaprak et al., 2007)
- ▶ Many tx found efficacious, including EMDR, psychosocial tx, earthquake simulators and medications
 - hard to implement widely following a disaster
 - side effects problematic



February 22nd 2011 12:51 pm



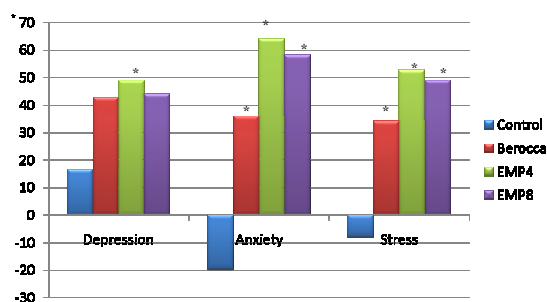
Investigation into impact of micronutrients on stress, anxiety and PTSD symptoms in general population; Rucklidge, Andridge, Boggis, Gorman, Blampied & Gordon, under review

- ▶ Recruited on-line via Trade Me, Facebook, Community Websites
 - ▶ 201 completed survey: 127 eligible
- ▶ 91 randomized
 - 30 to Berocca (29 completed)
 - 31 to EMP4 (30 completed) – aka CNE4
 - 30 to EMP8 (27 completed) – aka CNE8
- ▶ 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

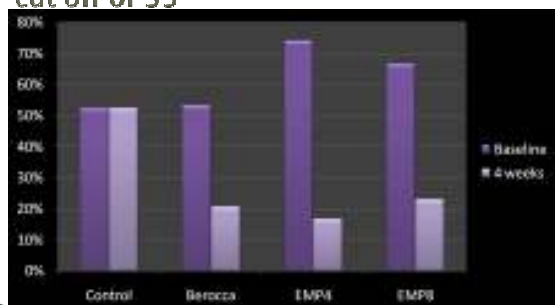
- ▶ No grp diff in exercise, hx of mental illness, zoning, counselling, SES, age, sex, leaving town, diet
- ▶ All 3 tx groups showed large (Berocca) or very large (EMP both doses) changes from baseline
 - ▶ All 3 significantly better than controls
- ▶ EMP (both doses) showed superiority to Berocca for intrusions, and higher dose for CGI 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 CNE:
 - ▶ five times more of these participants stayed on CNE micronutrients compared with those in the Berocca™ group

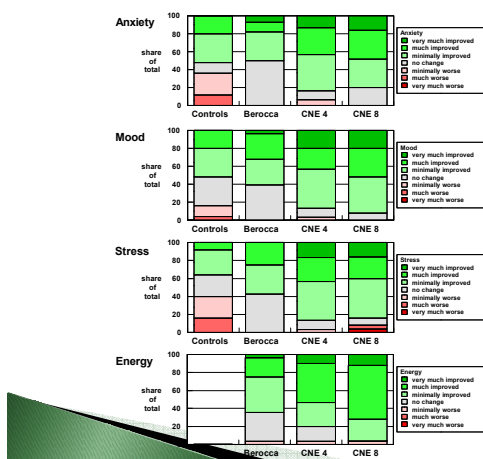
Percent change from baseline to 4 weeks



*sig different from control

% with significant PTSD symptoms baseline and 4 weeks based on IES-R cut off of 33





Would symptoms have remitted over time?

- ▶ Repeated baseline for 30% – got worse
- ▶ Control group suggests otherwise
- ▶ Stress was ongoing
 - zoning of residential houses released during study period
 - June 13th earthquakes occurred during data collection
- ▶ Contact with investigators minimal (on-line survey)
- ▶ Substantial change noted in difficult to treat presentation (PTSD symptoms)
- ▶ Berocca shown to be superior to placebo

Does any of this amount to evidence?

- ▶ 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 (confidence)
- ▶ Consistency across sites, studies
- ▶ Temporality (must precede B)
- ▶ Experimental evidence (RCTs and others – such as studies where the effect is manipulated like ABAB)

More research

Side effects?



minor and transitory

Compliance?



No difficulties with the regimen†

Impact on blood results?



None to date...*

Long-term effects?



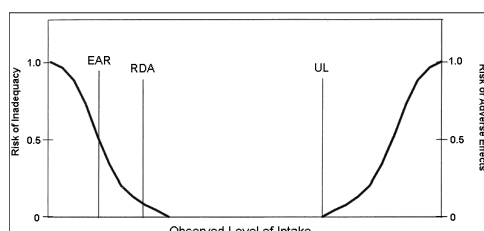
Needs to be studied *properly*

*lack of difference in fasting glucose, lipids, white blood cell count, and neutrophils

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

Simpson, JSA, Crawford, SG, Goldstein, ET, Field, C, Burgess, E, Kaplan, BJ (2011). Safety and tolerability of a complex micronutrient formula used in mental health: A compilation of eight datasets. *BMC Psychiatry*. 11:62.

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.”

Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes*. National Academy Press, Washington, D.C., 2001.

But *if* this actually proves to work... suggests a larger problem

- ▶ Supports growing international cries for investigations into declining quality of food supply and poor remineralization of soil
- ▶ Is supplementation only providing a band-aid solution to a more fundamental problem with food we eat?



- ▶ **Solution?** Drastic change in our food choices with **supplementation for those who require more...** although this isn't always easy and many factors impede success



Some of our challenges

- › Need to complete placebo controlled trials to address concerns re experimenter bias, regression to mean, halo effects, etc.
- › Participants often stop taking micronutrients even if benefitted
- › Non-responders
- › Availability and cost to patient
- › Issue of dose and variation of combination of nutrients across studies
- › Generalizability to children and different conditions
- › How does it work in conjunction with psychological therapies
- › Hard to get funding, publish and hard to get researchers interested...



Conclusions...

- › We should be paying more attention to food our clients eat, **especially the pregnant ones!**
- › Suggesting alternative option when medications/other treatments don't work/not tolerated
- › Physiologically, makes sense for *some psychiatric conditions* to provide body/brain with a broad spectrum of nutrients to correct possible metabolic deficiencies and to optimize functioning
- › After decades of research, most studies positive across different countries, different formulas
 - › Evidence gathering for use with depression, bipolar, anxiety, ADHD, autism and general health
- › Viable in future for psychologists to include discussions on supplementation with clients alongside exercise, diet and other health-related behaviours

Messages I am *not* giving



- › The only cause of mental disorders is nutritional insufficiency-- **NO**
- › Everything can be cured with nutrients--**NO**
- › Psychiatric medication is bad--**NO**
- › Psychosocial variables are not important -- **NO**

Medicine Woman – Witi Ihimaera

- › "Paraiti looks at the girl – she places her hands on the girls' stomach. E hika, this girl is very cold.
- › She smells her breath; aue, she smokes Pakeha cigarettes. She looks at her eyes; they are milky and clouded, and her fingernails and toenails are brittle and dry.
- › "A baby in the womb is like a kumara being fed nutrients from the vine of your body. But your vine is not giving your baby the right foods. Your circulation is sluggish, and therefore, the nourishment is not getting to the child..."
- › Paraiti looks at Florence's mother: "I will put you daughter on a diet which she must follow without straying...the diet is rich in nutrients. I will also put her on a regime of exercise which will improve her circulation. Florence must stop smoking Pakeha cigarettes immediately. Also it is important that her blood temperature is increased. I will show you massage to make her body a whare tangata that is nice and cosy. Keep to the diet, the massages, and make sure she stays in sunlight and eats vegetables and fruits and fish, especially shellfish. Try to make she is always warm."

Where are we heading next?

- › Complete RCT with adults (>16) with ADHD!
 - › End in sight – aiming for June 2012 with 6 month follow ups complete by Dec 2012
- › Feasibility trial –Case series (ABAB) of children (8–12) with ADHD
 - › 8 recruited, aiming for 15, complete Dec 2012
- › Open label trial of 15 anxious children (due to earthquakes) using EMP+ and multiple baseline design
- › Pending funding:
 - › RCT comparing probiotics with placebo for reduction of stress/anxiety induced by earthquakes
 - › RCT comparing EMP with placebo with Mediterranean diet for tx of depression
- › Investigating mechanisms of action and animal research

What's in *your* brain's 'bathwater'?

How often do you ask what
your clients are eating?

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