Exploring medication, standard treatments, nutrition and micronutrients in ADHD

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Professor of Psychology, University of Canterbury
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Disclosure

No commercial interest in any company or sale of any product
ADHD: TREATMENT COMPONENTS

- medication
- Therapy: home and school
- Everything else
Long-term studies on medications – controversial
good news!
Robust short-term effects on core symptoms of ADHD
stimulant effects maintain to at least 2 years
  - eg MTA Cooperative Group, 1999; Abikoff et al., 2004; Ercan et al., 2014
Naturalistic study suggest in males, 4 year methylphenidate tx leads to:
  - fewer ADHD symptoms
  - lower drug & alcohol abuse
  - less functional impairment
  - increased quality of life compared with those not medicated
    - Ginsberg et al., 2014
Swedish register-based study indicated:
  - lower rates of substance abuse and lower rates of criminality with longer duration of ADHD medication although effect lost at 4 yr follow up
    - Lichenstein et al., 2012; Chang et al., 2014
Possible benefit for reduced smoking in adolescents at 2 years
  - Hammerness et al., 2013
Bad news
Bad news

- Even when medicated, outcomes still poor and worse than those unmedicated based on 3 & 8 year data from MTA trial
  - Group with current treatment showed a tendency to disadvantage
    - Swanson et al., 2008; Molina et al., 2009

- Greater comorbidity leads to poorer prognosis
  - Lensing et al., 2013

- More than 30 years of research shows stimulants do not improve academic performance in children & college students
  - Loe & Feldman, 2007; Advokat, 2010

- A birth cohort showed that at 14 yrs, children using stimulants more likely to perform below grade level & have greater diastolic blood pressure if consistently received stimulants over time
  - Raine Study; Smith et al., 2010
More Bad news

- Study of mostly unmedicated population of adolescents in Finland found functioning very similarly, despite lack of medical input, to American counterparts generally well medicated
  - Smalley et al., 2007

- Higher BMI in long-term as compared to unmedicated
  - Schwartz et al., 2014

- Currie et al. (2014) determined outcomes worse for kids on meds at 3 yrs based on drop-outs (boys) and depression (girls)

- Cardiovascular concerns - minor mean elevations in blood pressure and heart rate
  - Hammernes et al., 2014

- Small effect sizes when used with preschoolers (PATS study) with > risks
  - Ghuman et al., 2013
Stimulants: Potential Side Effects

(Effects occurring in >5% of patients and >placebo)

- Appetite loss, abdominal pain
- Insomnia
- Nervousness

- Mild increase in pulse, blood pressure
- Psychiatric effects, irritability, dysphoria, and rebound (withdrawal?)

Controversies:

growth deficits, tic exacerbation, seizures, substance abuse
Pills are no substitute for skills

Meds *turn the volume down* on symptoms but can’t teach concrete coping skills
# Psychosocial treatments: The current evidence

<table>
<thead>
<tr>
<th>Level 1: Well-established</th>
<th>Level 2: Probably efficacious</th>
<th>Level 3: Possibly efficacious</th>
<th>Level 4: Experimental</th>
<th>Level 5: Not effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral Parent Training</td>
<td>Combined Training Interventions</td>
<td>Neurofeedback Training</td>
<td>Cognitive Training</td>
<td>Social Skills Training</td>
</tr>
<tr>
<td>Behavioral Classroom Management</td>
<td></td>
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<tr>
<td>Behavioral Peer Intervention</td>
<td></td>
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<tr>
<td>Organization Training</td>
<td></td>
<td></td>
<td></td>
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<td>Combined Behavior Management Interventions</td>
<td></td>
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Evans, Owens, and Bunford, 2014
Positive effects of behavioural intervention? Sonuga-Barke et al., 2013

Overall SMD=0.40, 95% CI=0.20, 0.60
Test for overall effect: Z=3.88, p=0.0001
Heterogeneity: $\chi^2=30.73$, df=14, p=0.006, $I^2=54\%$
But not when controlling for informant bias!

BUT must appreciate that they excluded MOST studies due to focus on only ADHD symptoms.
Consider advances in our knowledge of responses of ADHD children to rewards and punishments
Rewards become abnormally low in reinforcing power as they become more distant in time – results in abnormal relative weighting of delayed and immediate incentives resulting in overactive and impulsive behavior.
TREATMENT: Main Issues

- Teaching skills only generally inadequate
- Treatments must be at point of performance
- Treatments must be sustained:
  - Analogy to wheelchair and the disability
## Treatment approaches

- Keep work periods short
- Reduce delays, externalize time
- Externalize important information
- Externalize motivation
- Externalize problem-solving
- Use immediate feedback
- Increase frequency of consequences
- Firm and consistent parenting is best

- Use more salient rewards
- Change rewards periodically
- Use rewards before punishment
- Anticipate problem settings – make a plan
- Keep a sense of priorities
- Improve parental attending skills
- Maintain a disability perspective
Key is to persist with these methods until they become *automatic*

(That may be a very long time)
Neurofeedback
Neurofeedback and ADHD

- Also known as EEG biofeedback; effectiveness based on operant conditioning of bioelectrical neuroregulation
- Targets inattention, may need more sessions if accompanied by hyperactivity
- Follow-up sessions may be required to maintain gains
- No side effects
- Involves minimum of 30-40 biweekly 1 hour sessions of feedback
- Growing body of literature over last decade, some empirical studies, utilized since 1970s
- Based on theory that ADHD individuals have excess slow wave activity and reduced fast wave activity
- Provides immediate feedback to individual about brain wave activity in form of a video game
  - action is influenced by individual's meeting predetermined thresholds of brain activity
FIGURE 1 | Forest plots with Standardized Mean Difference (SMD), effect size, and homogeneity statistics for the meta-analysis examining total scores of ADHD symptoms, inattention dimension and hyperactivity/impulsivity dimension assessed by parent (left) and by teacher (right).
Computerized Working Memory Training (Cogmed JM/RM/QM)

- 45 min training/day
- 5 days/week, 5 weeks
- Adaptive algorithm
  - individually-based
- Reinforcement
  - Immediate performance-based feedback;
  - internal reinforcement activities
  - external reinforcement for completing pre-specified # sessions
- Weekly monitoring calls from licensed provider, using uploaded tracking data

Cogmed/Pearson
Question: Does cognitive training enhance attention or working memory in students with ADHD?

Answer: Growing evidence indicates that cognitive training may improve performance on standardized tests of working memory.

BUT, no robust evidence that such improvements generalize to everyday functioning - attentive behaviour, other aspects of cognitive function, academic learning – meta analysis confirms lack of effect (Hodgson et al., 2012).

Still experimental treatment as results equivocal (Evans et al., 2014).

Recent study showed NO benefit of CogMed over placebo across the board for 5-7 year olds (van Dongen-Boomsma et al., 2014).
Reduce working memory loads when necessary

- **Reduce**
  - overall amount of material to be remembered
  - degree of unfamiliarity and increasing meaningfulness of material to be remembered
  - difficulty of cognitive processing

- **Simplify**
  - linguistic structures of verbal material

- **Re-structure**
  - complex tasks into separate independent steps

- **Make available/encourage use of memory aids**
Does physical activity improve ADHD?

A child cannot ‘run off ADHD’
But some evidence that ADHD in children is a risk factor for later obesity & physical inactivity in adolescence
Also evidence that moderate-vigorous intensity activity in childhood (11yr olds) has LT beneficial effects on academic performance at age 16
moderate ES (0.3; Cortese, 2013)
What about “alternative” treatments?
A revised look at nonpharmacological txs not too positive... (effect sizes)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proximal assessment</th>
<th>Blinded</th>
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<tbody>
<tr>
<td>Restricted elimination diets</td>
<td>1.48</td>
<td>.51</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>.21</td>
<td>.16</td>
</tr>
<tr>
<td>Artificial food colour exclusion</td>
<td>.32</td>
<td>.42</td>
</tr>
<tr>
<td>Cognitive training</td>
<td>.64</td>
<td>.24</td>
</tr>
<tr>
<td>Neurofeedback</td>
<td>.59</td>
<td>.29</td>
</tr>
<tr>
<td>Behavioural interventions</td>
<td>.40</td>
<td>.02</td>
</tr>
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Sonuga-Barke et al., 2013, AJP
Diet manipulation as a treatment for ADHD

- restricted elimination diets (RED)
- artificial food colour elimination (AFCE)
- supplementation with free fatty acids (FFA)

Do any of these diets work?
Show potential – but no solid evidence yet

Stevenson (2014) An appraisal of diet in the treatment of ADHD. *JCPP*
How about dietary patterns?
Your Brain & Food

Consumes 420 calories/day
60% daily glucose
20% of daily calories
Composed of 60% Fat
High concentrations of PUFAs
## Food Additions to Hominid Diet

<table>
<thead>
<tr>
<th>Years Ago</th>
<th>Type of Food</th>
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<tr>
<td>23 to 5 million</td>
<td>Plants, Insects, Larvae</td>
</tr>
<tr>
<td>2 million</td>
<td>+ Seafood, meat, bone marrow</td>
</tr>
<tr>
<td>1-2 million</td>
<td>+ Tubers, bulbs</td>
</tr>
<tr>
<td>10,000</td>
<td>+ Grains, Dairy, legumes</td>
</tr>
<tr>
<td>100</td>
<td>+ Cheerios, Twinkies, Spam</td>
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- **0.05%**
- **5%**
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.
Kuntsi et al., 2006: genes and ADHD

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 using a relative risk calculator [URL]. This process assumes a standard normal trait distribution, such that the QTL variance for the discrete category will be the same as the QTL variance for the continuous measure. Assuming an additive genetic model, the variance explained by the associated genes is around 3.2%. The number of families needed to replicate with an 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>
</tr>
</thead>
<tbody>
<tr>
<td>DRD4</td>
<td>1.16</td>
<td>1.03</td>
<td>1.31</td>
<td>0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>DRD5</td>
<td>1.24</td>
<td>1.12</td>
<td>1.65</td>
<td>0.35</td>
<td>0.004</td>
</tr>
<tr>
<td>DATI</td>
<td>1.13</td>
<td>1.03</td>
<td>1.24</td>
<td>0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>DBH</td>
<td>1.33</td>
<td>1.11</td>
<td>1.59</td>
<td>0.5</td>
<td>0.007</td>
</tr>
<tr>
<td>SNAP-25 (T1065G)</td>
<td>1.19</td>
<td>1.03</td>
<td>1.38</td>
<td>0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>SERT (HTTLPR)</td>
<td>1.31</td>
<td>1.09</td>
<td>1.59</td>
<td>0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>HTR1B</td>
<td>1.44</td>
<td>1.14</td>
<td>1.83</td>
<td>0.71</td>
<td>0.010</td>
</tr>
</tbody>
</table>
Early poor nutrition/malnutrition is proving a risk factor for ongoing psychological symptoms

- "Western" diet during pregnancy and early years of life increases risk for offspring developing depression, anxiety, ADHD and other behavioural problems like aggression and tantrums
  - Oddy et al, 2011; Jacka et al., 2011, 2013; Sanchez-Villegas et al., 2009, 2012

- Children malnourished in first 6 months of life at greater risk for developing ADHD, depression, and personality problems 30-40 years later
  - Galler et al., 2010; 2012; 2013
What’s **wrong** with ‘western, processed’ diets?

**Fewer vitamins and minerals**
Western diet is associated with a smaller hippocampus
What’s good about ‘Mediterranean, prudent’ diets?

More vitamins and minerals
Nutrition: there are 2 sides to this coin

What we eat that *maybe*

we should *not* eat

- Gluten
- Casein/dairy
- Artificial additives
What are we NOT eating enough of

- Vitamins
- Minerals
- Omega-3 fatty acids
Tell everyone to eat better
But would a change in diet work for everyone?

Not sure...but unlikely...why?
Eating better is a good thing....
BUT
And if we do supplement, single or multiple?
One nutrient, one problem?

- 6-Hydroxykynurenate
- 5-Hydroxy-N-formylkynurenine
- 5-Hydroxyindole-acetyaldehyde
- 5-Hydroxyindole-pyruvate
- Serotonin
- 3-Formylaminobenzaldehyde
- Indole
- Tryptophan
- 3-Indole-glycolaldehyde

Key nutrients:
- Vit. B₆
- Copper
- Iron
- Molybdenum
- Vitamin B6
Krebs (Citric Acid) Cycle

- **Pyruvate**
  - Pyruvate dehydrogenase - Thiamine
  - Oxaloacetate
  - Citrate
  - Aconitate hydratase - [4Iron-4Sulphur]
  - Isocitrate
  - Isocitrate dehydrogenase - Mn$^{2+}$ or Mg$^{2+}$, Nicotinamide
  - Oxalosuccinate
  - Isocitrate dehydrogenase - Manganese or Magnesium, Nicotinamide
  - Oxoglutarate dehydrogenase - Thiamine
  - 2-Oxoglutarate synthase - Thiamine and 2 [4Fe-4S] clusters
  - Dihydrolipoyl dehydrogenase - Riboflavin

- **Pyruvate dehydrogenase** - Thiamine
- **Acetyl-CoA**
- **Citrate**
- **Isocitrate dehydrogenase** - Mn$^{2+}$ or Mg$^{2+}$, Nicotinamide
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- **Dihydrolipoyl dehydrogenase** - Riboflavin

- **NAD**
  - NADH + H$^+$
- **Succinate**
- **Fumarate**
- **(S)-Malate**
- **GTP**
  - GDP

**Redox Equations**

- NAD$^+$ + H$^+$ + 2H$^+$ → NADH + H$
\text{(S)-Malate}

\begin{align*}
\text{Pyruvate} & \rightarrow \text{Acetyl-CoA} \\
\text{Acetyl-CoA} & \rightarrow \text{Citrate} \\
\text{Citrate} & \rightarrow \text{Isocitrate} \\
\text{Isocitrate} & \rightarrow \text{Oxalosuccinate} \\
\text{Oxalosuccinate} & \rightarrow \text{Oxoglutarate} \\
\text{Oxoglutarate} & \rightarrow \text{Fumarate} \\
\text{Fumarate} & \rightarrow \text{(S)-Malate} \\
\text{(S)-Malate} & \rightarrow \text{Pyruvate}
\end{align*}

**Metabolic Pathways**

- **Pyruvate dehydrogenase**
- **Acetyl-CoA to Citrate**
- **Isocitrate dehydrogenase**
- **Oxalosuccinate to Oxoglutarate**
- **Isocitrate dehydrogenase**
- **Oxoglutarate dehydrogenase**
- **2-Oxoglutarate synthase**
- **Dihydrolipoyl dehydrogenase**

**Additional Information**

- [www.genome.jp/kegg/pathway/map/map00020.html](http://www.genome.jp/kegg/pathway/map/map00020.html)
Nutrients work most effectively together

So supplementing with only ONE doesn’t usually make physiological sense...
NOT Getting Enough

http://www.ba.ars.usda.gov/cnrg/services/cnmapfr.html
ADHD and micronutrients

- Early studies mostly negative
  - used single ingredients, megadoses or too small a dose; short trials
    - e.g. Arnold et al., 1978; Haslam et al., 1984; Sinn et al., 2007; Bilici et al., 2004; Coleman et al., 1979
- Evidence in last decade growing based on using broad spectrum of nutrients:
  - Designs include:
    - open-label; retrospective database analyses
    - case reports; reversal designs
    - patient preference studies
    - RCTs
EMPowerplus/Daily Essential Nutrients

- 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
Change in self-rated ADHD symptoms

- Change in CAARS Hyp/Imp Self: $p = 0.041$, $ES = 0.47$
- Change in CAARS Inattention Self: $p = 0.007$, $ES = 0.62$
CGI – I – ADHD post RCT

\[ p < .02, ES = 0.53 \]
But what about unexpected effects?

When people do well many others changes occur...
ADHD and .... Earthquakes
7.1 earthquake in Christchurch occurred during active trials

September 4th 2010 4:35am
In three weeks following the earthquake there were about 1000 aftershocks.
A “natural experiment”

Sept 2010: we happened to be conducting trials on ADHD using EMP

- Participants all assessed prior to the quake (t0)
- Some taking EMP
- Some not taking EMP
- Surveyed by phone 1 and 2 weeks post-quake (t1, t2)
- Used Depression, Anxiety, Stress Scale (DASS)

- Rucklidge et al., 2011, Psychiatry Research; Rucklidge & Blampied, 2011, NZJP
Mood and general functioning
MADRS: only those clinically depressed at baseline

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

\[ p = 0.039, \text{ES} = 0.64 \]
And we are also seeing improved symptoms in kids...

Pilot trial on 14 children using reversal design
Combined ADHD symptoms; Gordon et al., in press

**T score**

ES = 2.17

ES = 1.3

ES = .78

*** sig different from baseline (p < .001)
Other “co-occurring” disorders
Case study of ADHD with Bipolar and anxiety

*Rucklidge & Harrison, 2010, CNS Spectrums*

- “Katie” 21 year old female
- In 2008, diagnosed ADHD Combined Type, Social Anxiety, PTSD, BP II, Panic Disorder
- 8 years of well documented history of ongoing interventions with conventional treatments with minimal benefit
- Past meds: fluoxetine and methylphenidate
- CGI: moderately ill range at baseline
- GAF = 45
Depression and mania scores across time and micronutrient use

MADRS=Montgomery-Asberg Depression Rating Scale, YMRS=Young Mania Rating Scale
Substance Abuse
“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
- On (8 weeks)-off (8 weeks)-on (4 months)- “natural” off (5 months)
On-off change in Brian’s symptoms over 1 year

T-Scores

Inattentive symptoms

Hyperactive/Impulsive symptoms

Baseline

On

Off

On 2

Off 2
What happened to Brian’s substance abuse?

Harrison et al, 2013, J of Psychoactive Drugs
And long-term maintenance?
Naturalistic follow-up one year post-baseline: ADHD symptoms;
Rucklidge et al., 2015; *J Attention Disorders*

ES btwn grps: 0.87

- **Stayed on micronutrients (n=14)**
- **Switched to medications (n=17)**
- **Not taking medications or micronutrients (n=41)**
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

Therapeutic range?

Risk of Inadequacy

Observed Level of Intake

RDA

EAR

UL

Risk of Adverse Effects

Food and Nutrition Board, Institute of Medicine
Conventional medicine

- medication
- therapy
- other
Integrative medicine

lifestyle/diet/exercise/supplements

stress reduction/therapy

meds
Steps to healthy children

1. Wellness diet (get rid of crap food, replace with vegetables, water, exercise, fruit, protein, small amount of carbs, nuts)
2. AFC free diet (Additives-Flavours-Colours)
3. Elimination diet (could be eggs, peanuts, soy, fish, wheat, dairy) – remove 7-21 days
4. Gluten-free Casein Free diet
5. Supplement?
Conflicts of interest
British Nutrition Foundation
It’s our choice...
Acknowledgements

- **Current Graduate students working on nutrient studies**
  - Heather Gordon
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  - Kathryn Whitehead
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Which commercial broad spectrum micronutrients have any evidence of benefit with mental symptoms?
Current studies at the UC Mental Health and Nutrition Research Lab

- RCT for children 7-12 years with ADHD
- RCT for PMS
- Go to: bit.ly/Ucnutritionresearch or bit.ly/childadhd
- www.facebook.com/mentalhealthandnutrition
- Julia.rucklidge@canterbury.ac.nz
- Follow me on : @JuliaRucklidge