NON DRUG TREATMENTS FOR AD(H)D

RICHARD BROWN, MD
Richard P. Brown, MD has no financial conflicts regarding the treatments or described in this lecture.
ADD STATISTICS

• ADHD is the most common behavioral disorder in children
• 5% of youth have ADHD
• Boys: Girls = (4-9): 1
• 50% or more have symptoms into adulthood
ADD AND ASSOCIATED DISORDERS

- Conduct Disorder (10-20%)
- Oppositional Disorder (40-60%)
- Anxiety Disorder (30-40%)
- Depression (20-30%)
- Bipolar Disorder
- Tourettes or Tic Disorder

- Obsessive-Compulsive Disorder
- Autism/Pervasive Developmental Disorder
- Substance Abuse
- Antisocial Personality Disorder
- Learning Disabilities
- Dyslexia
POSSIBLE EXTERNAL FACTORS IN ADD

• Food and additive allergies
• Heavy metals (lead) & other toxins
• Mineral deficiencies
• Essential fatty acid and phospholipid deficiencies
• Amino acid deficiencies
• Low protein, high carbohydrate diet
• B vitamin & phytonutrient deficiencies

(Grant. ADD and ADHD. Complementary medicine Solutions. Syracuse NY: Mindmenders Press 1999)
HOW MANY PARENTS USE CAM FOR A CHILD WITH ADHD?

**2000**
- 54% used CAM
- Diet: 26%
- Vitamins/Nutrients: 39%
- Art: 39%
- Told their MD: 11%

**1998**
- 38% used CAM
- Diet: 76%
- Vitamins: 45%
- Herbs: 21%

RITALIN vs SUPPLEMENTS FOR ADHD

• 10 children on Ritalin by choice
• 10 children on supplements by choice
• Standardized continuous performance task for attention (6 scales) and behavior scales
• Equivalent improvement in both groups
• Needs further study

IRON DEFICITS IN ADHD KIDS

- 53 ADHD kids (4-14 yrs) vs 27 matched controls
- Ferritin levels (measure of iron stores) low in 84% ADHD kids and 18% of controls
- Low ferritin levels correlated with greater cognitive deficit and more severe ADHD symptoms
- Iron deficiency can cause restless leg syndrome, mistaken as ADHD symptom
IRON SUPPLEMENTS IN ADHD

- Iron necessary for dopamine synthesis and downstream dopaminergic receptor activity
- RCT 23 children (ages 5–8 years) with low serum ferritin, iron supplementation (80mg/day) improved ADHD symptoms (Konofal et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatric Neurology. 2008; 38:20–26.).
- Low serum ferritin correlated with baseline ADHD symptoms and with the dose of amphetamines required for clinical improvement
ZINC IMPROVES MENTAL PERFORMANCE

- Zinc is cofactor regulating serotonin & norepinephrine transmission. Also crucial for melatonin, and free fatty acid metabolism.
- RCT 209 7th graders (111 girls) randomized to 0, 10, or 20 mg zinc, or placebo each school day for 10-12 wks.
- 20 mg zinc improved speed and accuracy on memory and sustained attention.
- No correlation with zinc levels prior to study.
- Girls on placebo had 10% increase in conduct problems.
- Zinc levels low in ADHD kids, especially males. (Arnold. Ann NY Acad Sci 2001)
ZINC FOR ADHD

- 328 boys, 72 girls with ADHD in a PRDB Trial of Zinc (40 mg element) or placebo x 12 wks
- Turkey has low soil zinc and ↑ zinc deficiency
- Zinc helped hyperactive, impulsive, and socialization symptoms, not attention deficit, especially in older children, with low Zinc & free fatty acid levels
- Low Zinc level impairs response to amphetamine
- In US studies more equivocal using zinc for ADHD

ZINC ADDED TO RITALIN FOR ADHD

• 44 children (5-11 yo) RDB X 6 wks to have zinc 15 mg/day or placebo added to Ritalin 1 mg/kg/day
• Zinc group did much better on parent & teacher ratings by wk 6
• Well tolerated (metallic taste, slight nausea)
• Needs replication with a full placebo group

(Akhondzadeh et al. BMC Psychiatry 2004;4:9)
FOOD ADDITIVES AND HYPERACTIVITY

- Confusing literature with many DB studies showing slight effect on kids’ behavior
- Better study: 277 3-yr-olds/1246 children on Isle of Wight in complex 4 wk DB crossover study got either food additives or placebo for 2/4 weeks with washout in between
- Parents detected hyperactivity during additive week while blinded PhD could not (without relation to prior hyperactivity or allergy)

(Bateman et al. Arch Dis Child 2004;89(6):506-511)
DIETARY ELIMINATION
(Few-foods Diet)

• 8 controlled studies from 1982-2001 improve without dye vs full diet or worsen on placebo challenge
• Sugar restriction has not gotten support despite multiple controlled studies

(See review: Arnold LE: Ann NY Acad Sci 2001; 931:310-341)
FOOD ELIMINATION DIETS


• Meta-analysis of DBRPCTs: ~ 33% of children with ADHD may respond to dietary interventions, only 8% have symptoms related to synthetic food colors (Nigg, Lewis, Edinger & Falk, 2012).

• Effect sizes on ADHD of elimination diets and artificial food color exclusions are modest 0.51 0.42)(Sonuga-Barke et al., 2013
GENETIC POLYMORPHISMS

• Polymorphisms in the histamine degradation gene (HNMT) result in impaired clearance of histamine which is released following challenge with food additives.

• DBRPCT: Children with ADHD with specific HNMT or DAT1 polymorphisms experienced worsening clinical symptoms when challenged with food additives vs children lacking these polymorphisms. Genetic link between histamine risk alleles and ADHD symptoms following exposure to food additives.

OMEGA-3 FATTY ACIDS

• Meta-analysis of 10 trials (n=699) found small but significant overall improvement in ADHD with omega-3 fatty acid supplementation (standardized mean difference [SMD] = 0.31, confidence interval [CI] = 0.16–0.4, p~.0001). Similar results for inattentive and hyperactivity symptoms.

• Higher doses EPA significantly associated with reduction of ADHD symptoms

• Effective dose: 600–1000mg/day of omega-3 (with 2:1 ratio of EPA to DHA)

• (Bloch & Qawasmi, 2011).
VITAMIN-MINERAL SUPPLEMENT IMPROVES IQ IN SUBSET OF SCHOOL CHILDREN

• 245 working class kids (6-12 yo) in DBRPC trial of supplement to raise nutrients to balanced diet levels (50% RDA) or placebo x 3 months
• Net gain of 2.5 nonverbal IQ points vs placebo
• 8 1 sex, age, IQ matched pairs showed no change
• 24 matched pairs gained 16 points vs 19 placebo controls

EFFECT OF BIO-STRATH IN CHILDREN

• B Vitamins and antioxidants
• 4 studies of children: Most important:
  • 123 children with mental retardation – 59 (8-10yo), 64 (13-16 yo)
  • PDBRPC trial with 3 groups: Bio-Strath, Placebo, or no supplement
  • Bio-Strath group had better concentration
  • Needs replication (industry sponsored)

(Defores et al. Research on Bio-Strath on file, Zurich)
AMINO ACIDS FOR ADHD

• Low levels of amino acids in ADHD especially precursors of dopamine, norepinephrine, serotonin

• However multiple studies in kids and adults show minimal temporary effect at best

(Arnold, 2001)
DIMETHYLAMINOETHANOL (DMAE)

• Choline precursor
• 6 studies but most flawed
• Possibly mild effect

(Arnold, 2001)
CENTROPHENOXINE
(Meclofenoxate, Lucidril)

- **Mechanism:**
  - Dimethyl-aminoethanol (DMAE) and PCPA (plant auxin)
  - \( \uparrow \) choline levels in brain
  - \( \uparrow \) neuronal and glial energy metabolism
  - Protects against hypoxia
  - Stimulates reticular system
  - \( \downarrow \) lipid peroxidation
  - \( \downarrow \) lipofuscin + age-related synaptic loss
  - Synergistic with ginkgo, racetams
PYRROLIDONES (RACETAMS)

• Piracetam, Pramiracetam, Aniracetam, Oxiracetam
• Mechanisms: ↑ neuronal ATP
  ↑ cell membrane fluidity
  ↓ overactive platelet aggregations
  ↑ muscarinic cholinergic receptors, DA, NE, 5HT, choline
  ↑ NMDA glutamate receptors
  ↑ LTP in hippocampus and intercallosal info transfer

Protects against hypoxia in animal models
Synergistic with CDP-choline, CPH, caffeine
Activates EEG (esp. verbal left hemisphere areas)
PIRACETAM FOR DYSLEXIA

• DBRCT 225 children with dyslexia (ages 7–12)
• 3,600mg/day of piracetam resulted in significant improvements in reading and comprehension.
• Improvements were evident after 12 weeks and remained throughout the 36 weeks of the trial.
• There were no adverse reactions to piracetam

• (Wilsher et al., 1987).
PYRROLIDONES (RACETAMS)

• Indications:
  Most robust effects in aphasia, dyslexia, post-concussion syndrome
  complementary treatment for patients with ADHD with learning or language-related disabilities
• Side Effects:
  Non-toxic
• Dosage:
  Aniracetam 750 mg 2X/day (adult dose)
S-ADENOSYLMETHIONINE SAM-E

- Delays brain aging in rat studies
- Monkeys recover better post-stroke
- DBPC study for post-concussion syndrome positive effects (300 mg/day)
- One small open series in adult ADD (2400 mg/day) improved symptoms

RHODIOLA ROSEA: GOLDEN ROOT, ARCTIC ROOT

• Adaptogen: Plants that protect organisms from numerous kinds of stressors—environmental, chemical, infectious, hypoxic, toxic, and others (Brown & Gerbarg 2004, 2009)

• Stimulates reticular activating system

• ↑s levels of dopamine, serotonin and norepinephrine. (Petkov et al., 1986; Stancheva & Mosharrof, 1987; van Diermen, et al. 2009).

• Balances stress-response system - prevents excessive release of stress hormones eg. cortisol (Panossian et al., 2010).
RHOLDIOLA ROSEA INCREASES ATP & CP

↑ ATP and Creatine Phosphate in rat brain cells
   (Saratikov AS, Krasnov EA (1987) Rhodiola rosea is a valuable medicinal plant. Tomsk. Russia Pp 91-105.)

R. rosea extract 50 mg/kg in rats vs placebo
   ↑ time to exhaustion swimming by 24.6%
   ↑ synthesis skeletal muscle mitochondrial ATP
   ↑ reparative energy processes after intense exertion

R. ROSEA – COGNITIVE FUNCTION

• 11 RCTs evaluating its effects on mental health conditions, mental performance and physical performance in high school students, college students and military cadets

• Improves cognitive functions such as attention, accuracy and memory

RHODIOLA AND INTELLECT

120 students given a baseline symbol correction test, randomized to Rhodiola or placebo

The % of errors compared to baseline over time showed:

<table>
<thead>
<tr>
<th></th>
<th>Rhodiola</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>1 hr</td>
<td>4% less</td>
<td>13% more</td>
</tr>
<tr>
<td>4 hr</td>
<td>56% less</td>
<td>37% more</td>
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<tr>
<td>6 hr</td>
<td>&lt; 5% more</td>
<td>88%</td>
</tr>
<tr>
<td>8 hr</td>
<td>&lt; 5% more</td>
<td>180% more</td>
</tr>
<tr>
<td>24 hr</td>
<td>- no difference from baseline –</td>
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EFFECT OF RHODIOLA ON MENTAL WORK CAPACITY UNDER STRESS

11 Subjects crossover sequential study R. rosea 300-400 mg/Schizandra/Acanthopanax at baseline, on placebo, and on adaptogen under stress conditions:

↓ subjective fatigue
objective signs of ↑ alertness
↓ errors by 10-15%
↑ memory, attention, coordination
↑ work attitude and self evaluation
↓ eye fatigue and eye irritation

(Baranov VM et al. Russian Federation Ministry of Health. Institute of Medical and Biological Problems. Phase One and Phase Two. Moscow 1994.)
RHODIOLA FOR EXAM PERIOD FATIGUE AND STRESS IN COLLEGE STUDENTS

Low dose R. rosea (100 mg) or placebo given in a RDB parallel study, 40 subjects for 20 days of final exams 1st year at University.

Significant Improvement in:
mental fatigue, psychomotor function
overall well-being (self-evaluation)
physical work capacity and heart rate
final exam marks

EFFECT OF R. ROSEA ON COGNITIVE AND PHYSICAL FITNESS IN FOREIGN HIGH SCHOOL STUDENTS

3 groups of 20 high school students (Indians in Russia): control, placebo, Rhodiola 600 mg

Results:
- better general well-being
- less fatigue and anxiety
- better neuromotor performance
- better physical fitness on testing

• Meta-analyses indicate that Ginkgo significantly improved selective attention, fluid intelligence, memory, executive function and processing speed compared to placebo (Diamond & Bailey, 2013). These cognitive domains are often impaired in ADHD patients.
• Pilot study adolescents (n = 6) with ADHD + co-morbid disorders 200mg/daily of EGb 761 significantly improved arousal, hyperactivity, anxiety, frustration tolerance and cognitive aspects of attentional processing 6 week DBRPCT 50 children with ADHD

• 80–120mg of G Biloba TD vs 20–30mg methylphenidate

• Methylphenidate far more effective than G. Biloba TD (Salehi et al., 2010)

• Subtherapeutic dose, less potent G. Biloba T.D.

• (Niederhofer, 2010).
AMERICAN GINSENG + GINKGO

- Open study 36 ADHD kids (3-17 yo)
- Am Ginseng 200 mg/Ginkgo 50 mg 2X/day for 4 wks gave marked improvement in ADHD scales by parents
- Am Ginseng + Ginkgo
  - activate EEG like stimulants
  - improve dopamine/norepinephrine systems
- Controlled studies needed

(Lyon et al. J Psychiatry Neurosci. 2001;26:221-8)
MELATONIN FOR INSOMNIA IN CHILDREN

- Sleep problems in 25–55% of ADHD patients
- DBRPCT Melatonin 5.0 mg at 6 PM vs placebo in 40 children (6-12 yo) with 1 year chronic sleep-onset insomnia; 1 wk baseline with 4 wks treatment
- Melatonin group fell asleep about 1 hour earlier and slept 40 minutes more than the placebo group

(Smits et al. J Child Neurol 2001; 16(2): 86-92)
MELATONIN: INSOMNIA AND ADHD

- 4-week DBRPCT 105 children (ages 6–12) with sleep onset insomnia and ADHD
- Melatonin: significant improvements in sleep latency ($p=.01$) and sleep efficiency ($p=.01$)
- 3-year follow-up: 65% continued to use melatonin every evening and 12% used it occasionally.
- Long term melatonin was effective treatment for sleep onset problems in 88% of cases.
- After 4 weeks, parents reported improvements in behavior (71%) and mood (61%). No adverse effects or safety concern
- (van der Heijden, Smits, et al. 2007)
MELATONIN PEDIATRIC DOSES

• children weighing 100 pounds (40 kg) or less
  Dosing starts at 0.3–1mg, final range of 1 to 3mg
• children over 100 pounds (40 kg)
  Dosing starts at 0.5–1mg, final range 3–6 mg

• Fast-release formulation for sleep onset problems
• Slow-release for sleep maintenance
• Combination of both formulations.
MELATONIN FOR SLEEP IN AUTISM

- Fifteen children: PDD/autism with severe insomnia
- Double blind placebo-controlled: 3-14 years old
- All improved in sleep, less irritable, more alert, more sociable
- 3 epileptics showed better seizure control
- Doses: 2-10 mg, mean of 5 mg

(Jan et al. Dev Med Child Neurol 36: 97-107, 1994)
MELATONIN IMPROVES SEIZURES AND SLEEP IN CHILDREN

• Open Study: 10 children, 5 mos. to 12 yrs old
• After 6 baseline salivary melatonin levels, 5-10mg given HS for several weeks or months
• 8/10 slept better, with ↑ alertness in the day; 2 nonresponders got ≤5mg
• 6/8 responders had ↑ seizure control and regained normal patterns of nocturnal melatonin secretion

ANS BIOFEEDBACK HELPS ADHD

• Open pilot study using biofeedback in 19 ADHD subjects
• Child and teacher ratings improved
• Improvement correlated with improvement in heart rate variability (HRV)

MEDITATION FOR ADHD

• 2 controlled studies of 24 and 23 children showed improvement on different scales
• Compliance is an issue

(Arnold, 2001)
• Open trial and 3 single-blind trials show rotational stimulation improves ADHD ratings
• Stimulates vagal input

(Arnold, 2001)
YOGA BENEFITS IN ADHD

- Controlled study 19 boys (8-13) ADHD
- Yoga breathing, postures and relaxation
- Improvements on Conner’s Parent Rating Scales, TOVA, Response Time Variability, & Global Emotional Lability subscale correlated with # of sessions attended & amount of home practice.

YOGA FOR ADHD

- RCT 19 children with ADHD (ages 8–13)
- yoga program (twenty weekly 1 hour yoga group) or conventional program of motor exercises for 34 weeks
- The yoga training was superior for all outcome measures of ADHD rating scale for parents and teachers.
- Small sample size, attendance variability and exclusion of children with co-morbid behavioral conditions were limitations of this study

- (Haffner, Roos, Goldstein, Parzer, &Resch, 2006)
YOGIC POSTURES & BREATHING FOR KIDS

- Executive control function on 4 measures Tower of London Test (frontal lobe) improved greatly in 10 girls doing yoga 1.25 hrs/d X 1 month vs 10 girls doing physical training.
- Incarcerated kids (& adults) showed better sleep, appetite, well-being and ↓ ed arousal over 6 months yoga.

(For review and refs see Telles S, Naveen KU. Indian J Medical Science 1997:123-27)
YOGA IMPROVES SPATIAL BUT NOT VERBAL MEMORY IN CHILDREN

• 30 children yoga group (asanas, pranayam, kriyas, meditation, singing, guided relaxation) 8 hrs/day x 10 days
• 30 children in fine arts camp (drama, dance, singing, painting, pottery, games) 8 hrs/day x 10 days
• 30 children no intervention x10 days (11-16 yo)
• Yoga group had improved spatial but not verbal memory on day 10

AUTONOMIC RESPONSES IN ANTISOCIAL DISORDER

• Hyporesponsive Autonomic Nervous Systems (SNS & PNS) and faster habituation to orienting and aversive startling stimuli is found in antisocial adults, boys with conduct disorder and oppositional defiant disorder with or without ADHD

INFANT AFFECT AND RSA

• High RSA in infants correlates with a better capacity to respond to the environment, both (+) and (–) affective response

• Low RSA is found in timid, fearful, or depressed infants

(Beauchaiine, T. 2001)
HEART RATE VARIABILITY (HRV)

• But RSA is influenced by:
  1. sympathetic and vagal input
  2. respiratory rate and volume

• Heart Rate Variability (HRV) gives a more accurate measure of parasympathetic tone
HIGH RSA IN BOYS

• High RSA predicts:
  1. more empathic responsiveness and
  2. social competence, especially in boys in grade school
AGGRESSIVE AND ANTISOCIAL

• Aggressive or antisocial adolescents and hostile adults show:
  ↓ Heart Rate and ↓ RSA

• Consistent with:
  ↓ Sympathetic and
  ↓ Parasympathetic Activity

(Carney, RM. J Psychosom Res 1988, 32:159-164)
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Vagus Nerve Effects

Cerebral Cortex

Corpus Callosum

Thalamus

Limbic System

Brainstem Relay Stations

PB parabrachial nucleus

NTS nucleus tractus solitarius

Vagus Nerve

Calm the Gastrointestinal Tract

Slows Heart Rate and Slows Respiratory Rate
NEUROPHYSIOLOGICAL MODEL OF VAGUS NERVE STIMULATION PATHWAYS

Stimulation
- Hyperventilation
- Electronic
- Sudarshan Kriya (SKY)

Vagus Nerve → NTS → PBN → Thalamic Nuclei
- Thalamic Generators

→ Diffuse Cortical Areas
- Frontal – quiet, worry
- Parieto-occipital
- SMR – calm + relaxed
- attention + vigilance

Limbic Pathways
- MRS
- Anterior Limbic Cortex
- PRS – reward, satiety, pleasure

Hypothalamus
- Amygdala
- Stria Terminalis

Emotion & Memories
- reward & oxytocin receptors

Pituitary Release
- Prolactin, Vasopressin
- Oxytocin - bonding

NTS = nucleus tractus solitarius; PBN = parabrachial nucleus; MRS = mesolimbic reward system
SMR = sensori-motor rhythm; PRS = post-reinforcement synchronization
NEUROFEEDBACK (1)

• MC DBRCT 102 children (ages 8–12) with untreated ADHD
• neurofeedback training: block of theta/beta training and a block of slow cortical potential training (36 sessions, 50 minutes per session
• vs computerized attention skill training program
• NF group: statistically significant improvements in parent and teacher ratings of ADHD symptoms with medium effect sizes of 0.4–0.6.
• (Gevensleben et al., 2009).
NEUROFEEDBACK (2)

• 6-month follow-up of 61 patients: sustained superior scores for the NF group vs control group in core ADHD symptoms and other functional domains.
• For theta/beta training: decreased theta activity in the resting EEG was associated with improvement in ADHD symptoms.
• Change in alpha activity predicted clinical improvement following SCP training.
• These results suggest specificity of treatment effects (Gevensleben et al., 2010).
Patients with increased theta or theta/beta ratios are more likely to benefit from treatment with NF.

NF is most effective for inattention and impulsivity (Sherlin et al., 2011).

Side effects may include headache, nausea, dizziness, sleepiness or agitation.

Frequent (1–3/week) and prolonged (2–12 months) treatments may be needed.

The International Society for Neurofeedback (www.isnr.org) information, training, and certification.