



Complementary and Alternative treatments of ADHD: a critical review

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Prevalence and Etiology

- Estimated prevalence 2 to 30% (Barkley 1998)
- High concordance rate in identical twins (Biederman & Faraone 2005)
- Genes regulating CNS transport of dopamine and serotonin implicated (Wallis et al., 2008)
- Some cases caused by delayed development of frontal and temporal lobes relative to rapid maturation of motor areas (Brennan et al., 2008)

Etiology

- One fifth of ADHD cases caused by perinatal brain injury or toxic exposure (tobacco smoke, lead, EtOH) (Swanson et al., 2007)
- Certain food preservatives exacerbate symptoms but do *not cause* ADHD (Cruz & Bahna 2006)
- Early childhood neglect or abuse may increase risk of ADHD

Conventional Rx of ADHD

Limitations and risks



"I have a couple of other projects I'm excited about."

Limitations and risks of conventional Rx

- Stimulant medications have high abuse potential when started in late adolescence or adulthood but may reduce abuse risk when started in childhood (Faraone & Wilens 2003)
- Chronic amphetamine use in childhood associated with delayed growth
- Sporadic cases of stimulant-induced psychosis reported (Berman et al., 2008)
- Stimulants for ADHD cause significant adverse effects in 1/3 patients: insomnia, decreased appetite, abdominal pain (Schachter et al 2001)

Limitations and risks of conventional Rx

- **Atomoxetine AEs:** hypertension, decreased appetite, nausea, fatigue, liver toxicity, insomnia, and seizures
- But non-stimulant medications and extended release stimulants *less likely to be abused* (Upadhyaya 2007)
- Stimulants in adult ADHD probably half as effective as in children (Newcorn et al. 2007)

CAM use in ADHD

- 12 to 64% of children and adults diagnosed with ADHD use CAM alone or adjunctively (Russing et al., 2002)
- 50% of pediatricians are asked (by parents) about CAM for ADHD (American Academy of Pediatrics, 1997)
- Over half of parents of ADHD children treat their children's symptoms using one or more CAM Rx
- Major CAM in ADHD—vitamins, dietary changes
- 10% disclose CAM use to pediatrician (Chan et al. 2003).



Complementary and Alternative treatments of ADHD

A critical review of the evidence

CAM use in ADHD

- Few studies on most CAM Rx now widely used to treat ADHD
- In spite of limited research data when herbal or other natural Rx used they are regarded as the primary treatment (by parents of ADHD children or adults being treated) over 80% of the time (Chan et al., 2003)

The evidence for CAM Rx in ADHD

What is known and questions

CAM Rx in ADHD

- Dietary changes
 - Feingold diet
 - Oligoantigenic diet (OAD)
 - Restricting sugar and high glycemic index foods
- EEG biofeedback
- Essential fatty acids (Omega-3s)
- Herbals (Ginkgo, American Ginseng, Bacopa, French maritime pine)
- Trace elements (zinc, iron)
- Acetyl-L-carnitine
- Homeopathic remedies

Elimination diets

- Early studies on a highly restrictive diet that eliminates all processed foods reported promising findings in children with ADHD (Feingold 1975)
- Systematic review of RCTs did not confirm efficacy (Wender 1986)
- Oligoantigenic diet (OAD) is a highly restrictive diet. Eliminates food colorings and additives, dairy products, sugar, wheat, corn, citrus, eggs, soy, yeast, nuts and chocolate

Elimination diets—OAD

- RCTs on OAD—significant reductions in hyperactivity when specific food items eliminated using an open-label protocol which recurred when challenged in a placebo-controlled phase (Rojas & Chan 2005)
- Findings difficult to interpret—heterogeneity of patient populations, absence of standardized outcome measures, high drop out rates, non-blinded raters

The putative role of sugar

- Suspected role but mixed findings
- 9-week PCRT, non-ADHD children randomized to high-sucrose vs aspartame vs saccharin found no differences in behavior (Wolraich et al. 1994)
- Study design did not control for fruits, juices or other *high-glycemic* sources of sugar (Weber & Newmark 2007). Studies needed

Putative role of sugar

- Parental expectations may *bias perceptions* of children's behavior following consumption of large quantities of sugar
- Small PCRT: mothers more likely to label behavior *hyperactive* when *believed* children had eaten sugar (Hoover & Milich 1994)
- Large prospective trials on dietary restrictions in ADHD difficult because hard to control eating (Cormier 2007)

EEG biofeedback in ADHD

What the evidence suggests

EEG biofeedback

- Up to 90% of children and adults diagnosed with ADHD have abnormal brain electrical activity: “under-arousal” in frontal and midline cortical regions and frontal “hyper-arousal” more often in patients who have not responded to stimulants (Butnik 2005).
- EEG biofeedback (“neurotherapy”) aimed at normalizing EEG activity, correcting relative under-arousal and optimizing cognitive and behavioral functioning (Monastra et al. 2002)

EEG biofeedback

- Two EEG biofeedback protocols have been extensively studied in ADHD
- Sensori-motor rhythm (SMR) training –reinforces faster “beta” frequency activity (16-20 Hz) and reduces impulsivity and hyperactivity
- “Theta suppression” reduces activity in the slower “theta” range (4 -8 Hz) used mainly for inattention
- Most data from case studies claiming consistent benefit for both hyperactive and inattentive sx

EEG biofeedback

- RCTs comparing EEG biofeedback to stimulant vs. waitlist report consistent benefits and EEG normalization with some protocols
- Unclear whether improved alertness associated with increased or decreased alpha activity (12-18 Hz) (Monestra et al. 2005; Ramirez et al 2001)
- ***Findings limited*** by small study sizes, heterogeneous populations, absence of sham group, inconsistent outcome measures, self-selection bias (the majority of enrolled subjects were highly motivated), and limited or no long-term follow-up.

EEG biofeedback—*limitations and progress*

- Findings suggest efficacy of specific protocols however *large RCTs needed* including randomized Rx allocation to true vs sham biofeedback to rule out group expectation effects
- QEEG analysis using normative database may help identify most efficacious protocols
- Play Attention therapy expands EEG biofeedback training to create new neural networks for improved attention, memory, auditory processing and social learning (Othmer 2000)



Essential fatty acids in ADHD

What the evidence suggests

Essential fatty acids in ADHD

- ADHD children have lower plasma concentrations of certain EFAs (Gedik et al., 1996)
- **Hypothesis:** fatty acid deficiencies during critical developmental phases increase ADHD risk (Richardson & Puri 2000)
- ***But...*** few controlled studies to date and findings inconsistent

Essential fatty acids in ADHD


- RCT on adjunctive EFAs found no differential benefit over stimulants plus a placebo (Voigt et al. 2001)
- RCT on adjunctive EFAs found modest improvements over placebo in disruptive behavior and attention (Stevens et al. 1995)
- RCT on EFAs as monotherapy in childhood ADHD: parents of children in verum group reported more improvement than parents of children receiving palm oil placebo (Sinn & Bryan 2007)...*however..*

Essential fatty acids in ADHD— limitations of findings

- *Study criticized*—high drop-out rate biases findings in positive direction (Weber & Newmark 2007)
- *Study criticized*—olive oil *placebo* may mask beneficial effects of EFAs (constituent of olive oil converted into oleamide which affects brain function) (Richardson & Puri 2002)
- *Short durations and low doses* of EFAs used in studies may not be adequate for changes in neuronal membrane structure required for clinical improvement (Voigt et al., 2001)



"I'm going to be late, dear. It's total craziness here."



Higher dosing may be key to
improved efficacy

Essential fatty acids in ADHD— dosing

- Small 8-week open-label study (N=9) ADHD children received high dose EPA/DHA concentrates (16.2g/day) while continuing stimulant and rated by a blinded psychiatrist
- Significant improvements in inattention and hyperactivity tracked reductions in AA:EPA ratio at end of treatment period (Sorgi et al., 2007)
- **Large prospective trials needed** to replicate findings and determine optimal dosing strategies

Herbals in ADHD

Ginkgo biloba

American ginseng (*Panax quinquefolius*)

French maritime pine (*Pinus pinaster*)

Bacopa monnieri ("Brahmi")

What the evidence suggests

Herbals in ADHD

- Many herbals used but very few published controlled studies
- 4-week RCT (N=36 ADHD children) randomized to *Ginkgo biloba* and American ginseng (*Panax quinquefolius*) + stimulant improved more than herbal preparation alone (Lyon et al., 2001)...*however...*
- Findings limited by **absence of stimulant-only comparison group** and **small sample size**

Herbals in ADHD—French maritime pine bark (Pycnogenol™)

- Open studies suggest standardized extract of French maritime pine (*Pinus pinaster*) bark beneficial in ADHD
- 1-mo RCT (N=61 children and adolescents) randomized to (Pycnogenol™) 1mg/kg/day had significant reductions in hyperactivity, inattention and visual-motor coordination over placebo (Trebaticka et al., 2006)
- Sx returned to pre-treatment baseline after one-month
- One case of mild GI distress; no serious AEs.
- ***Large prospective trials needed*** to replicate findings and determine optimal dosing

Herbals in ADHD—*Bacopa monnieri* ("Brahmi")

- *Bacopa monnieri* (Brahmi)—Ayurvedic herbal used as tonic and memory enhancer
- Limited human trials data but increasingly used to treat childhood ADHD and learning disorders
- RCT (N=85) healthy men and women randomized to combined extract of *Ginkgo* and *Bacopa* showed no improvements over placebo in short-term memory, executive processing, planning, problem solving and information processing speed (Nathan et al., 2004)

Herbals in ADHD—*Bacopa monnieri*

- *Criticism:* findings suggest ineffective for core ADHD symptoms and study population was healthy adults
- 12-week RCT (N=36 ADHD children) *Bacopa* 50 mg BID showed significant improvement over placebo in tests of sentence repetition, logical memory and pair-associative learning
- **Large prospective trials needed** to confirm efficacy, dosing using standardized preparation

Trace elements in ADHD

Zinc

Iron

What the evidence suggests

Trace elements—*zinc*

- ADHD children frequently have abnormal low plasma zinc levels—may interfere with information processing and correlate with severity of inattentive symptoms (Yorbik et al., 2007; Arnold et al., 2005)
- Zinc supplementation now widely used in ADHD however *few studies* and *inconsistent findings*

Trace elements in ADHD—*zinc*

- 12 week RCT(N=400 children and adolescents) high dose zinc (150mg/day) showed significant improvement in hyperactivity and impulsivity but *not* inattention over placebo (Bilici et al., 2004)
- **High drop out rate limits significance**
- RCT found zinc + methylphenidate superior to methylphenidate alone (Akhondzadeh et al. 2004)
- **Large prospective needed** to replicate findings and confirm optimum form and dosing of zinc (Arnold & DiSilvestra 2005)

Trace elements in ADHD—*iron*

- ADHD children may have higher incidence of iron deficiency as measured by serum ferritin levels compared with a matched population (Konofal et al. 2004)
- **Hypothesis:** abnormal low serum ferritin levels associated with relatively greater hyperactivity in non-anemic ADHD children but no differences in cognitive performance tasks (Oner et al. 2008)

Trace elements in ADHD—*iron*

- Open 1-mo trial non-iron-deficient ADHD children given oral iron perceived as less hyperactive and distractible by teachers but *not* parents (Sever 1997)
- Small 12-week RCT non-anemic ADHD children with abnormal low serum ferritin levels randomized to ferrous sulfate 80mg/day showed progressive improvements in the severity of ADHD symptoms over placebo throughout study *comparable to stimulants* (Konofal et al., 2008)
- **Large prospective studies needed** to confirm efficacy and determine optimal form and dosing

Acetyl-L-carnitine (ALC)

- Required for energy metabolism and synthesis of fatty acids
- Small RCT suggests ALC may significantly reduce ADHD sx severity however design problems— ***failure to report pre- and post-treatment sx*** (Van Oudheusden & Scholte 2002)
- Multi-site 16-week pilot study (N=112 ADHD children ages 5-12) randomized to ALC (500 to 1500 mg b.i.d) vs placebo (Arnold et al., 2007)
- Superiority of ALC throughout study in inattentive children but *not* combined type

Acetyl-L-carnitine in ADHD

- Small RCT found improvement with ALC (50mg/kg/day) in hyperactivity in young boys with fragile X syndrome and ADHD (Torrioli et al. 2008)
- No significant AEs reported
- **Prospective studies needed** to verify efficacy and find optimal dose

Homeopathic remedies in ADHD

- Widely used in U.S. to treat or self-treat ADHD but limited evidence
- Systematic review of RCTs on homeopathic Rx in ADHD concluded **no evidence of beneficial effects** of homeopathy on symptom severity, core symptoms or course of ADHD (Coulter & Dean 2007)

Homeopathic remedies in ADHD

- *However* conventional RCT designs may preclude demonstration of clinical efficacy of specific homeopathic remedies for ADHD
- Frei et al suggest long-term (12 mo +) studies needed with initial open-label phase to identify **“optimal” treatment for every unique patient**
- Subsequent placebo-controlled phase for randomized Rx allocation to “optimum” remedy vs random homeopathic remedy

Yoga and massage for ADHD

- Small pilot study—ADHD children randomized to yoga improved more compared to conventional exercise
- Children who continued stimulants while practicing yoga had greatest improvements (Haffner et al. 2006)
- Two small RCTs suggest yoga and massage reduce severity of ADHD symptoms
- **Large prospective studies needed** to confirm beneficial effects and rule out group expectation effects (Jensen & Kenny 2004; Khilnani et al., 2003).

Green play environments

- **Hypothesis:** ADHD results from “attention fatigue” caused by limited contact with “green spaces”
- **Observational study**—ADHD children who spend more time playing in natural environments have fewer and less severe symptoms of ADHD (Kuo & Taylor 2004)
- ***Criticism***—heterogeneous population included children with severe symptoms or co-morbid ODD, absence of independent raters, the absence of comparison group, and reliance on parents “impressions” using non-standardized rating scales (Canu & Gordon 2005).

Summing up

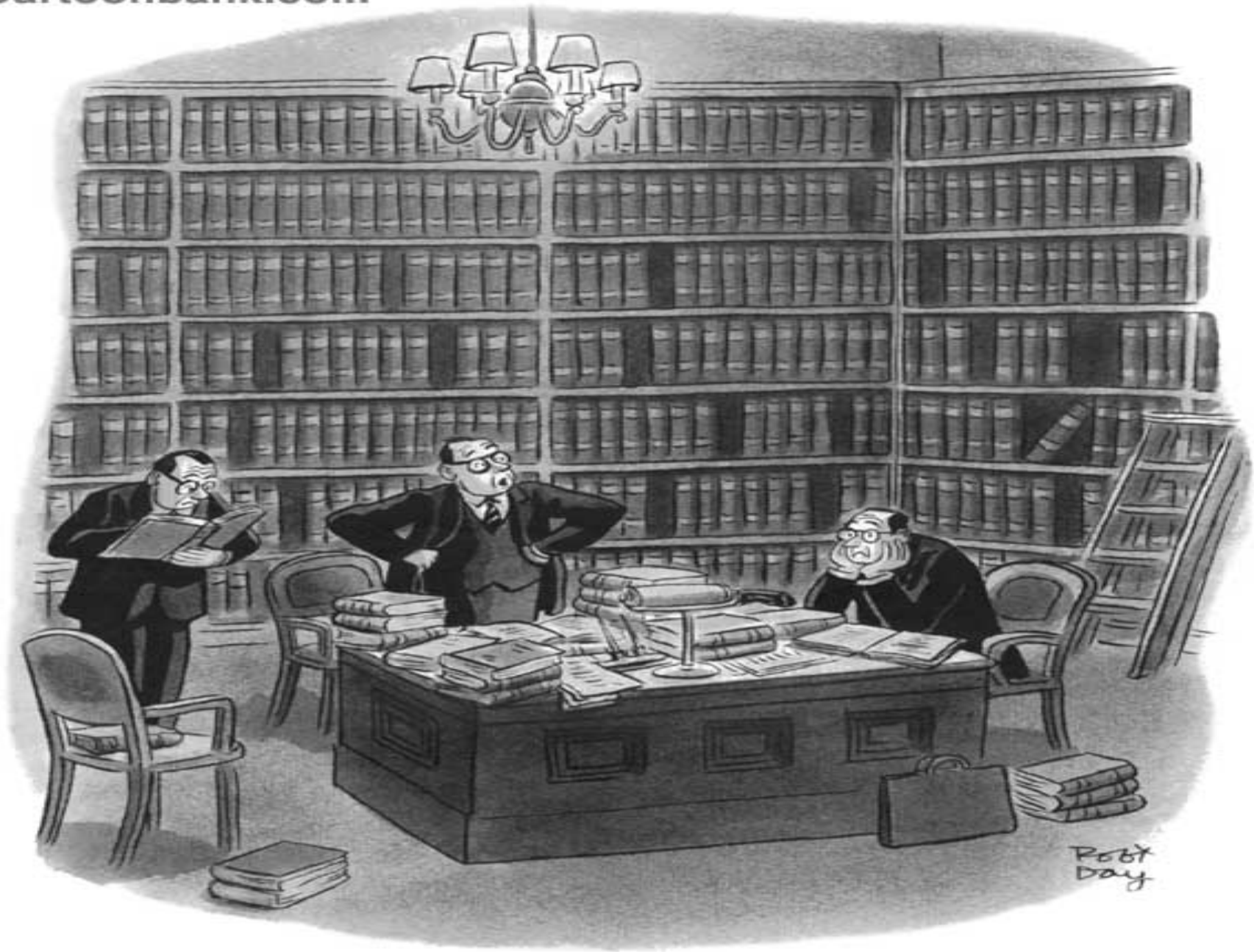
- Effective integrative management of ADHD should take into account complex causes including genetic factors, perinatal insults or toxic exposure, food sensitivities, social factors and others.
- Stimulant and non-stimulant Rx are effective and well tolerated in many children, adolescents and adults.
- Restrictive diets may significantly reduce symptoms of hyperactivity in some cases.
- When stimulants ineffective, not tolerated or refused, consider validated EEG biofeedback protocols: SMR training for primarily hyperactive type ADHD; theta suppression for primarily inattentive type. *More studies needed*

Summing up

- Zinc supplementation may be especially helpful when hyperactivity and impulsive behavior do not respond to stimulants alone. ***More studies needed***
- Iron and ALC supplementation may be especially helpful for core symptoms of distractibility and inattention. ***More studies needed***
- High doses of omega-3s (up to 16g/day) may have therapeutic effects on both inattention and hyperactivity. ***Large RCTs needed***
- *Ginkgo biloba, Panax quinquefolius, Pinus pinaster and Bacopa monnieri* may be beneficial in ADHD. **More studies needed**



More Studies Needed



“What burns me up is that the answer is right here somewhere, staring us in the face.”

Resources

- Textbook of Integrative Mental Health Care, J. Lake, Thieme Medical Publishers, 2006
- Complimentary and Alternative Treatments in Mental Health, Eds. J. Lake, D. Spiegel, American Psychiatric Press Inc., 2007
- The A.D.D. Book: New Understandings, New Approaches to Parenting Your Child, Sears and Thompson, Little Brown, 1998

Resources on Safety

- Bratman, S. & Girman, A.M. (2003). Mosby's Handbook of Herbs and Supplements and their Therapeutic Uses. St. Louis: Mosby, Inc
- Harkness, R. & Bratman, S. (2003) Mosby's Handbook of Drug-Herb and Drug-Supplement Interactions. St. Louis: Mosby, Inc.
- www.naturaldatabase.com (Natural Medicines Comprehensive Database)
- www.healthnotes.com



