ADHD

- Neither I nor my immediate family members have a personal financial relationship with a manufacturer of pharmaceutical products or services that will be discussed in this presentation

KS

- 6 yo male brought in by parents with complaint he is constantly in trouble in 1st grade
- He has always been very active, but also has been very bright, so they had not worried
- He does not complete tasks, loses his school supplies, is easily distracted, cannot wait his turn, fidgets and has trouble staying seated

Do you:

1. Refer to a doc to prescribe a stimulant
2. Send home with questionnaires
3. Recommend an elimination diet

Attention-Deficit/Hyperactivity Disorder (ADHD) DSM-V Diagnostic Criteria

- Sx present before 12 years of age (used to be 7)
- Sx present in ≥ 2 settings (e.g., school, work, home)
- Sx have persisted for at least 6 months severe enough to be maladaptive, inconsistent w/developmental age
- Causes clinically significant distress or impairment in social, academic, or occupational functioning
- At least 6 inattention symptoms and/or at least 6 hyperactive and impulsive symptoms

Vanderbilt Scoring - kids

- Symptoms
  - Assessment scales for the 9 inattentive and hyperactive criteria (positive response is 2 or 3 on at least 6 of 9 items)
- Performance
  - Impairment assessment – positive is score of 4 or 5 on at least 1 item
- Screening for comorbidities
  - Sx screen for ODD, Conduct, depression/anxiety

Parent Assessment Scale	Teacher Assessment Scale
Predominantly Inattentive subtype ■ Must score a 2 or 3 on 6 out of 9 items on questions 1–9 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 **Predominantly Hyperactive/Impulsive subtype** ■ Must score a 2 or 3 on 6 out of 9 items on questions 10–18 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 **ADHD Combined Inattention/Hyperactivity** ■ Requires the above criteria on both inattention and hyperactivity/impulsivity **Oppositional-Defiant Disorder Screen** ■ Must score a 2 or 3 on 4 out of 8 behaviors on questions 19–26 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 **Conduct Disorder Screen** ■ Must score a 2 or 3 on 3 out of 14 behaviors on questions 27–40 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 **Anxiety/Depression Screen** ■ Must score a 2 or 3 on 3 out of 7 behaviors on questions 41–47 AND ■ Score a 4 or 5 on any of the Performance questions 48–55	**Predominantly Inattentive subtype** ■ Must score a 2 or 3 on 6 out of 9 items on questions 1–9 AND ■ Score a 4 or 5 on any of the Performance questions 36–43 **Predominantly Hyperactive/Impulsive subtype** ■ Must score a 2 or 3 on 6 out of 9 items on questions 10–18 AND ■ Score a 4 or 5 on any of the Performance questions 36–43 **ADHD Combined Inattention/Hyperactivity** ■ Requires the above criteria on both inattention and hyperactivity/impulsivity **Oppositional-Defiant/Conduct Disorder Screen** ■ Must score a 2 or 3 on 3 out of 10 items on questions 19–28 AND ■ Score a 4 or 5 on any of the Performance questions 36–43 **Anxiety/Depression Screen** ■ Must score a 2 or 3 on 3 out of 7 items on questions 29–35 AND ■ Score a 4 or 5 on any of the Performance questions 36–43

Adult ADHD

- Screening:
  - Adult ADHD Self-Report Scale (ASRS) per WHO
    - Widely available on the internet
- Conners' Adult ADHD Rating scale (CAARS) –
  - Proprietary ($379)

Differential Diagnosis in Adults

- Depression – diminished ability to think or concentrate during episodes of depression
- Mania – " "
- Anxiety disorders – distractability during anxiety
- Substance Use Disorders – poor attention, distractability, hyperactivity can also be seen in SUDs

- Prevalence estimated at 4.4% in adults

Incidence of ADHD

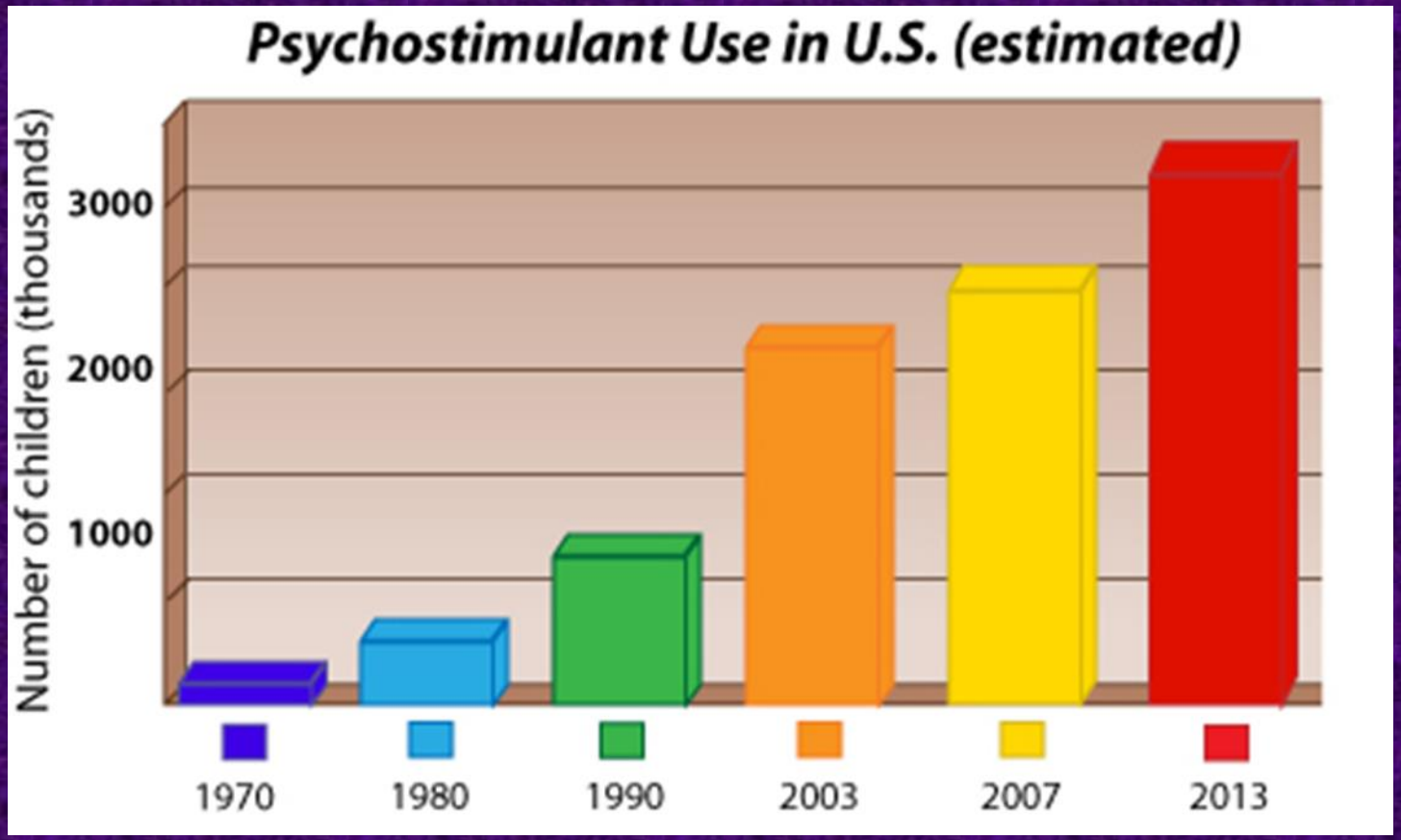
- In 2007, approximately **5.4 million** children aged 4—17 years (9.5%) were reported to have a history of ADHD diagnosis
- 2.7 million were receiving medication treatment
- Increased by 22% between 2003 and 2007
- Rates of ADHD diagnosis increased an average of
  - 3% per year from 1997 to 2006
  - 5.5% per year from 2003 to 2007

- CDC - from the 2007 National Survey of Children's Health (NSCH).

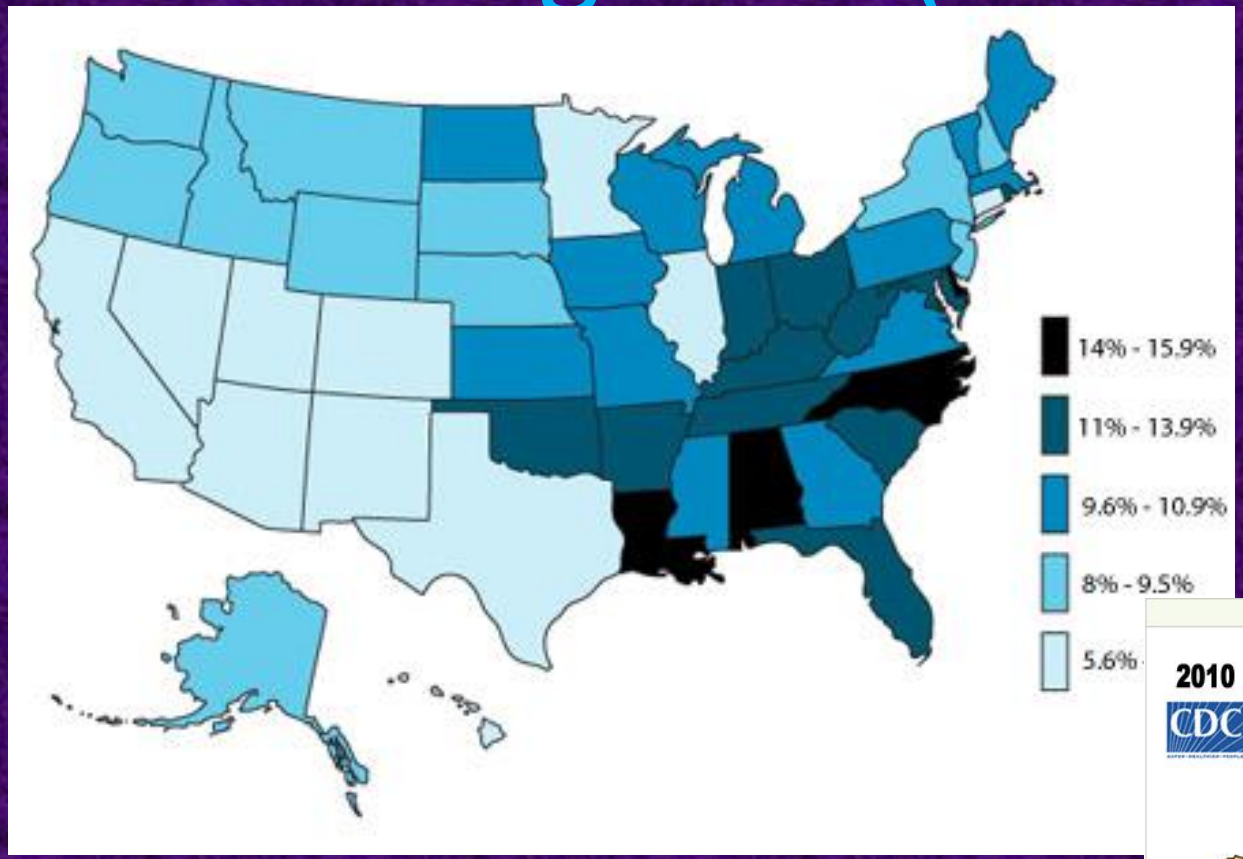
2012 CDC Data

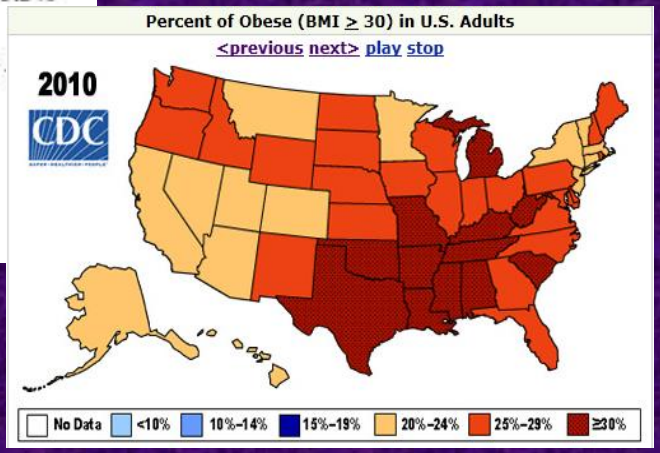
- **11% of all children and now almost 20% of high school boys have received a diagnosis of ADHD.**
- 2/3 with current dx receive stimulants
- Medicaid Pts 14% prevalence (33% higher)
- Sales of stimulants more than doubled to $9 billion in 2012 from $4 billion in 2007.

Psychostimulants – 1970-2012



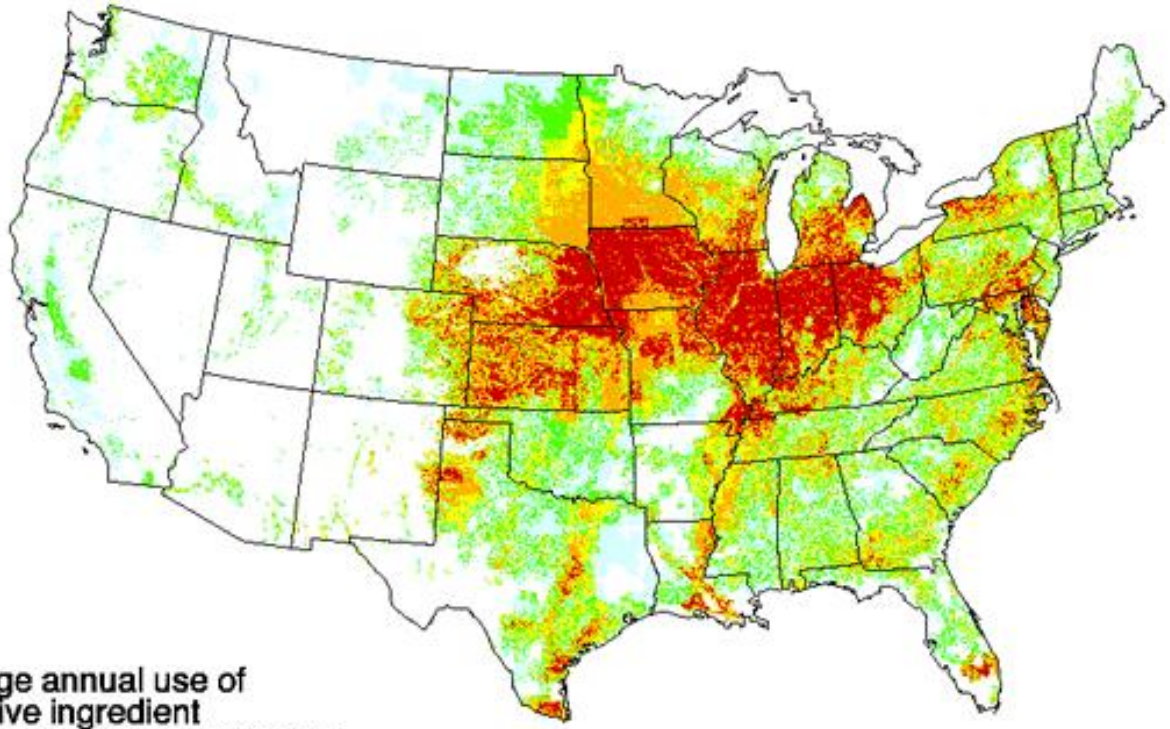
State-based Prevalence Data of ADHD Diagnosis (2007-2008)





ATRAZINE - herbicide

1997 estimated annual agricultural use



Average annual use of active ingredient
(pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.358
- 0.359 to 2.151
- 2.152 to 9.855
- 9.856 to 32.77
- >= 32.771

Crops	Total pounds applied	Percent national use
corn	62, 381, 038	84. 00
sorghum	6, 750, 038	9. 09
summer fallow	2, 539, 169	3. 42
sugarcane	2, 203, 421	2. 97
sweet corn	340, 452	0. 46
sod harvested	30, 214	0. 04
other hay	13, 224	0. 02
seed crops	5, 833	0. 01

Associated Features – why we care

- Aggression and antisocial behavior
- Academic underachievement
- Peer rejection
- Family dysfunction

Hinshaw, SP (1994). Attention Deficits & Hyperactivity in Children. Thousand Oaks: SAGE.

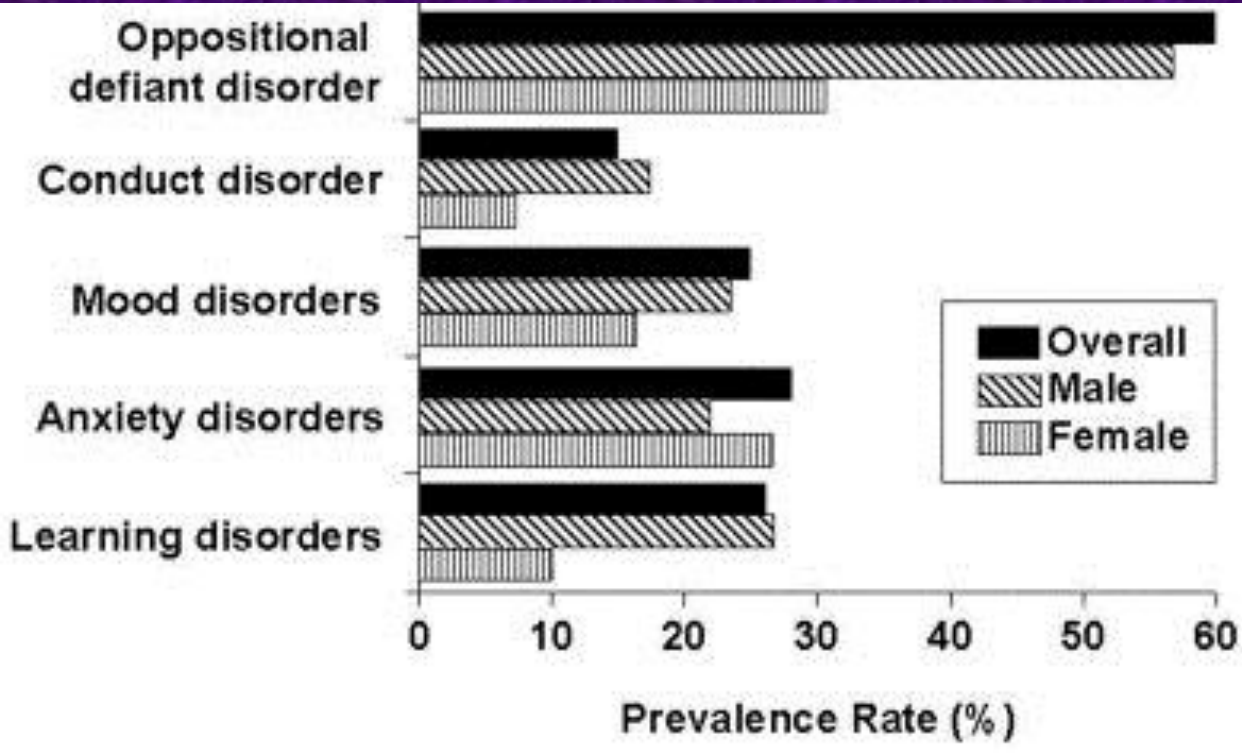
Aggression and Antisocial Behavior

- Inattention/disorganization and particularly hyperactivity/impulsivity correlate moderately with aggressive and antisocial behavior Psychol Bull. 1987 May;101(3):443-63

- ADHD overlaps with CD and ODD
  - ODD in 58% boys and 31% girls
  - CD in 14.6%

    J Dev Behav Pediatr. 2008 Dec;29(6):501-7

Comorbidity - kids



Academic Underachievement

- Majority display some underachievement
  - Need for special education
  - Grade retention
  - Expulsion
  - Reading and arithmetic skills 1 SD below peers matched for IQ and SES J Consult Clin Psych 1990, 58(5):580-8
- Comorbidity with formally diagnosed Learning Disability: 17% J Am Acad Child Adolesc Psych 1992; 31(3):439-448

Associated Features of ADHD
Peer Rejection

- Kids with ADHD can be rapidly identified and overwhelmingly rejected by peers
  - J Cons Clin Psych 1994 62(4):833-42
  - Child Dev 1987 58(3):816-28

- Peer rejection is a strong predictor of future social problems, including school dropout, delinquency, etc.

Family Dysfunction

- Disorder is familial:
  - 1st degree relatives 20% ADHD Biol Psych 1971 3:189-195
- High levels of stress in the family system
  - Chronic family conflict
  - Decreased family cohesion
  - Exposure to parental psychopathology
    - Arch Gen Psych 52:464-470

Associated pathology

- Kids with ADHD not on meds 1.5 x as likely to be overweight *Pediatrics* July 2008; 122:e1-e6

Hypothesized Causes for Increased ADHD Dx/Tx

- Environmental and Food toxicity
- Inadequate parenting, as families get more busy and stressed
- Early television
- Increased demands/altered perceptions of teachers/parents
- Sloppy diagnosis

Parental Biases in Dx

- Parental Depression
- 24 women with depression
  - Conners' Parent Rating Scale of child behavior improvements correlated with maternal improvements in Beck Depression Inventory; Fam Med 2001 Oct;33(9):691

Differential Diagnosis should include:

- Depression or bipolar disease
- Anxiety Disorder
- Learning disabilities
- Misfits between the child and school, or even the child and teacher
- Relative age – youngest 1/3 of class 50% more likely to be prescribed stimulants age 7-14 Pediatrics. 2012 Nov 19 PMID: 23166340
- The Gifted Child – boredom

Treatment

Of course, look for the tacks. . .

The Rules of Tacks

- If you are sitting on a tack, it takes a lot of aspirin to make the pain go away.
- If you are sitting on 2 tacks, removing one does not lead to a 50% improvement in symptoms.

-Sid Baker, M.D.

(and removing tacks is free, unlike “aspirin” such as Ritalin, fish oil, etc. . .)

And of course, look for the tacks. . .

- Exposures
  - Nutritional factors – more later
  - Lead toxicity
  - Other toxins
  - Allergy
- Parenting issues
  - TV Exposure
- Sleep Apnea or Upper Airway Obstruction

Environmental Toxins and ADHD

- Persistent Organic Pollutants
  - ADHD 3x more prevalent in those with detectable concentrations
  - LD 2.5 times more prevalent

Journal of Epidemiology & Community Health. 61(7):591-6, 2007 Jul

Environmental Influences on ADHD

- Phthalates – assoc with ADHD Biol Psychiatry. 2009 Nov 15;66(10):958-63.
- BPA – Attention deficit in animal models
- Prenatal exposure to organophosphate pesticides - ↑ADHD at 5 years Eskenazi, B Env Health Perspectives Aug 19 2010;
- Organophosphates ↑ in urine in kids with ADHD Bouchard MF PEDIATRICS Vol. 125 No. 6 June 2010, pp. e1270-e1277
  - For the most-commonly detected DMAP metabolite, dimethyl thiophosphate, **children with levels higher than the median of detectable concentrations had twice the odds of ADHD**

More Environmental Influences

- Preschoolers with gas appliances in their homes scored lower on cognitive tests & were more likely to have ADHD than peers Am J Epidemiol. 2009 Jun 1;169(11):1327-36.
- PFC's – food packaging, non-stick pan coatings; ↑ levels in ADHD kids Environ Health Perspect :-. doi:10.1289/ehp.1001898
- Maternal Smoking in pregnancy increases risk of ADHD Biol Psych 2005 57(11):1215-20
- Second-hand smoke in childhood AOR 1.5 after controlling for above. Int J Nurs Stud 2012 Oct 26 PMID: 23107006

And of course, look for the tacks. . .

- Exposures
  - Nutritional factors
  - Lead toxicity
  - Other toxins
  - Allergy
- Parenting issues
  - TV Exposure
- Sleep Apnea or Upper Airway Obstruction

Television and ADHD

- The Average Child Spends almost **4 hours a day** watching Television
- Increased television watching at 2 years old, 5 years old, and adolescence is associated with an increased incidence of ADHD both in cross-sectional and longitudinal studies

TV, Video and ADHD

- Both TV and Video game time associated with ADHD
- A 13 month longitudinal study in middle schoolers demonstrated that this was not just a correlation but likely a causal relationship.
  - Screen media time was associated with attention problems 13 months later even when previous attention problems were controlled for

Edward L. Swing et al. Pediatrics 2010;126:214-221

Back to KS

- Meets criteria on parent and teacher reports for ADHD Hyperactive/Impulsive with significant impairment
- No comorbidities identified on Vanderbilt screening

- Do you recommend any lab tests?

- What do you recommend for treatment?

Treatment Options

What do we know?

Multi-Modal Treatment of ADHD (MTA) Study

- (N=579) Largest randomized treatment study of any childhood psychiatric disorder
- Cosponsorship by NIMH and Department of Education
- Enrolled age 7-9.9
- RCT for 14 months, naturalistic follow-up thereafter

MTA Treatment Groups

- Community Care (CC)
- Medication (MED)
- Behavioral Therapy (BEH)
- Combination (COMB)

Community Care (CC) Treatment MTA Study

- Referred to community mental health resources
- Non-specific treatment
- 67% received some type of treatment including medication

Medication (MED) Treatment
MTA Study

- Double-blinded protocol
- Methylphenidate under 5 drug conditions (placebo, 5, 10, 15, and 20 mg) randomly ordered across subjects
- Doses given at breakfast and lunch and half dose in the afternoon

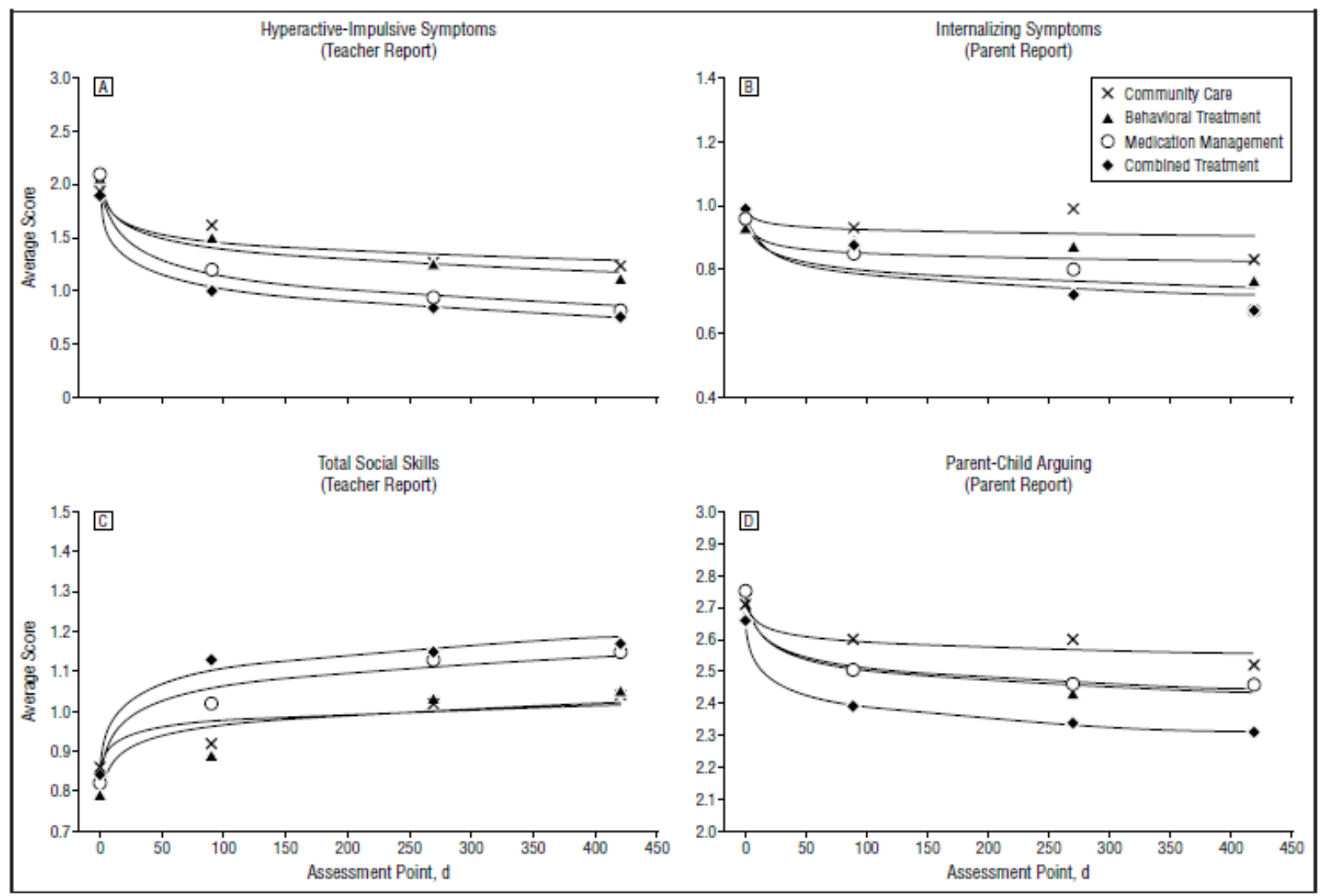
Behavioral Therapy (BEH) Treatment MTA Study - structure

- 27 group parent training sessions
- 8 individual parent training sessions
- Child-focused therapy in Pelham's STP
- School consultation: 10-16 biweekly teacher training sessions; 12 weeks of a classroom aide; daily school report card linked to home consequences

Combination (COMB) Treatment MTA Study

- Combination of BEH and MED treatment procedures

14 months


Hyperactive-Impulsive Symptoms
(Teacher Report)
A
Average Score
3.0
2.5
2.0
1.5
1.0
0.5
0
Internalizing Symptoms
(Parent Report)
B
1.4
1.2
1.0
0.8
0.6
0.4
Community Care
Behavioral Treatment
Medication Management
Combined Treatment
Total Social Skills
(Teacher Report)
C
Average Score
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
50
100
150
200
250
300
350
400
450
Assessment Point, d
Parent-Child Arguing
(Parent Report)
D
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
0
50
100
150
200
250
300
350
400
450
Assessment Point, d

Major Findings of the MTA Study at the 14 Month Endpoint

- Combined treatment is superior to medication alone (although there was controversy in this interpretation)
- Medication is often superior to behavioral treatment

Findings of the MTA at 36 months and beyond

- **No benefits sustained** on ITT analysis
- Early tx did not protect vs. later adverse outcomes (eg substance abuse)
- This result did not go away when statistical adjustment was made for
  - Actual treatment received: No benefits noted for those continuously on medication (despite ↑dose)
  - Severity of symptoms at earlier endpoints (in case more severe cases were more likely to be on meds)
- Definite impact of medication on growth *J. of Att. Dis. 2008; 12(1) 15-43*

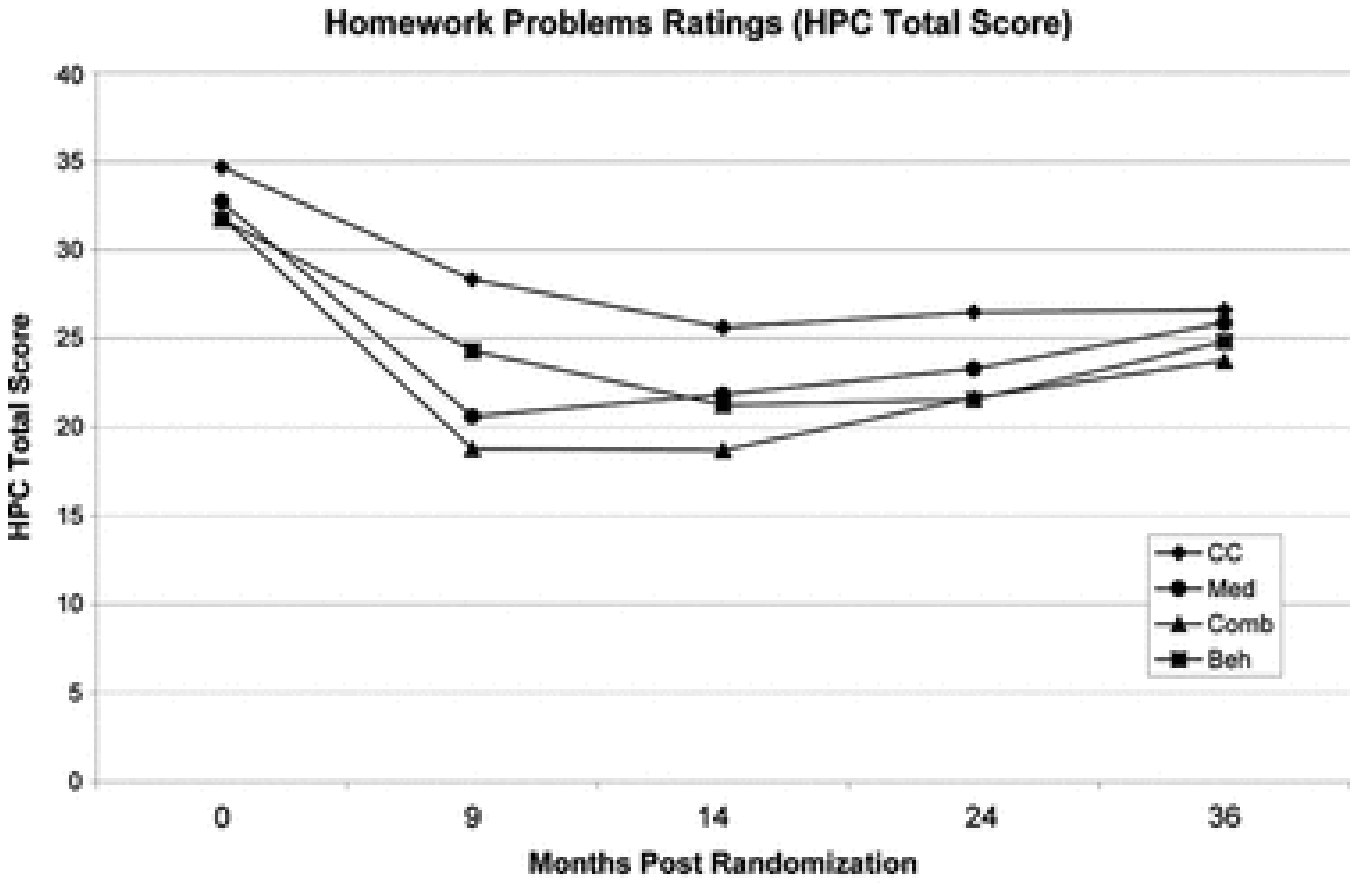


FIGURE 3

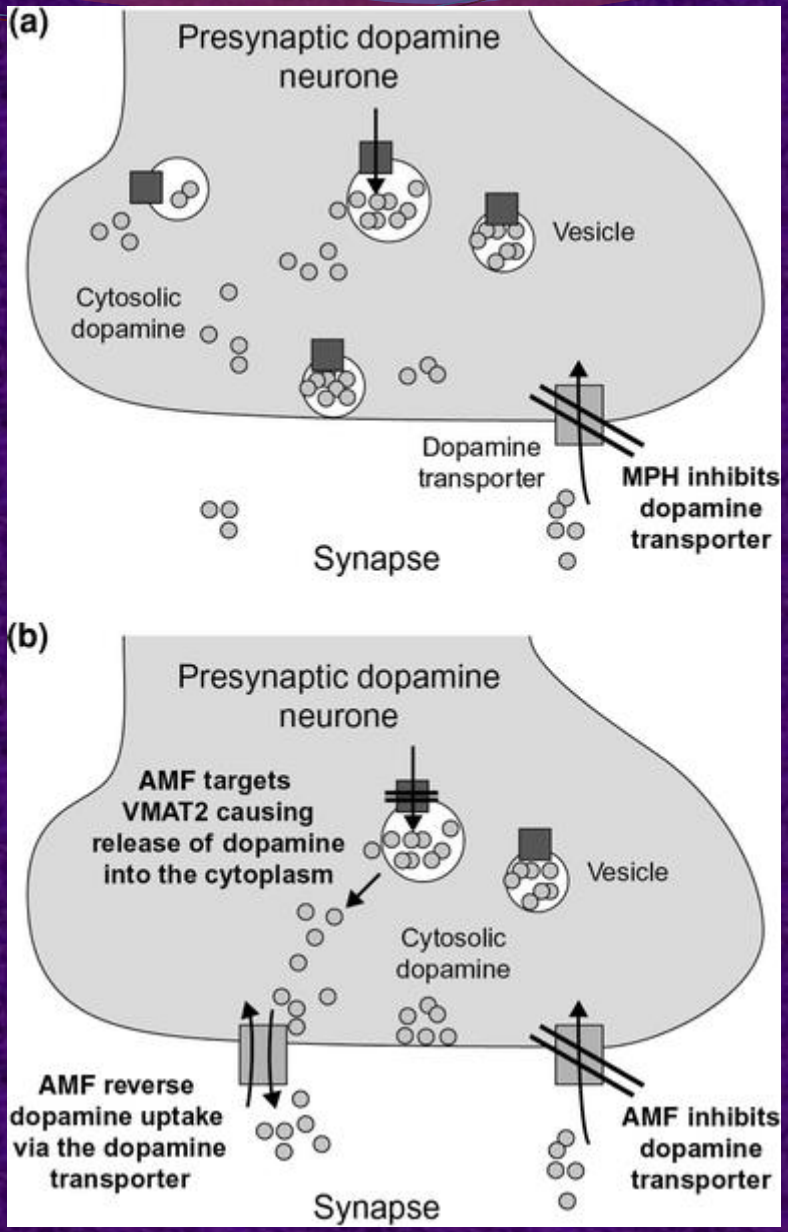
- Only behavioral treatment produced sustained improvements in homework performance
- J Clin Child & Adol Psych 39(2):220-33, 2010

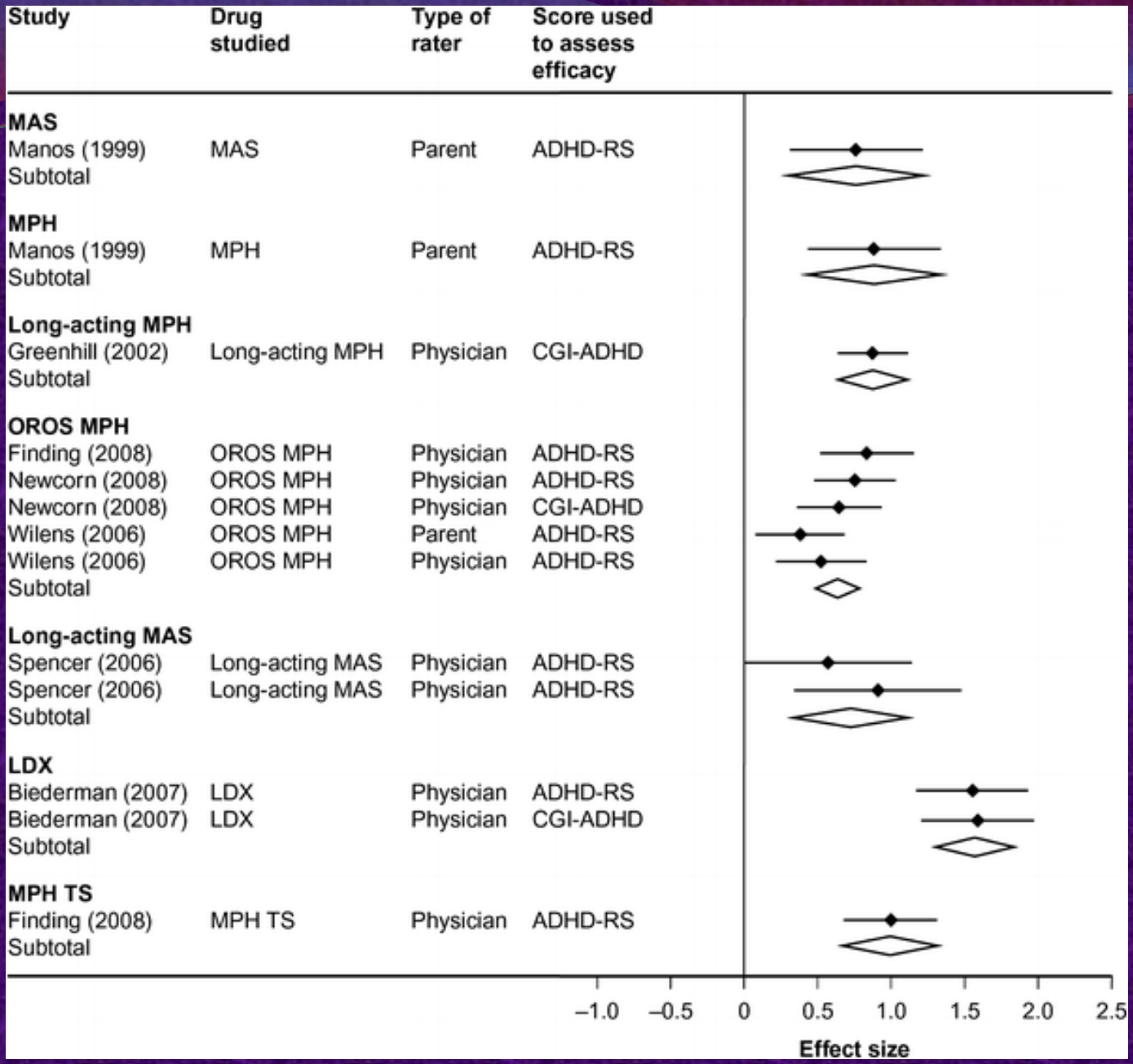
Medications

- Stimulants
  - Methylphenidate
  - Amphetamines
- Non-stimulants
  - Atomoxetine
  - Time-release Guanfacine
  - Clonidine
  - Bupropion

Stimulants

- Methylphenidate
  - Inhibit DA and NE reuptake
- AMF also
  - Inhibits 5-HT reuptake
  - Stimulates release monoamines





Vyvanse

- European Child & Adolescent Psychiatry 2012 Hodgkins et al

Medication choice - Stimulants

	Methylphenidate family	Amphetamine family
Response rate	65% - 81%	68 - 90% (sl more effective)
Side effects (insomnia, loss of appetite)	4%	12-24%
Appetite suppression	+1	+2
Duration	4 hr	4-6 hr
Short-Acting forms	Focalin Methylin Ritalin	Adderall Dexedrine
Time-release forms	Methylphenidate Oral Release Osmotic System (Concerta) Focalin XR Ritalin SR	Adderall XR Dexedrine spansule Lisdexampfetamine (Vyvanse)
Administration	Concerta swallow whole, do not crush or chew	Vyvanse – may dissolve in water

Side Effects

- Decreased Appetite
- Trouble Sleeping
- Abdominal Pain
- Headaches
- Tics – Controlled trials do NOT confirm this association
- Bizarre Behavior
- Hallucinations (at least 1:100)
- Potential for Addiction –controversial
- Sudden death increased – minimal effect in kids, significant in adults PMID: 23160939 CNS Drugs. 2012 Nov 17; BMC Cardiovasc Disord. 2012

- Generally, all of these stop when the medication is stopped, except of course the death part

- SNPs in COMT may predict risk for side effects Aust N Z J Psychiatry 2012 PMID: 22689336

Concern about subtle or long-term effects

- Early Ritalin causes long-term depletion of density of striatal dopamine transporters in animals J Child Adolescent Psychopharmacol 2001, vol 11, pp 15-24
- Many books assert ritalin decreases creativity
  - Study looking at this saw no evidence of it Pediatrics. 1993 Apr;91(4):816-9
- Some parents raise concerns about personality change

- On the other hand:
  - Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication N Engl J Med. 2012 367(21):2006-14

Conclusions after the MTA:

- Medications provide immediate superiority
- Medications do not provide long-term superiority
- They may be useful as a bridge to facilitate behavioral measures
- Consider **double-blind "n of 1" trials**

Equal But Opposite?

Rats exposed to stimulants in adolescence have persistent neurobehavioral changes

- Less responsive to natural reward
- More sensitive to stress
- Enhanced anxiety and increased corticosterone
- Increased stress-induced emotionality

Neuroscience and Biobehavioral Reviews 2011

Non-stimulant Medications

- Strattera (atomoxetine) – less effective than stimulants
- Long-acting guanfacine, clonidine
- Bupropion

- See handout

Integrative Approaches

- Standard therapy
  - Behavioral Therapy
  - Medication
- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments
- Other modalities – meditation, EEG Neurofeedback

Behavioral Therapy

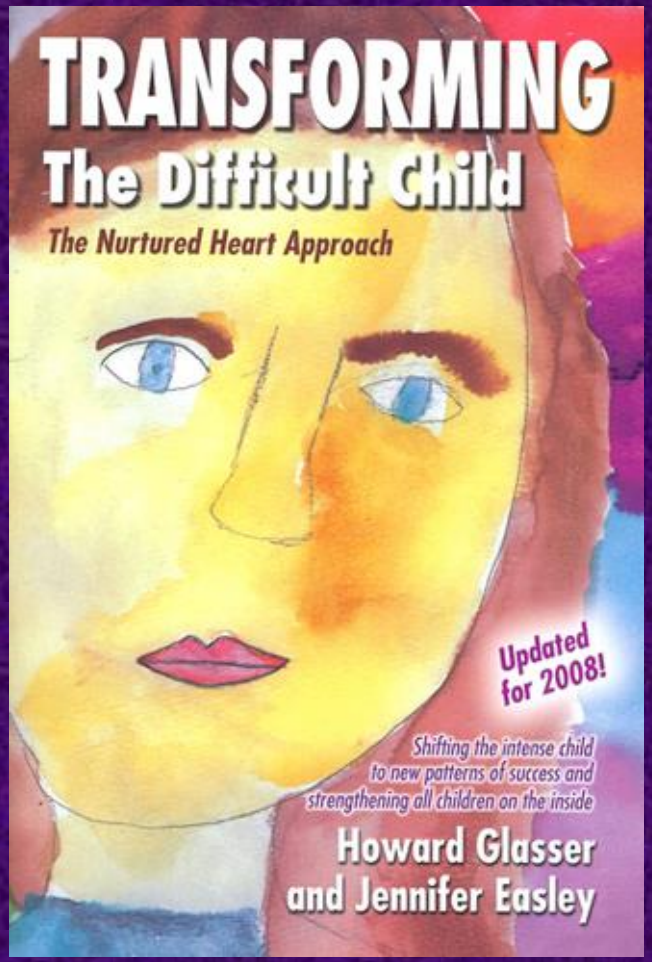
- Meta-analysis:
- Overall unweighted effect sizes in between group studies (.83), pre-post studies (.70), within group studies (2.64), and single subject studies (3.78) indicated that behavioral treatments are highly effective

- Clinical Psychology Review 29 (2009) 129–140

Behavioral therapy content

- Parent training:
  - Daily Report Card for communication btwn parents and teachers
  - Token economy system at home
  - Strategies for structuring the setting where homework is completed to ↓potential distractions
  - Structured limit setting
- School intervention
  - Teachers coached in Contingency Management to improve behavior - consistent positive rewards for good behavior
  - Half-time aide for 12 weeks using behavior modification

The Nurtured Heart Approach- Howard Glasser



Tolson School-the Nurtured Heart

- Tolson School, Tucson. “Failing School”75% of children from low income families.
- 1999 entire school began to apply the **Nurtured Heart** approach
- Behavioral management system based on **highly** increased positive feedback, clear rules, and well defined consequences, given without ‘energy”

Tolson School

- Discipline problems dropped sharply
- Special education dropped from 31 students to 7 students
- **2 of 519 students on medication for ADHD (0.3%)!**
- "Performing Plus School" - increasing test scores.

Other Therapy Targets

- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments
- Other modalities – meditation, EEG Neurofeedback

Sleep is worse in kids with ADHD

- 25-50% of kids with ADHD report sleep problems *J Dev Behav Pediatr* 26. (4): 312-322.2005
- PSG shows decreased sleep quality and quantity *Sleep Med* 10. (4): 446-456.2009
- MSLT shows shorter sleep latency in daytime in kids with ADHD *J Child Psychol Psychiatry* 41. (6): 803-812.2000; *Pediatrics* 109. (3): 449-456.2002

RLS and ADHD

- 44% of pts with ADHD have RLS
- 26% of those with RLS have ADHD symptoms
  Sleep 28. (8): 1007-1013.2005

- Some kids with "growing pains" may actually have RLS
  ***Sleep* 27. (4): 767-773.2004**

?Causal – Bidirectional Interaction

- Children with sleep-disordered breathing were more likely to have problem behaviors:
  - hyperactivity (OR 2.5)
  - inattention (OR 2.1)
  - aggressiveness (OR 2.1) *Pediatrics* - 01-OCT-2003; 112(4): 870-7
- PLM and sleep-disordered breathing are associated with inattention and hyperactivity *Sleep* 25. (2): 213-218.2002
- Acute sleep restriction causes inattention

Percept Mot Skills 93. (1): 213-229.2001

Interventions for sleep

- Melatonin 3-6 mg at night *Ann Pharmacother* 44. (1): 185-191.2010 *J Am Acad Child Adolesc Psychiatry* 46. (2): 233-241.2007; *Eur J Pediatr* 162. (7–8): 554-555.2003
- **Behavioral interventions – case series only**
- **Multiple other meds used: clonidine, diphenhydramine, cyproheptadine, trazodone, mirtazapine, guanfacine, and tricyclic antidepressants**

Sleep – The Ball Blanket

- Time it takes for a child to fall asleep is shortened when using a Ball Blanket.
- Teacher rating of symptoms show an improvement in both activity levels and attention span of approximately 10% after using the Ball Blankets

Nord J Psychiatry. 2010 Jul 22.

Bottom Line on Sleep

- Address TV hours, other factors that cut into sleep time
- Address Sleep Hygiene
  - Esp nighttime TV/video games, daytime vigorous exercise
- Assess for restless legs (think iron!) and sleep apnea
  - Sleep study or careful history, parental observation
- Consider other interventions
  - Heavy blankets
  - Meditation
  - Melatonin
  - ? Other meds (extreme caution!): clonidine, diphenhydramine, cyproheptadine, trazodone, mirtazapine, guanfacine, and tricyclic antidepressants

Other Therapy Targets

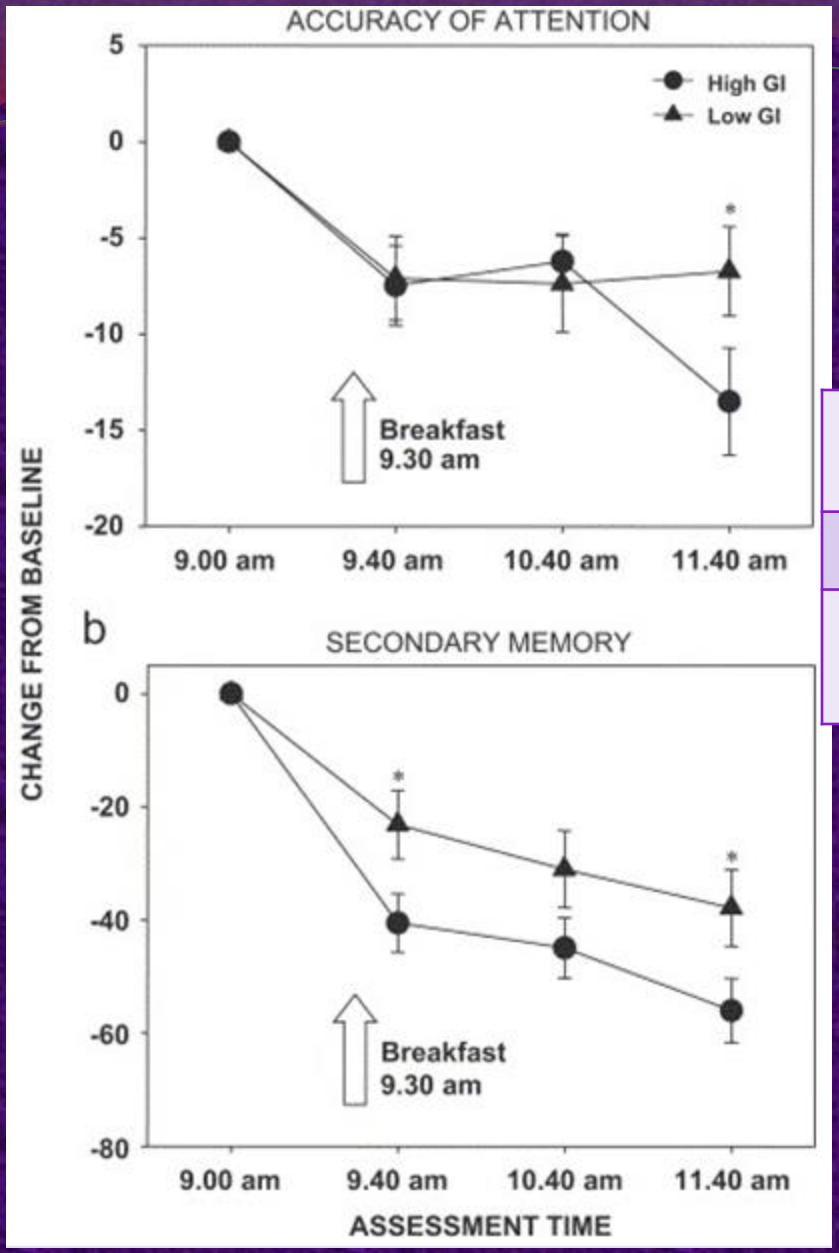
- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments
- Other modalities – meditation, EEG Neurofeedback

Basic Nutrition – or "When did **Pop Tarts** become a breakfast food?"

- High Glycemic Index Breakfast:
  - Lower blood sugar mid-morning
  - Adrenaline burst mid-morning
  - Inattention and decreased performance later in the morning
- Oatmeal: ↑cognitive performance compared to cereal or no breakfast in 9-11 year olds **Physiology & Behavior 2005** 85(5) 635-645

All-Bran vs. Coco Pops

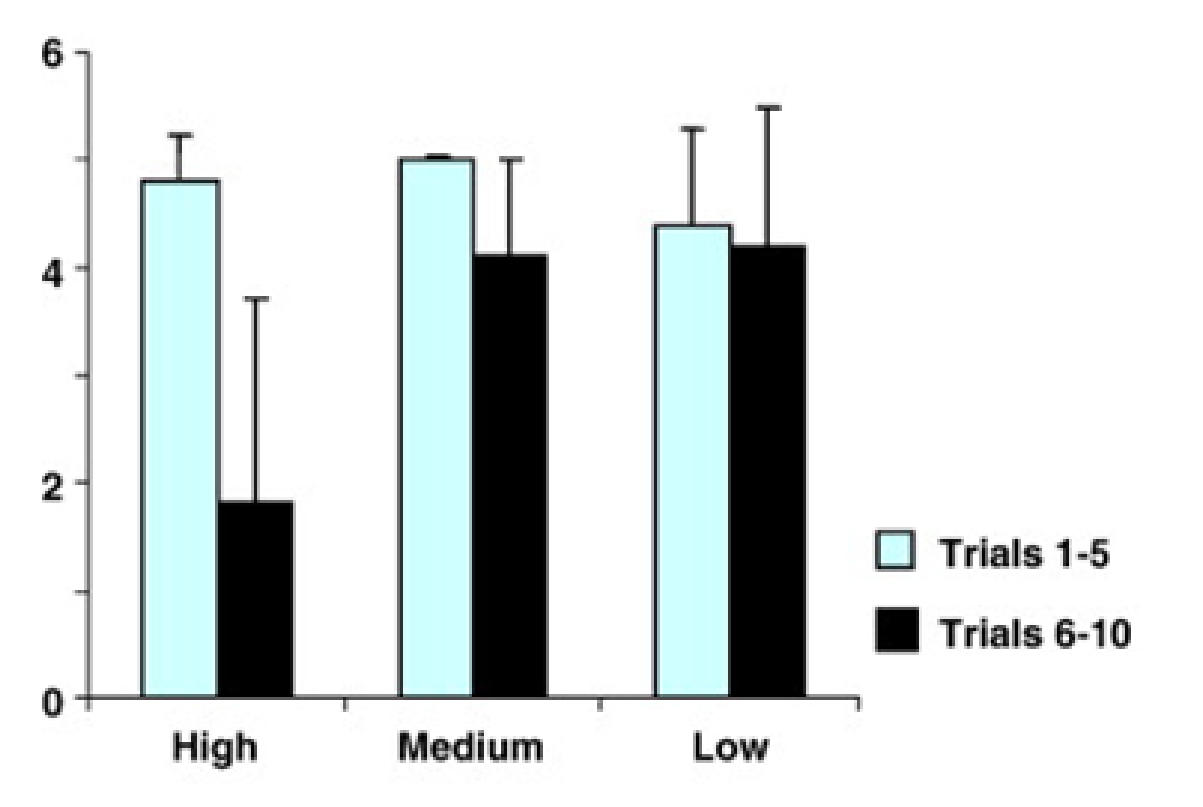
35g 35 g



	Kcal	Pro-tein	CHO	Fat	Fiber	GI
All Bran	98	4.9	16.1	1.6	9.5	42
Coco pops	133	1.6	29.8	0.9	0.7	77

Appetite 49(1):240-244 2007

Persistence with Frustrating Task



High, Medium, or Low GL breakfast

High: 39 cornflakes, waffle
Medium: 14.8 scrambled egg, toast and jam, yogurt
Low: 5.9
Ham, cheese, Burgen bread (soy, flax)

Kids age 6-7
Also imp verbal memory, fewer lapses in attention
Physiology & Behavior 92(4):717-724, 2007

Other Therapy Targets

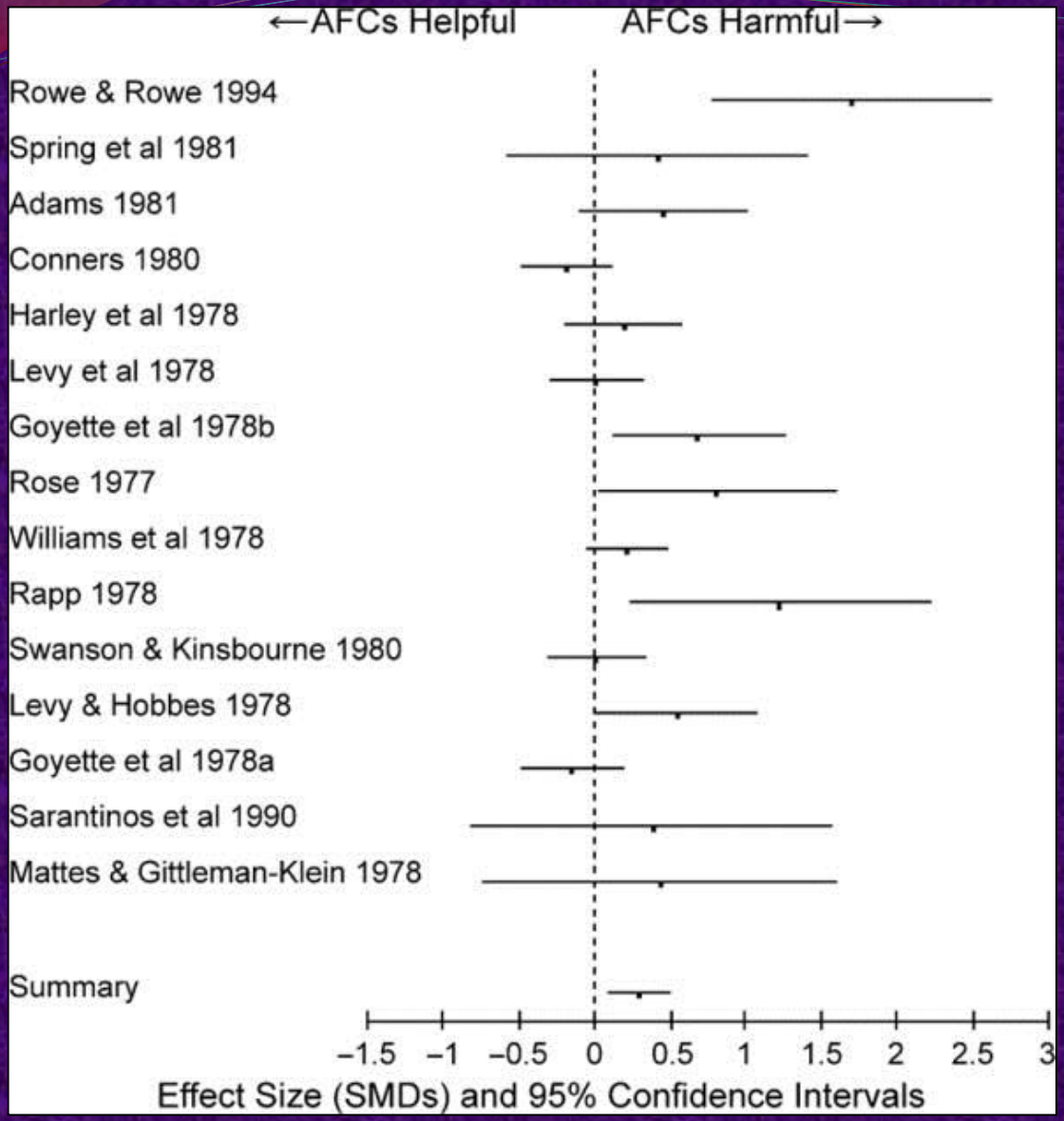
- Sleep
- Diet
  - General dietary principles
  - Specific Dietary Tacks
    - Colorings and Preservatives
    - Food Allergy
    - Pesticides
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments
- Other modalities – meditation, EEG Neurofeedback

Artificial Colors, Flavors, and Preservatives

- 273 three year olds with or without hyperactivity
- Given a diet free of food coloring and preservatives x 1 week
- Challenged with a daily drink with colorings and sodium benzoate or placebo (1 week washout in between.)
- Significant increases in hyperactivity when getting the active mixture.

- Bateman B et al *Archives of Disease in Childhood*. 89:512-515 2004

Metaanalysis Food Colors in ADHD



Do Artificial Food Colors Promote Hyperactivity in Children with Hyperactive Syndromes? A Meta-Analysis of Double-Blind Placebo-Controlled Trials.
SCHAB, DAVID; TRINH, NHI-HA

Journal of Developmental & Behavioral Pediatrics. 25(6):423-434, December 2004.

FIGURE 1 . The effect sizes from the 15 trials in the primary analysis and their resultant summary effect size. Trials are listed in an order broadly reflecting the comprehensiveness and rigor employed in the assignment of subjects' baseline diagnoses: the diagnostic processes of trials listed further down the page received higher marks, according to the criteria described at the foot of Table 1. AFC, artificial food color; SMD, standardized mean difference.

In Europe, Dyed Foods Get Warning Label

- Products with Yellow 5, Red 40, Other Dyes **"May Have an Adverse Effect on Activity and Attention in Children"** **July 20, 2010**

ADHD and Food Allergy

- 19 children responded favorably to a multiple food elimination diet.
- 16 then completed a DBPC Food Challenge.
- Symptoms improved significantly on days given placebo rather than foods they were sensitive to (P=0.003)

- Annals of Allergy. 72(5):462-8, 1994 May

ADHD and Food Allergy

- 76 children were treated with an Oligoantigenic diet, 62 improved.
- 28 who improved completed a DBPCFT
  - Foods thought to provoke symptoms were reintroduced
  - Symptoms worse on active foods than placebo. 48 foods were incriminated.
- Artificial colorants and preservatives were the commonest provoking substances.

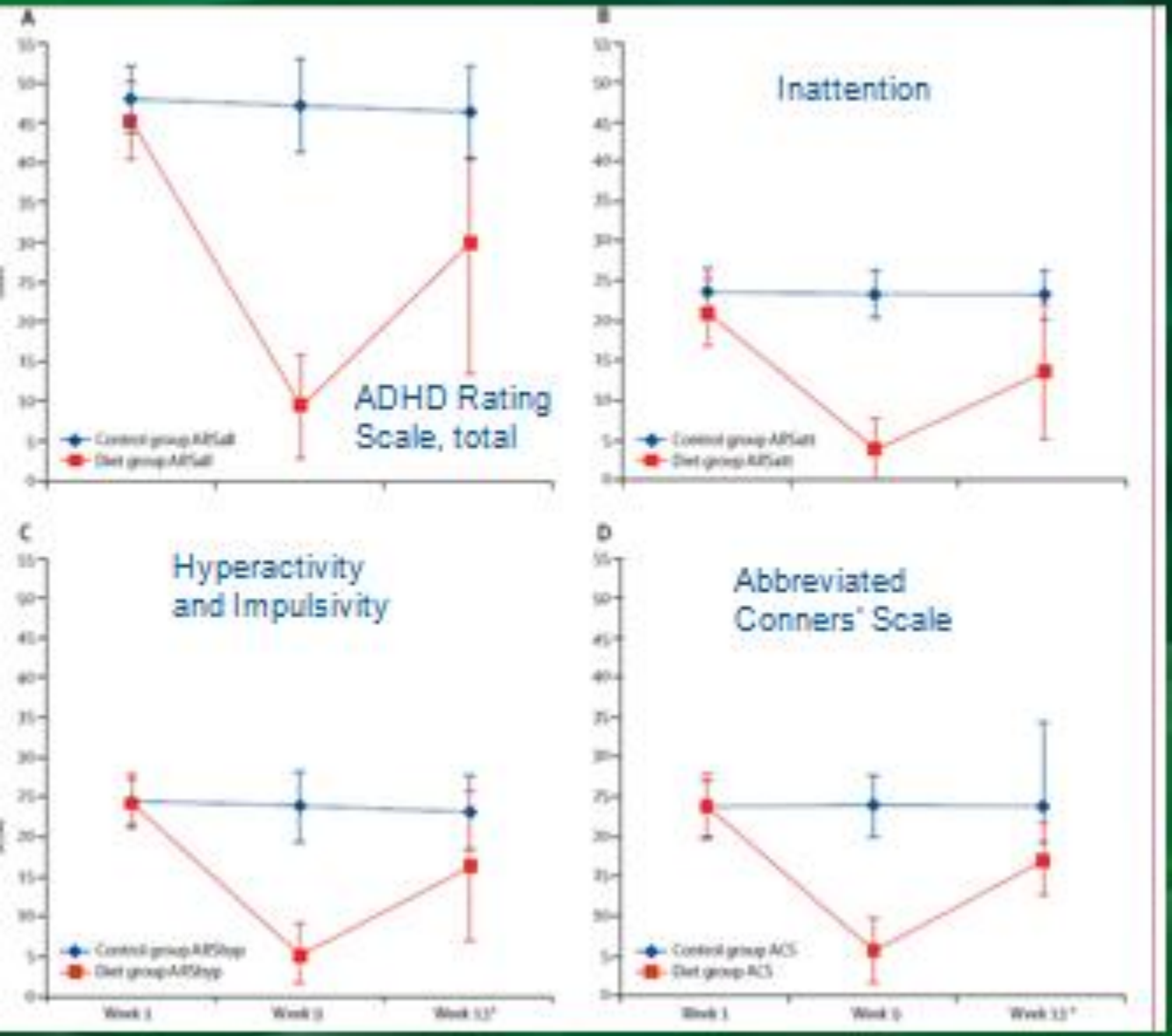
- Lancet. 1985 Mar 9.

Review on ADHD & Food Allergy

8 controlled studies found either significant improvement following a “few-food” (oligoantigenic) diet compared with placebo or worsening of symptoms in placebo-controlled challenges of offending substances following an open challenge to identify the substance.

J Atten Disord. 1999;3:30–48.

ADHD



- Significant improvement w/elimination diet (based on IgG testing) ($p<0.001$,) not seen on "healthy diet"
- 32/50 were responders

Lancet 2011 377:494-503

Week 4 elimination (oligoantigenic) Week 9 add high or low IgG foods(blinded)

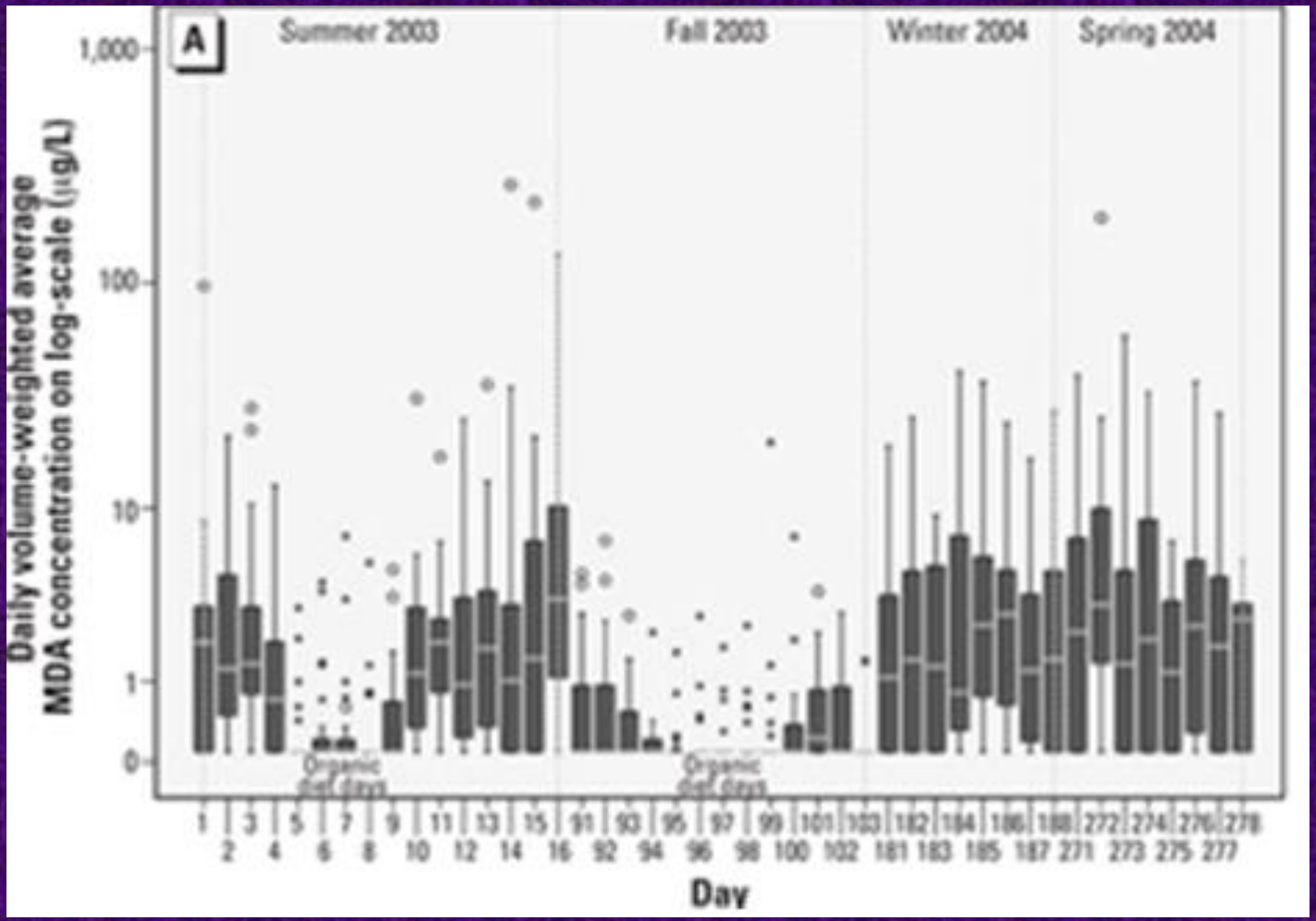
Effect of a Restricted Elimination Diet on the Behavior of Children with ADHD: (INCA Study) a Randomized Controlled Trial – Lancet, Feb 2011

- 100 children – 50 on restrictive diet – 50 controls for 5 weeks
- Restricted diet (few foods) Rice, meat, vegetables, pears, water as basic diet
- **After 5 weeks 64% of children had 40% improvement on ADHD rating Scales**
  - All P Values <0.0001
- Equal to or better than most stimulant trials.
- Assessor blinded, but parents and teachers not

Does Eating Organic Help?

- Children who ate organic fruits and vegetables had 1/5th the level of organophosphate pesticide metabolites in their urine as those who did not.
- Data suggests that children can "reduce exposure levels from 'uncertain' to 'negligible' risk"
  - **Environmental Heath Perspectives 2003**
  - **Impact on ADHD symptoms not studied, but I have some great anecdotes. . . .**

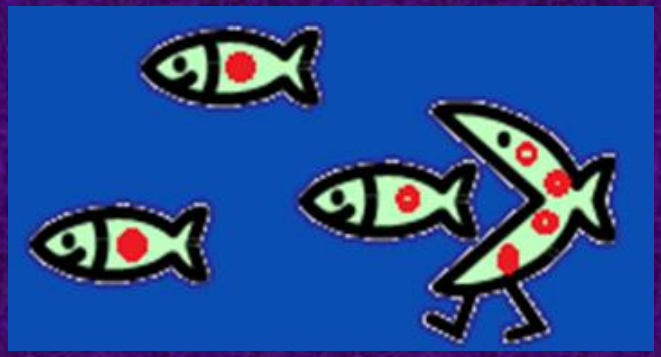
One-year exposure profile of DVWA of Organophosphate pesticide metabolite conc (µg/L) for CPES-WA children



- Days 5-9 and 95-99 were organic diet days Environ Health Perspect 116:537-542.

Limiting Pesticide Exposure

- Eat organic
- Eat low on the food chain



- Xenoestrogens (PCB's and phthalate esters) found in human serum in following relative concentrations:

urban fish eaters > rural fish eaters > urban vegetarians > rural vegetarians Fertil Steril 2002;78:1187–94

- Better partitioning of PCB's, solvents into feces if diet ↑ minimally processed grains and vegetables Chemosphere. 2002 Jan;46(3):449-57

- Note **Toxic effects of pesticide mixtures at a molecular level: Their relevance to human health.** Toxicology. 2012 Jun 21.


foodnews.org
Dirty Dozen™
buy these organic.
I Imported
D Domestic
EWG's 2011 Shopper's Guide
to Pesticides in Produce™
WORST
1. Apples
2. Celery
3. Strawberries
4. Peaches
5. Spinach
6. Nectarines I
7. Grapes I
8. Sweet bell peppers
9. Potatoes
10. Blueberries D
11. Lettuce
12. Kale/collard greens
Scan to see more!
Get a QR app from www.i-nigma.mobi
foodnews.org
Clean 15™
Lowest in Pesticides.
BEST
1. Onions
2. Corn
3. Pineapples
4. Avocado
5. Asparagus
6. Sweet peas
7. Mangoes
8. Eggplant
9. Cantaloupe D
10. Kiwi
11. Cabbage
12. Watermelon
13. Sweet potatoes
14. Grapefruit
15. Mushrooms

Other Therapy Targets

- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments
- Other modalities – meditation, EEG Neurofeedback

Iron

- Iron is a cofactor for tyrosine hydroxylase (makes L-DOPA)
- Multiple studies show inverse correlation between ferritin and ADHD scores

- Epidemiology
  - ADHD: 74% serum ferritin <30
  - Controls: 18% ferritin < 30 (P<0.001)

Arch Pediatr Adolesc Med 2004;158:1113-5

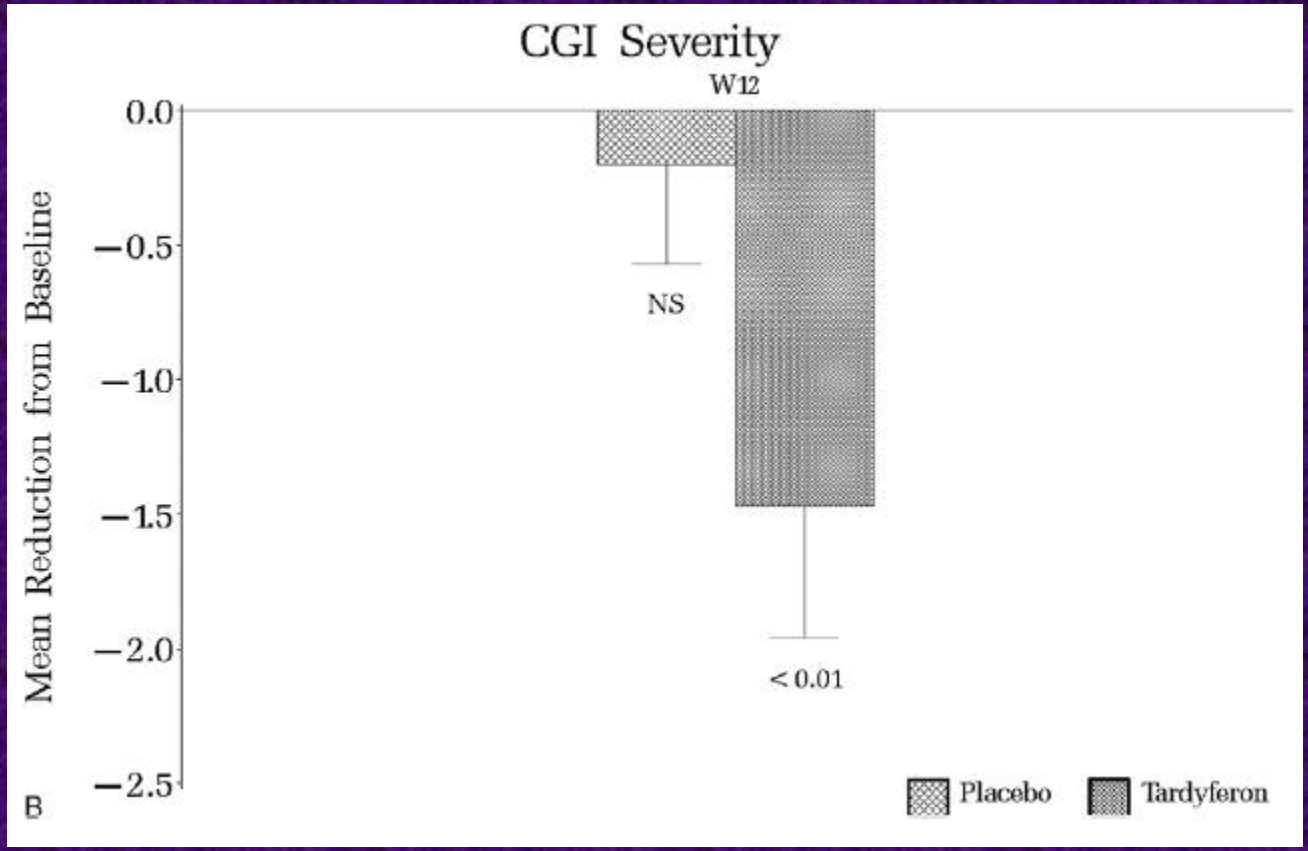
Iron – Open-label trial

- Non-anemic Boys age 7-11
- Ferrocal, 5 mg/kg/day for 30 days (no placebo)

	Ferritin	Parents' Connors Rating Scale
Before	25.9 +/- 9.2 ng.mL	17.6 +/- 4.5
After	44.6 +/- 18 ng/ml	12.7 +/- 5.4

- Neuropsychobiology. 1997;35(4):178-80

Iron – Placebo-controlled Trial



- Nonanemic kids with ferritin < 30
- Ferrous sulfate 80 mg/d x 12 weeks

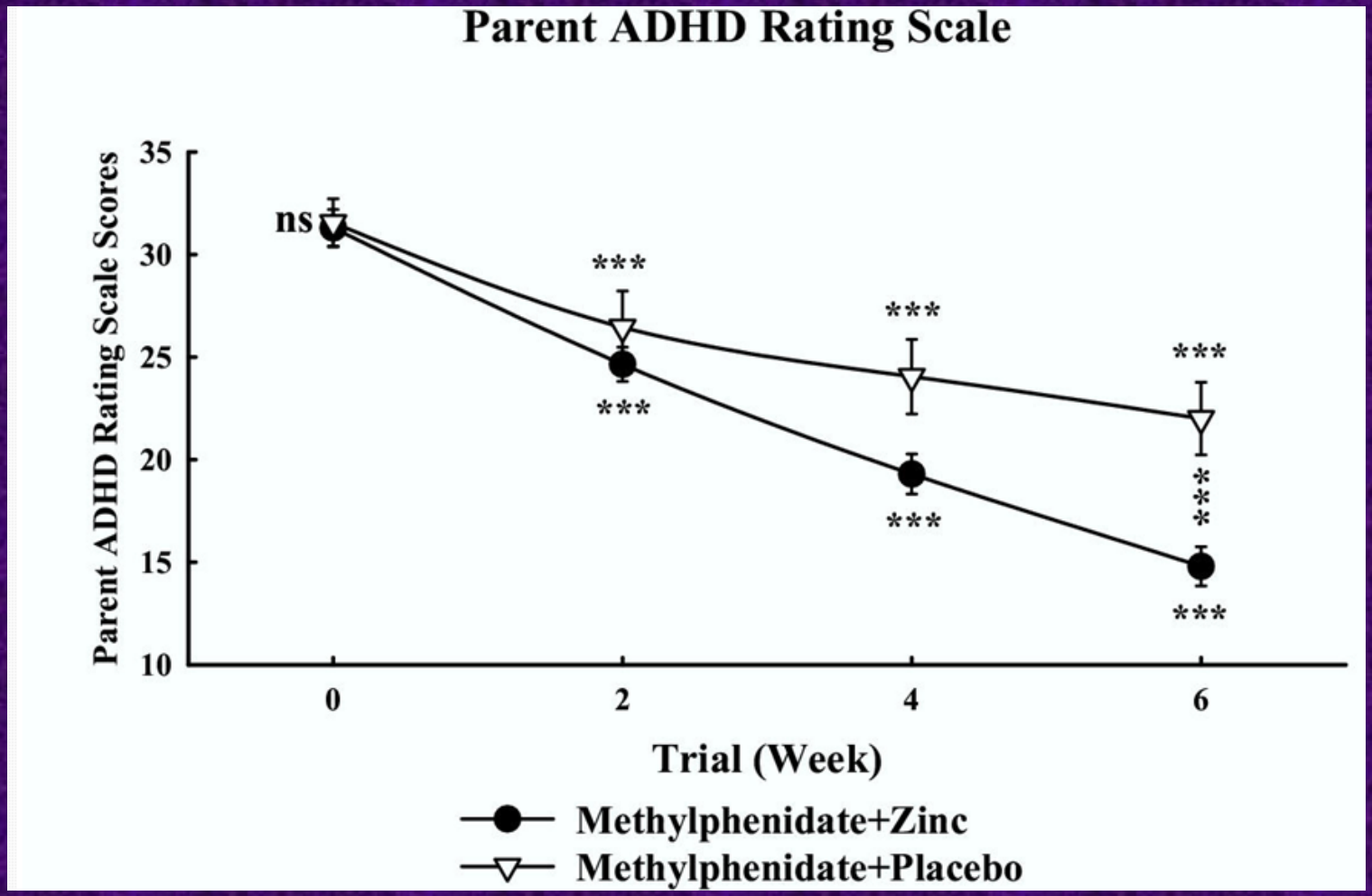
Pediatr Neurol 2008;38:20-26.

Zinc

- Zinc is an inhibitor of the dopamine transporter, which is also the main target of stimulant medications

- Low ferritin and low zinc are associated with high CPRS Hyperactivity score as well as high CPRS Anxiety, Conduct Problems and Total scores Child Psychiatry Hum Dev. 2010 Aug;41(4):441-7.

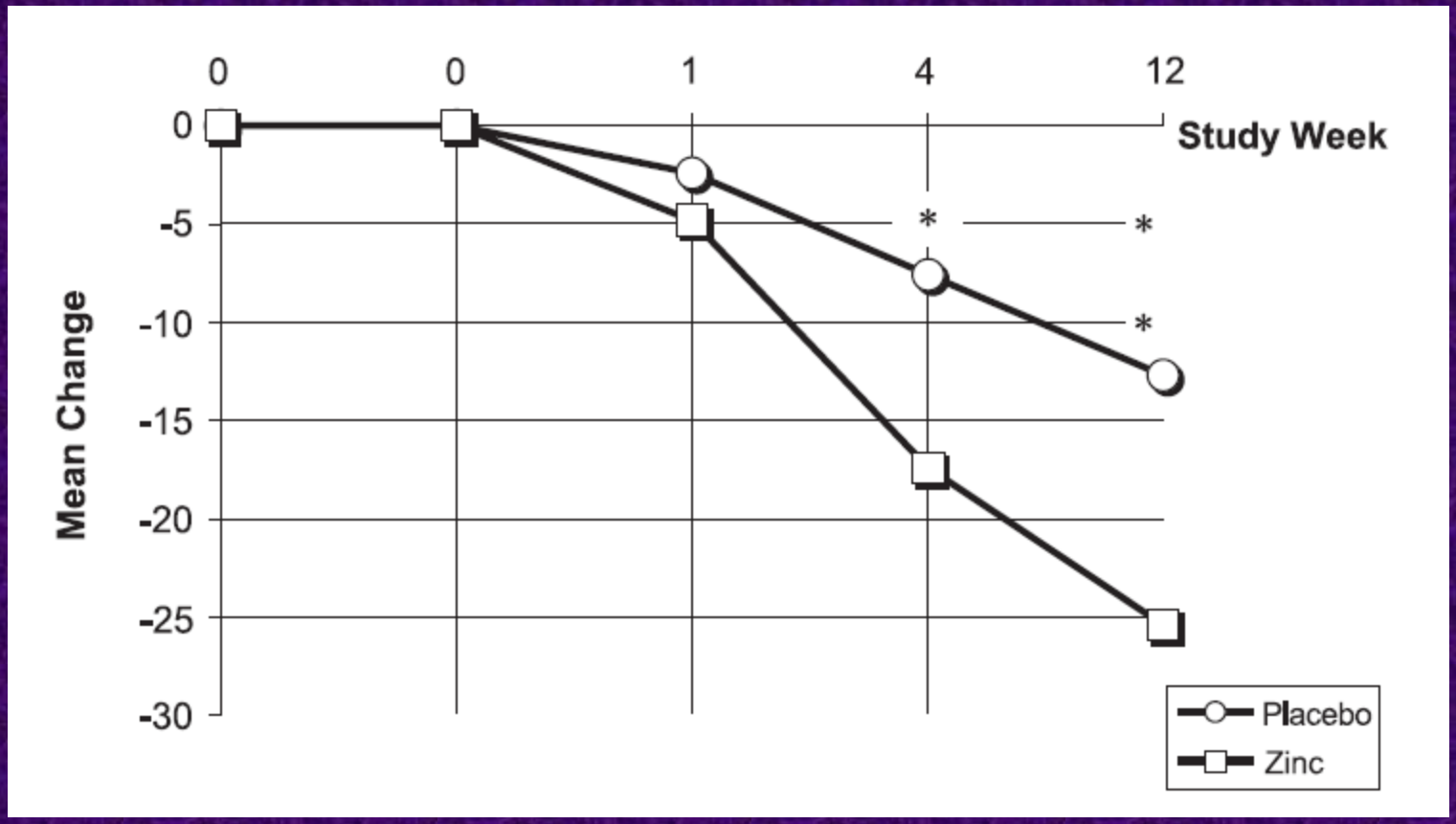
Zinc as adjunct to methylphenidate



Zinc sulfate 55 mg/day (with approximately 15 mg zinc element)

Akhondzadeh *et al. BMC Psychiatry* 2004 **4**:9

Zinc



- Zinc vs. placebo in unmedicated kids Zinc sulfate 150 mg (40 mg elemental zinc)

Progress in Neuro-Psychopharm and Biol Psychiatry 28(1):181-190, 2004

Omega 3 Fats

- Epidemiology linking low omega-3's to ADD is extensive and not controversial
- Treatment trials have been limited by dose/duration, but studies with adequate amounts have shown benefit

Change in Scores	Active	Placebo
Study Period 1		
ADHD-RS-IV total	-3.78	-1.65
CGI	-0.58	-0.13
Study Period 2		
ADHD-RS-IV total	-7.82	-5.81
CGI	-1.24	-0.93

Responders (%) During 0-3 months		Responders at 6months
Active	Placebo	
26%	7% (p=0.04)	47%

558 mg EPA, 174 mg DHA, 60 mg GLA, 10.8 mg Vit E vs. placebo for first 3 months; everyone treated 3-6 months

J Attention Disorders 12(5)394-401, 2009

	Group	Baseline	15 weeks	30 weeks
Cognitive Problems/ Inattention*	PUFAs	25.26	21.04	18.50
	Placebo	24.86	24.49	18.64
Global total*	PUFAs	17.95	14.45	12.72
	Placebo	16.36	16.05	13.27
DSM total*	PUFAs	36.19	29.01	25.54
	Placebo	34.33	33.97	26.37
ADHD Index*	PUFAs	26.68	21.90	18.88
	Placebo	26.67	25.76	19.53

*Treatment effect with $p<0.01$

EPA 558 mg, DHA 174 mg, GLA 60 mg, Vitamin E 10.8 mg or placebo for 15 weeks, then everyone was treated with PUFA

Journal of Dev & Behavioral Pediatrics 2007 28(2):82-91

Reading and Spelling Ages, CTRS-L

	Mean Increase in "Skill Age" (SD)		0- to 3-mo Group Comparisons, Mann-Whitney 2-Tailed Test	
	Active (n = 55)	Placebo (n = 57)	Z	P
Reading age	9.5 mos (13.9 mos)	3.3 mos (SD 6.7 mos)	2.87	<.004
Spelling age	6.6 mos (11.4 mos)	1.2 mos (5.0 mos)	3.36	<.001
Conners' Index	66.2 to 59.9	64.0 to 63.8	5.78	<0.00001

EPA 558 mg, DHA 174 mg, GLA 60 mg, Vit E 9.6 mg
PEDIATRICS 115(5)1360-6, 2005

ω3 and ω6 in kids refractory to stimulants

		3 months		6 months		P
		ω3 + ω6	Placebo	ω3 + ω6	Placebo	
Aggression	Imp	79.2	30.5	87.5	17.4	
	Same	18.8	54.3	8.3	73.9	
	Worse	2.1	15.2	4.2	8.7	0.000
Academic performance	Imp	81.2	32.6	77.1	21.7	
	Same	10.4	60.9	20.8	71.7	
	Worse	8.4	6.5	2.1	6.5	0.000

- Fish oil and EPO (296 mg ω3/180 mg ω6), 2 caps/d
- vs. sunflower oil *J Child Neurol* 2012 27: 747

Putting These Together

- Huss (2010) open label study. 800 children received for 3 months):
- **Omega-3 EPA** (eicosapentaenoic acid) 400 mg
- **Omega-3 DHA** (docosahexaenoic acid) 40 mg
- **Omega-6 GLA** (gamma-linolenic acid) 60 mg
- **Magnesium** 80 mg (21% of RDA)
- **Zinc** 5 mg (50% of RDA)

- **Lipids in Health and Disease 2010**

Overall Results

Table 4 Decrease in average point scores (APS) from baseline to the end of the study

	N	Decrease in points (mean)	Standard deviation	95% Confidence interval	p*
Attention deficit (APS)	754	5.36	5.23	4.98-5.73	< 0,001
Hyperactivity/impulsivity (APS)	756	3.65	5.11	3.29-4.02	< 0,001
SNAP-IV (total score)	734	8.99	9.02	8.33-9.64	< 0,001
Emotional problems (APS)	781	0.25	0.52	0.21-0.29	< 0.001

* two-sided t-test.

Improvements in Attention

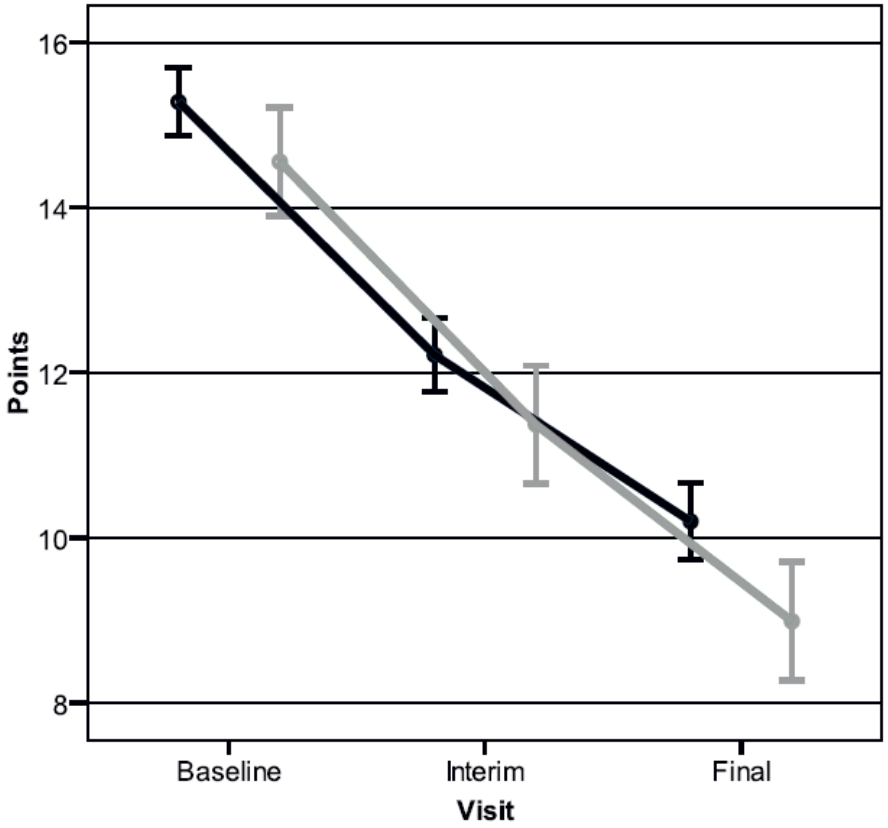


Figure 1 Decrease in average point scores (APS) for attention deficit assessed by SNAP-IV for 551 boys and 225 girls. Mean and 95% confidence interval.

Other Therapy Targets

- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments, other supplements
- Other modalities – meditation, EEG Neurofeedback

Herbal Compound – Nurture & Clarity

	Treatment Group[a]			
	Baseline	Post-trial	Difference	p-Value[c]
Omission	79.1 ± 25.9	93.3 ± 18.7	14.3 ± 22.9	<.0001
Commission	99.5 ± 14.9	106.6 ± 12.5	7.1 ± 13.8	<.0001
Response time	81.9 ± 15.7	95.5 ± 14.5	13.5 ± 17.5	<.0001
Variability	81.8 ± 15.8	96.3 ± 18.1	15.5 ± 22.6	<.0001
Overall score	85.6 ± 12.2	97.9 ± 11.3	12.4 ± 12.9	<.0001

Paeoniae Alba, Withania Somnifera , Centella Asiatica, Spirulina Platensis, Bacopa Monieri, and Melissa Officinalis.

Placebo Group[b]			
Baseline	Post-trial	Difference	p-Value[c]
78.6 ± 24.5	77.7 ± 23.5	−0.9 ± 27.6	.89
100.1 ± 11.1	98.8 ± 16.5	−1.3 ± 16.3	.74
90.1 ± 16.3	83.7 ± 23.9	−6.4 ± 17.8	.14
86.3 ± 13.7	76.9 ± 22.5	−9.4 ± 23.8	.10
88.8 ± 12.3	84.3 ± 15.7	−4.5 ± 16.7	.26

Katz, M et al A Compound Herbal Preparation (CHP) in the Treatment of Children With ADHD: A Randomized Controlled Trial. J Atten Disord 2010 Mar 12.

Magnesium

- Open-label trial, 6 mg/kg/d with B6

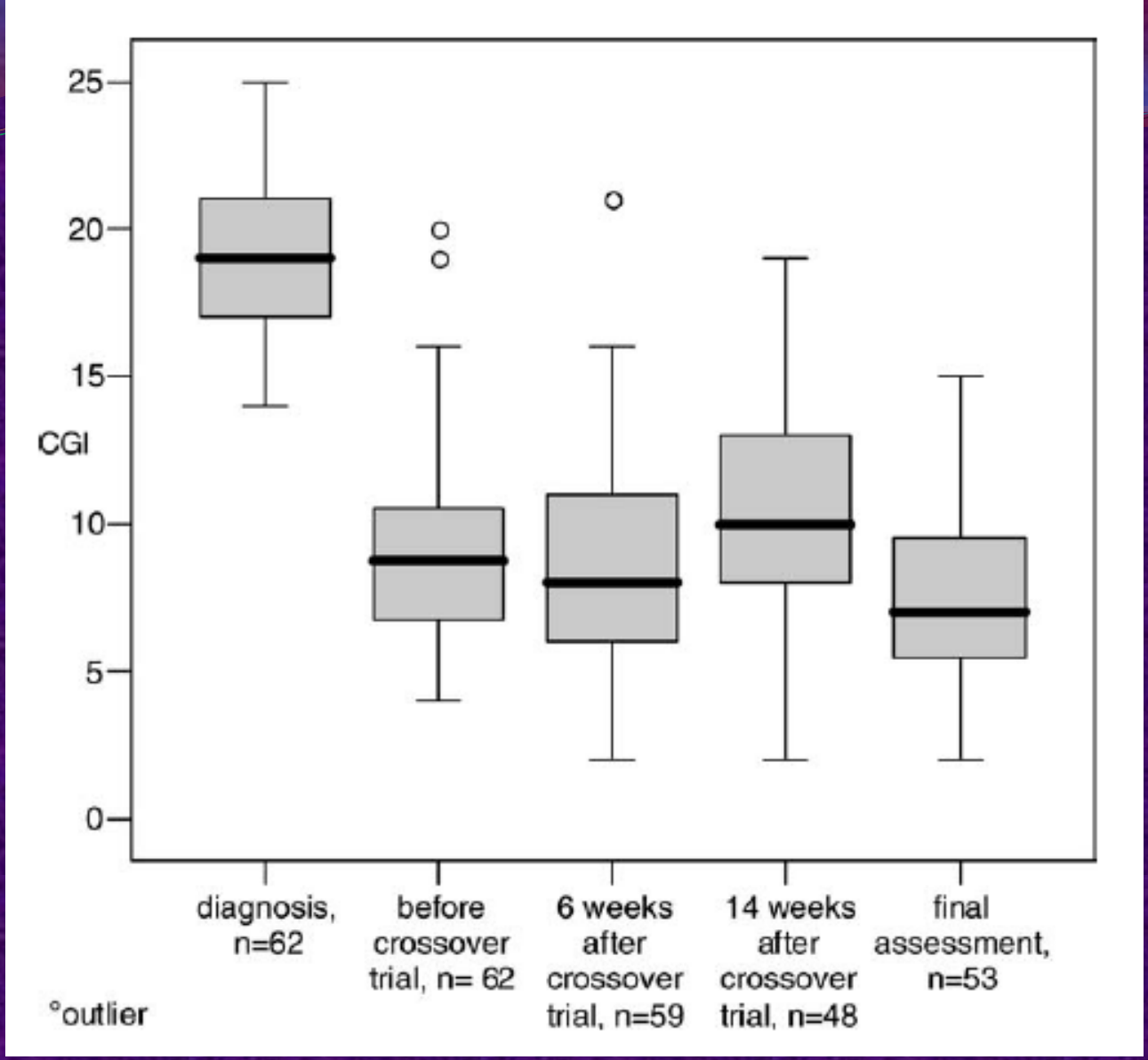
Clinical symptoms	Before treatment	After 2 months treatment	After 4 months treatment
hypertony	17/49	11/17	5/17
spasm			
myoclony			
tremors			
significance		$P < 0.05$	$P < 0.001$
physical aggressivity	26/49	20/26	6/26
instability			
scholar inattention			
significance		NS	$P < 0.01$
Developmental disorders	6/49	6/6	4/6
significance		NS	NS

Journal of the American College of Nutrition, Vol. 23, No. 5, 545S–548S (2004)

Homeopathy and ADHD

- Open Study Followed by Randomized Double Blind Crossover Study -62 patients
- In open study 84% showed significant improvement (Conners) – CGI score drop by 9 points or 50%
- Blinded Crossover study showed improvement decreased with placebo and increased with homeopathic treatment.

- European Journal of Pediatrics 2005



- Among responders, 63% drop in scores by end (19 months avg, range 10-30 months)

Other Therapy Targets

- Sleep
- Diet
  - General dietary principles
  - Dietary tacks
- Nutrients
  - Iron
  - Zinc
  - Omega-3's
- Herbal treatments, other supplements
- Other modalities – meditation, EEG Neurofeedback

Meditation

- Limited data due to problems with blinding:
  - Multiple tiny studies showed improved parent ratings as well as performance on attention tests with yoga or meditation
- Cochrane Review: no adequate data (lack of blinding increases risk of bias)
  - The one study they felt was appropriate for analysis showed:
  - No significant difference between meditation group and standard therapy group
- Side effects of meditation were not reported

Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD006507.

Other Meditation Data

- Improved performance on intelligence-related measures *Personality and Individual Differences*, 12, 1105–1116, 1991
- Improved ability to sustain attention J Neurosci. 2009 Oct 21;29(42):13418-27
- Some studies showing improved cognitive function may have been biased Wien Klin Wochenschr. 2003 115(21-22):758-66
- Improves school behavior in adolescents *Health and Quality of Life Outcomes* 1:10, 2003
- Reduces substance abuse *Alcoholism Treatment Quarterly* 11: 13-87, 1994

Movement Therapy

- Rough-and-tumble play helps hyperactivity in a rat model Brain Cogn. 2003 Jun;52(1):97-105

- Aerobic fitness affects prefrontal executive control and hippocampal function
  - Interference control better in fit kids (no change in response time) Developmental Psychology 2009 45(1):114-29
  - Relational memory performance better in 9-10 year olds who were more fit Med Sci Sports Exerc. 2010 PMID: 20508533
- Aerobic fitness correlates with scores on math and reading

EEG Neurofeedback

- Looks interesting, but cost-prohibitive
- Locally, Stan Vanella

So our prescription for KS:

So our prescription for KS:

- Check ferritin, iron if < 30
- Supplement Fish oil 800 – 1000 mg EPA + DHA
- Trial of elimination diet and track response to rechallenge
- Behavioral charting, rewards, ongoing counseling
- Stimulant-du-jour
- Activity: Join a soccer team/family bike rides, etc.
- +/- other herbs, zinc, pycnogenol, etc.

Resources

- http://www.nichq.org/ - Toolkit with parent and teacher questionnaires, handouts, etc.
- http://www.chadd.org – children and adults with ADD
- www.help4adhd.org – rating scales, thorough handouts on meds, etc
- http://www.allkindsofminds.org – some nice web modules and a parent toolkit
- http://difficultchild.com/ - Nurtured Heart Approach to Transforming the Difficult Child

More Resources

- Parenting Children With ADHD: 10 Lessons That Medicine Cannot Teach (APA Lifetools) by V. Monastra
- Healing ADD by Daniel Amen
- A Mind at a Time by Mel Levine
- How Your Child is Smart or Open Mind by Dawna Markova