

ADHD: A Longitudinal Approach

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Financial Disclosure

Role as PI in a Pfizer supported multicenter clinical trial: Oral ziprasidone in children and adolescents with bipolar 1 disorder. Completed.

Role as a Co-PI in a Shire supported (ADHD and lisdexamfetamine) study. Ongoing.

Overview

- ADHD: A Historical Perspective
- ADHD: The Basics. Etiology, Comorbidities, ADHD Across the Lifespan
- Treatment of ADHD
- Relevant New Research

Historical Perspective

- Around 1580, Falstaff in Shakespeare's King Henry IV characterized himself as having *“the disease of not listening, the malady of not marking.”*
- In 1775, Melchior Adam Weikard, a prominent German physician, published a textbook and talked about individuals who can't pay attention
- **Sir Alexander Crichton, 1775:** "The incapacity of attending with a necessary degree of constancy to any one object. It may be either born with a person, or it may be the effect of accidental diseases. What is very fortunate, it is generally diminished with age."

Previous Nomenclature

- Defect of Volitional Inhibition/Defective Moral Control (early 1900s)
- Restlessness Syndrome or Organic Drivenness (1920s to 1940s)
- Minimal Brain Dysfunction (1950s to 1970s)
- Hyperkinetic Child Syndrome (1960s)
- Attention Deficit Disorder (1980s)

DSM 5 Criteria

Inattention

- Fails to give close attention to details or makes careless mistakes.
- Has difficulty sustaining attention.
- Does not appear to listen.
- Struggles to follow through on instructions.
- Has difficulty with organization.
- Avoids or dislikes tasks requiring sustained mental effort.
- Loses things.
- Is easily distracted.
- Is forgetful in daily activities

Hyperactivity and Impulsivity

- Fidgets with hands or feet or squirms in chair.
- Has difficulty remaining seated.
- Runs about or climbs excessively in children; extreme restlessness in adults. Difficulty engaging in activities quietly.
- Acts as if driven by a motor; adults will often feel internally as if they were driven by a motor.
- Talks excessively.
- Blurts out answers before questions have been completed.
- Difficulty waiting or taking turns.
- Interrupts or intrudes upon others.

-Symptoms are present prior to age 12

-6 Month rule

-Two or more settings rule

-Decline in social, academic, or occupational functioning

Etiology

Genetic Factors

- Numerous twin studies have found mean heritability between 60 to 90%
- Several candidate genes are involved in dopaminergic and noradrenergic NT systems

Environmental Factors

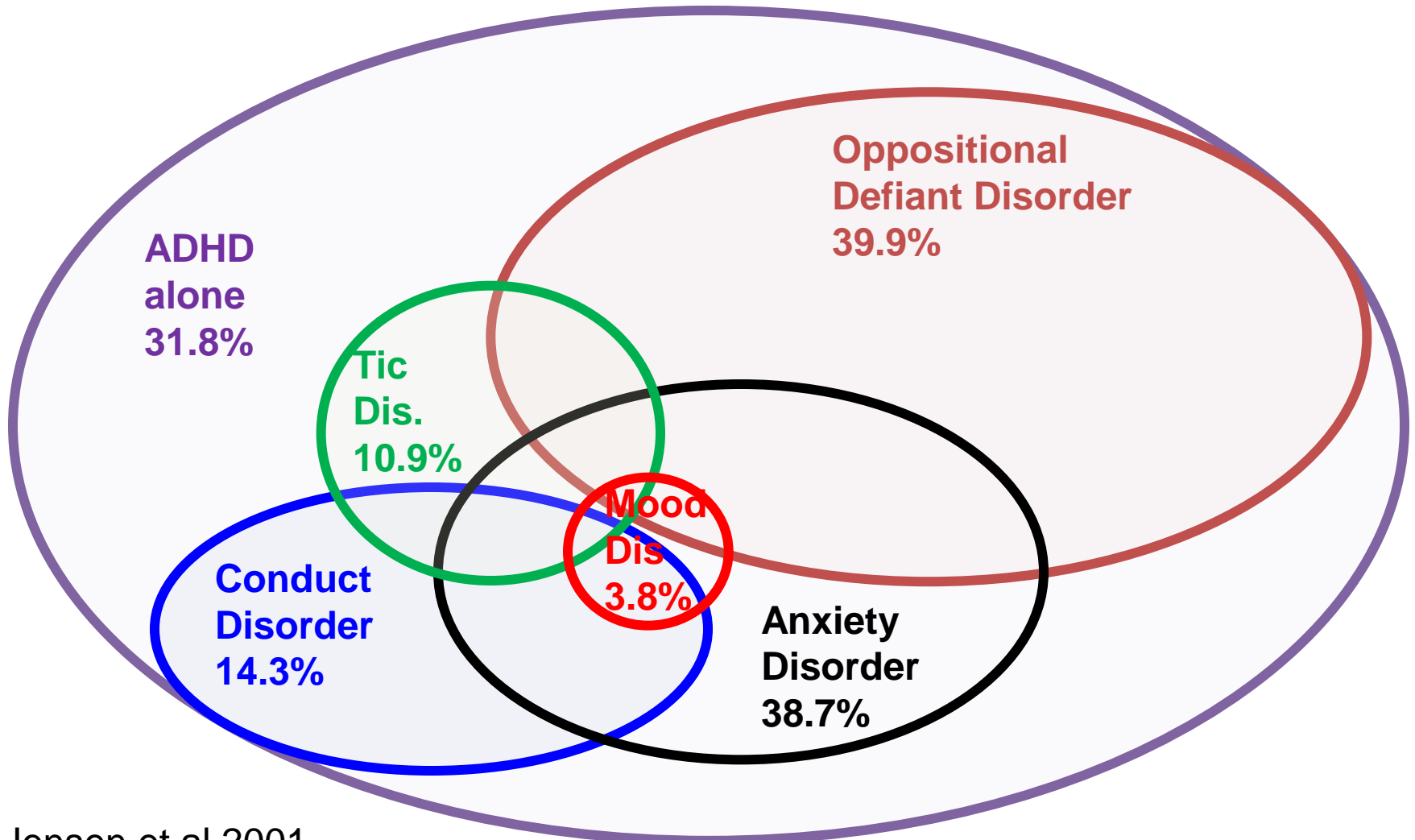
- Prematurity, maternal smoking/alcohol consumption, hypoxic states, and postnatal exposure to lead all increase risk

Still a surprisingly common question:

“So, is ADHD real?”

- Heritability
- Structural brain differences
- Long and a consistent history
- Present across cultures (world wide prevalence of 4.5 to 8%)
- Diagnostic validity

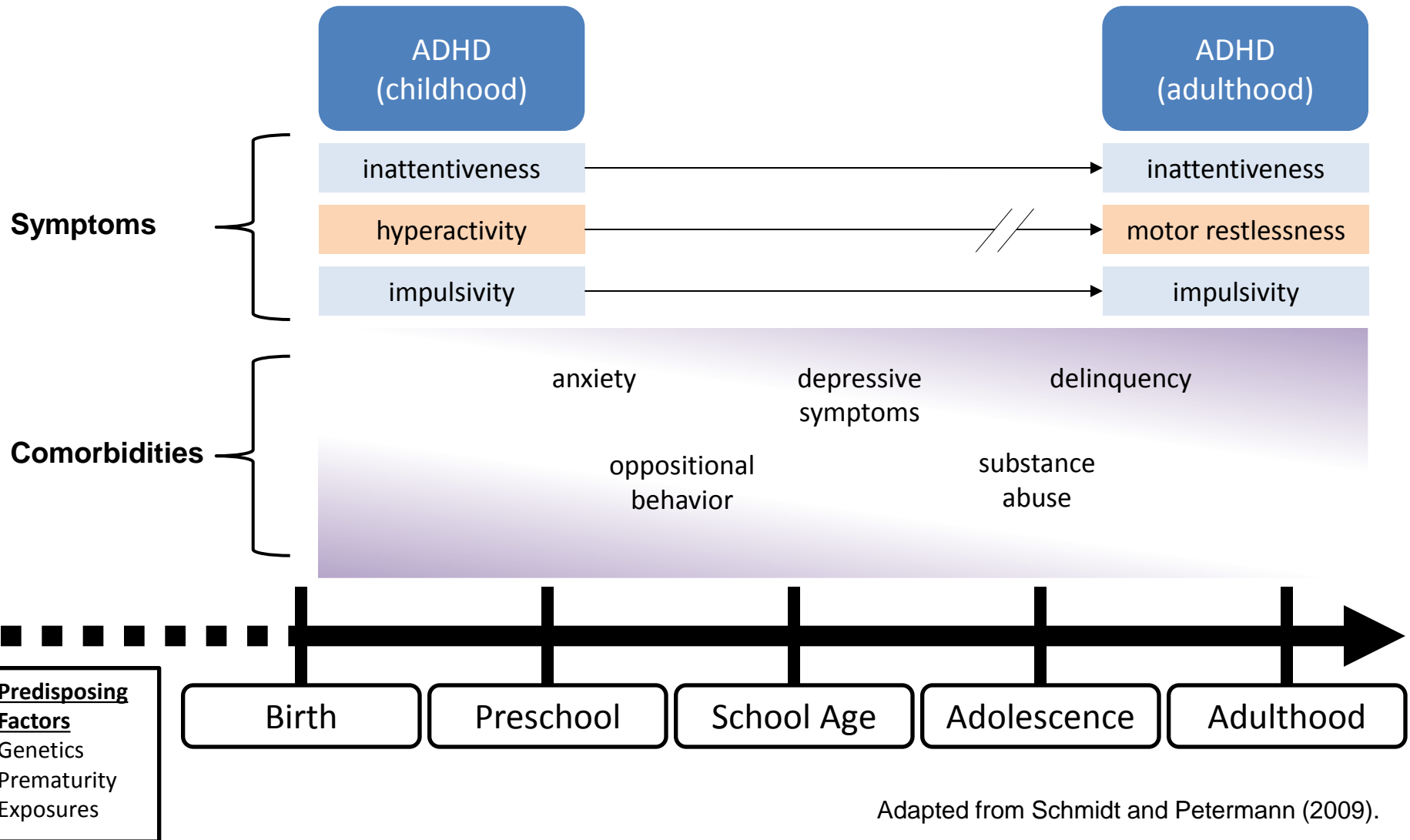
ADHD Comorbidities



Psychiatric Comorbidities in ADHD

- Conduct Disorder and ODD
- Depression: An interesting pattern
- Anxiety Disorders: An ongoing issue
- Bipolar Disorder: An asymmetrical risk?
- ASD
- Increased risk for suicide (both ideation and attempt)
- Increased alcohol, marijuana, and nicotine use
- Increased use of hard drugs if associated with CD-ODD

ADHD Across the Life Span



Adapted from Schmidt and Petermann (2009).

ADHD and Medical Comorbidities: Obesity

- ADHD and Obesity: Association between ADHD and obesity in children, regardless of possible confounding factors
- “The role of abnormal eating patterns, sedentary lifestyle, and possible common genetic alterations. Importantly, recent longitudinal studies support a causal role of ADHD in contributing to weight gain”

Cortese and Tessari, Jan 2017. Current Psychiatry Reports.

- Other medical comorbidities

Psychiatric Assessment of ADHD

- Developmental history
- Family history
- Mental health history
- Social History
- Behavior Rating Scales
- Psychoeducational testing not required unless a learning or intellectual disability is suspected
- If PMH unremarkable labs are not required
- Recent studies may support getting zinc, ferritin, and magnesium levels to rule out deficiencies in certain cases.

Multimodal Treatment of ADHD

Medications

- Stimulant
- Non-stimulant

School-Based Supports

- Student Support Teams
- 504 plans
- IEPs
- counseling / social skills programs

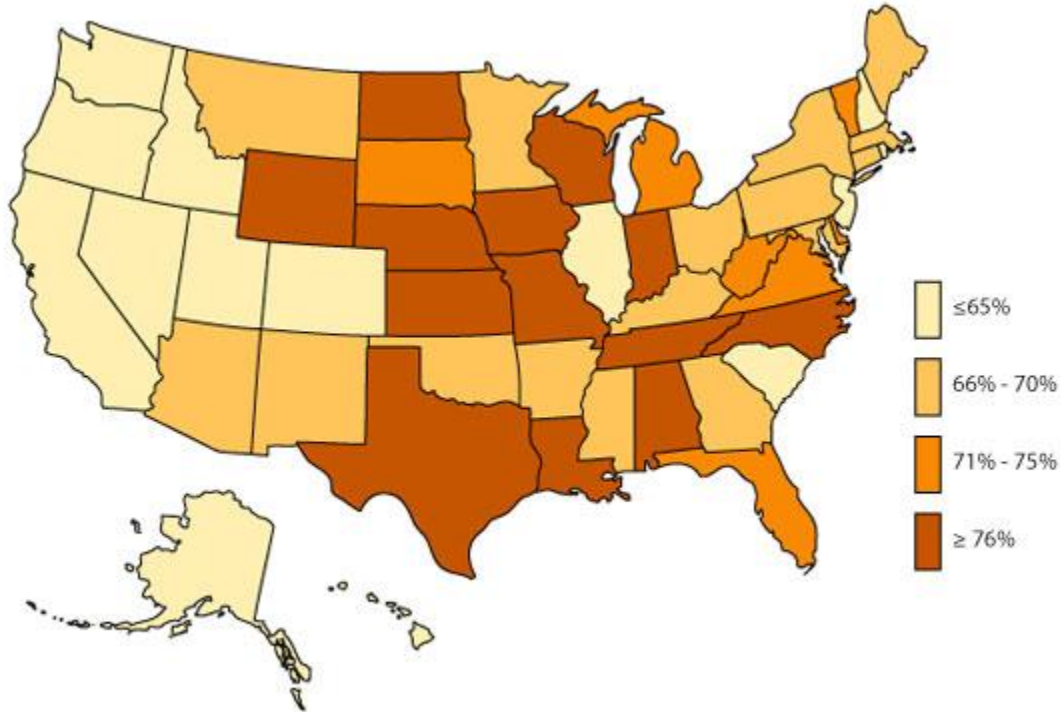
Behavioral Therapy

- Parent groups
- on-line training
- ADHD coaches
- Tutors
- CBT

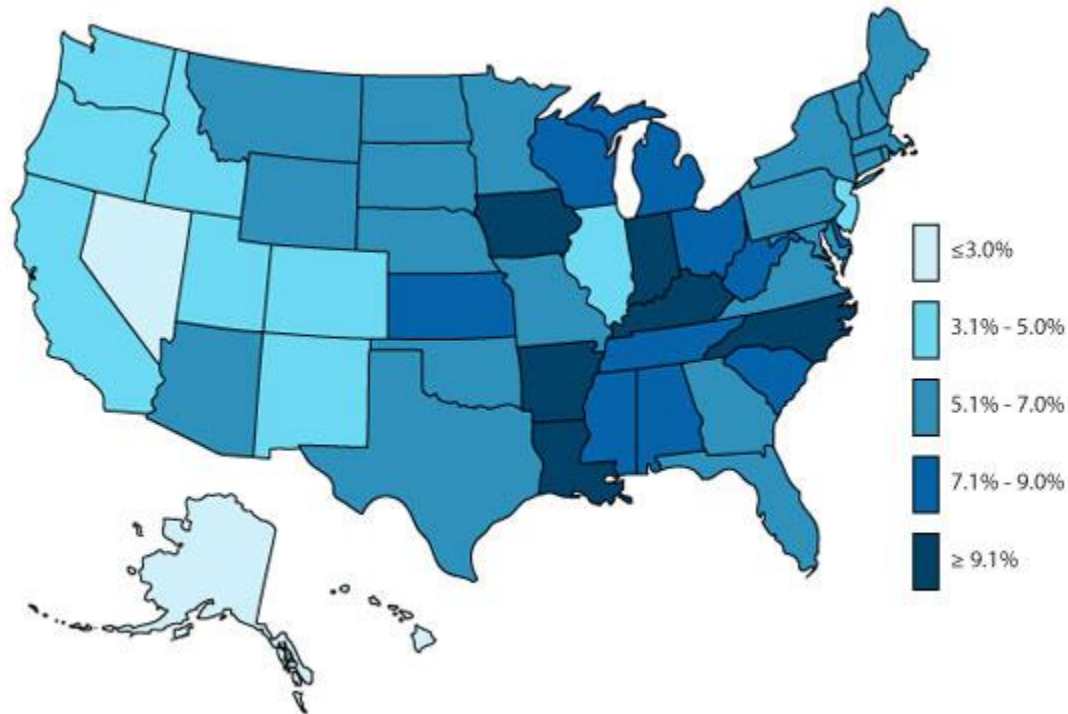
Complementary Treatments

- Exercise
- Nutritional Supplements
- Other

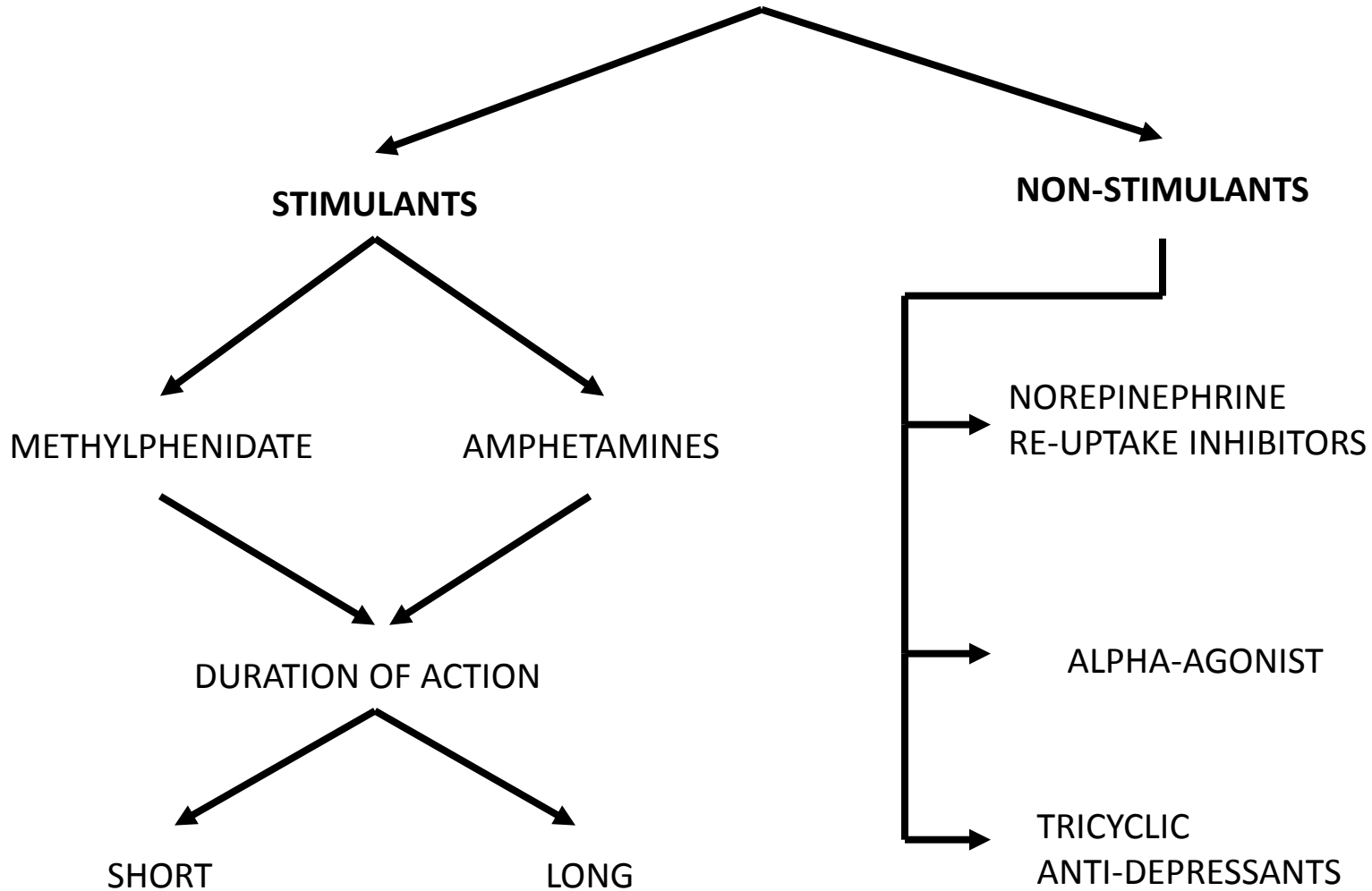
CDC Data 2011: Percent of Youth Aged 4-17 Currently with ADHD Receiving Medication Treatment by State: National Survey of Children's Health



CDC-2011: Percent of Youth Aged 4-17 Years Currently Taking Medication for ADHD by State: National Survey of Children's Health



ADHD MEDICATIONS



Stimulant Medication

Methylphenidate	Mixed Amphetamine Salts
Short Acting: Ritalin, Focalin	Short Acting: Adderall, Dexedrine
Long Acting: Concerta, Metadate CD* , Ritalin LA* , Focalin XR* , Quillivant (liquid), Daytrana (patch)	Long Acting: Adderall XR* , Vyvanse, Dexedrine Spansule

* Capsule may be opened and sprinkled on food

Stimulant Medication (cont'd)

- Short acting stimulants may be better for younger or more sensitive subgroups of children requiring lower doses
- Dual pulse stimulants (i.e., Ritalin LA, Focalin XR, Metadate CD) provide good effect during school day but wear off in afternoon. May be good choice for kids with appetite suppression and those with delayed sleep onset.
- Long acting medication provides coverage into early evening

Stimulant Side Effects

- Common Side Effects
 - Sleep Problems, Decreased Appetite, Headaches, Gastro-Intestinal Problems
- Other Side Effects
 - Irritability, Dysphoria, Behavioral Rebound, BP changes, Growth problems, Cardiac Issues, and Sudden Death

Non-Stimulants: Atomoxetine

- First non-stimulant treatment approved by the FDA. Norepinephrine reuptake inhibitor. Benefit is generally observed within 2-8 weeks of initiation.
- May be a good choice for the following children
 - co-morbid anxiety disorder, tic disorder, or substance abuse
 - Need for 24 hour action
 - Child cannot tolerate stimulant medication
- Side effect: Nausea, low appetite, fatigue, insomnia, BP increase, potential for liver injury, drug interaction with CYP2D6 inhibitors such as Fluoxetine and Paroxetine
- FDA black box warning for risk of increased suicidal thinking

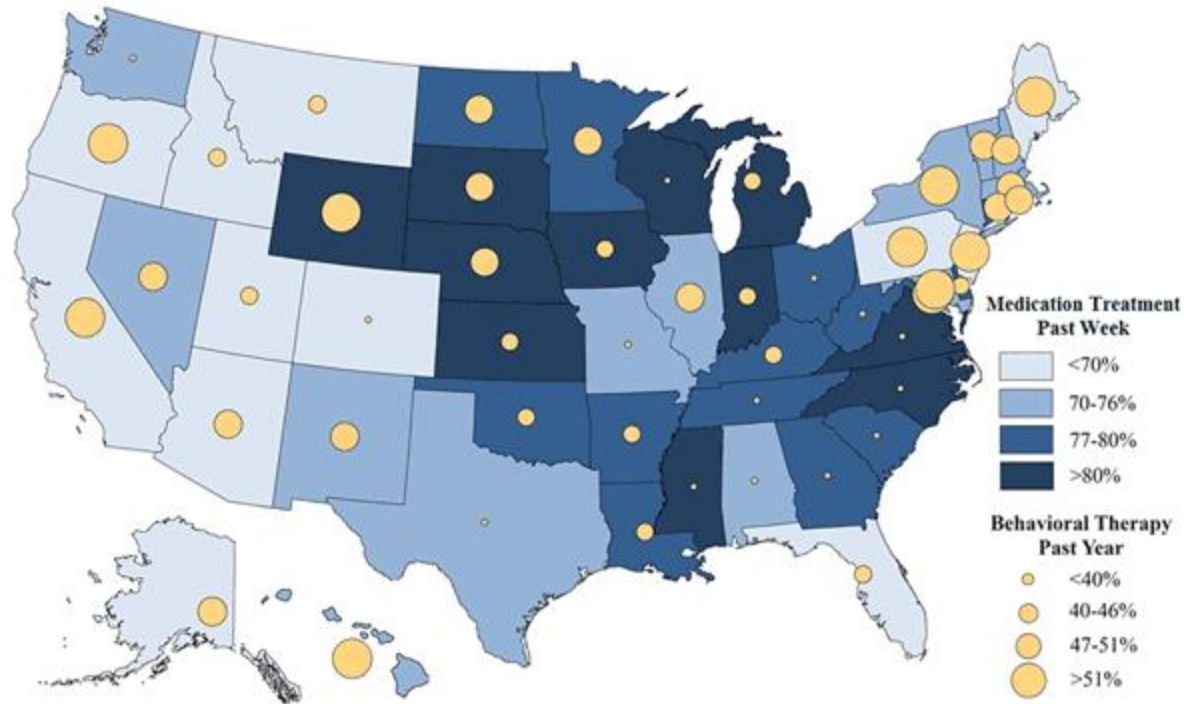
Non-Stimulants: Guanfacine and Clonidine

- Guanfacine and Clonidine
 - alpha-2 adrenoreceptor agonist
 - Can help with impulsivity, hyperactivity, tics, sleep
 - Side effects: sedation, dizziness, hypotension
 - Need to monitor for drops in blood pressure
 - Need to taper off to avoid rebound hypertension
- Guanfacine and Guanfacine XR
 - Guanfacine XR (Intuniv) is the first alpha-2 adrenoreceptor agonist to gain approval to treat ADHD, approved for the treatment of 6 to 17 year olds.
 - Less sedating than Clonidine
- Clonidine and Clonidine XR:
 - Short acting form, Catapres, has a fast onset and short half-life, causing somnolence.
 - Long acting form is Kapvay

ADHD Treatments: Effect Size Comparisons

Treatment	Effect Size
Methylphenidate <small>Schachter et al., 2001</small>	0.78
Atomoxetine (Strattera) <small>Cheng et al., 2007</small>	0.64
Clonidine <small>Conner, Fletcher, & Swanson, 1999</small>	0.58
Omega 3 Fatty Acid <small>Bloch and Qawasmi, 2011</small>	0.31

CDC 2011: ADHD medication and behavior therapy among children with ADHD (ages 4-17) with special health care needs



Treatment Considerations for Preschool Age Children

- AAP recommends behavioral therapy as first line treatment for preschool age children
- Preschool ADHD Study (PATs) found that children with three or more comorbid conditions were less likely to benefit from medication
- If medications are initiated, start low dose and titrate slowly.

Treatment Considerations for Adults with ADHD

- Long standing patterns and academic/social history, academic records
- Comorbid conditions such as anxiety disorder, alcohol and illicit drug abuse
- Adult checklists from the individual and family members
- Vocational support

Medication treatment for Adults with ADHD

- Spencer et al: A marked therapeutic response to MPH. Safe and well tolerated. Response independent of socioeconomic status, gender, and even comorbidity. 76% vs 19% of placebo.
- Wilens et al: Atomoxetine in adults with ADHD plus alcohol use disorder. Clinically significant ADHD improvement but less consistent impact on alcohol use

Medication and CBT

- Safren et al: Medication plus CBT. It may help achieve lower symptom severity for ADHD and lower anxiety symptoms.

MPH vs Atomoxetine in Adults with ADHD

- Ni et al: Significant symptom reduction in overall ADHD symptoms and improvement in social functions and quality of life for both groups. No group difference in the rates of adverse effects

Group Treatment for Young Adults with ADHD

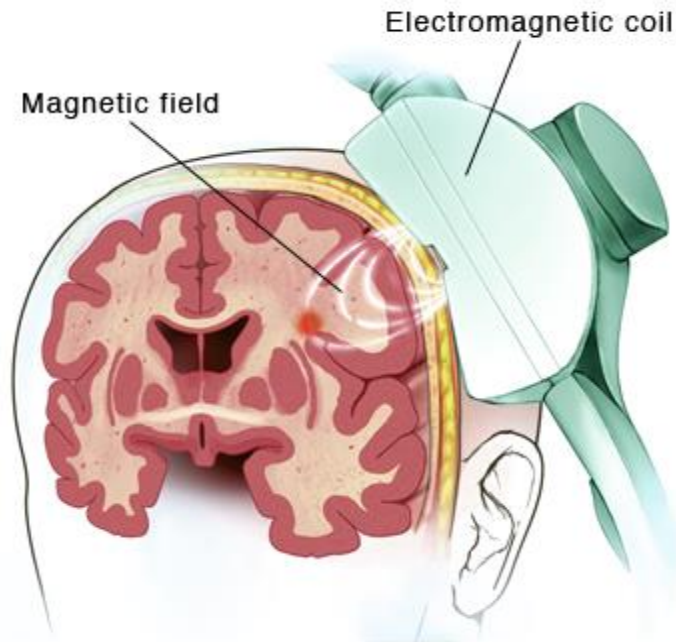
- A 14 week program
- CBT and DBT based manual
- Assessments at baseline, at 14 weeks, then 1 and 6 months after conclusion
- Result: All ADHD symptoms significantly decreased and remained stable for 6 months
- In addition, measures of depression, perceived stress, and anxiety were also reduced. Nasri et al, Feb 2017.

Complementary Treatments: Exercise

- Exercise has been associated with reduction of ADHD symptoms (i.e., improved executive functioning)
- Up-regulation of brain derived neurotrophic factor (BDNF), increase in catecholamine neurotransmission, and increased cerebral blood flow may underlie improved cognitive functioning.

Complementary Treatments: Omega 3 Fatty Acids

- Meta analysis of 10 randomized placebo controlled trials including 699 children with ADHD found that Omega 3 fatty acids have a modest effect in reducing ADHD symptoms (i.e., Effect size of 0.31)
- Higher doses of Omega 3 fatty acids correlated with greater response.
- Omega 3 fatty acids reduce inflammation and increase cell membrane fluidity
- Supplements should have both EPA and DHA to get full benefit.
 - Vegetarian sources provide ALA (alpha-linolenic acid), which must be converted to EPA and DHA
 - Fish oil has advantage of having good balance of DHA and EPA



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Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression. TMS is typically used when other depression treatments haven't been effective.

A Novel Treatment Approach: rTMS

- A. Zangen, March 2017. Clinical Neurophysiology
- Reduced rPFC excitability in ADHD. Drug-free adults with ADHD ($n = 53$) received 15 daily sessions of high-frequency repetitive TMS directed to the rPFC, using either deep (dTMS), standard (8TMS), or sham coils
- Standard ADHD questionnaires (CAARS) were administered, and EEG recordings were taken before, during, and after the first and the last days of treatment. Additional comparison group of healthy subjects ($n = 41$) was recorded under the same conditions. At baseline, amplitudes of TMS evoked potential (TEP) were significantly lower in subjects with ADHD than those of healthy controls.
- Following treatment, improvement in ADHD total symptoms was only evident in the dTMS group.
- These findings suggest that 3 weeks high frequency dTMS treatment can serve as a novel treatment for ADHD in adults, possibly by enhancing excitability of the rPFC.
- Not FDA approved.

Relevant New Research and Treatment Implications:

1- Tics and Stimulant Medications

- FDA has warnings against using psychostimulants for children who have tics or a family history of tics due to case reports from 1970s and 1980s.
- Treatment of ADHD in Children with Tics (TACT) Study by the NIH Tourette's Syndrome Study Group: Included 136 kids with ADHD and Chronic Tic Disorder randomized to treatment with methylphenidate, clonidine or placebo. Tics worsened in 20% of children in methylphenidate group, 26% in Clonidine group, and 22% in placebo group. Study concluded that waxing and waning nature of tics is substantial and frequent in the treatment initiation period.
- Meta-analysis of 22 randomized controlled trials did not support an association between new onset or worsening of tics with stimulant use (Cohen et al, 2015).
- No difference between MPH and amphetamine based stimulants
- AACAP guidelines recommend that if tics emerge with stimulant treatment to switch to another stimulant or consider non-stimulant treatment.

2- ADHD and Long Term Academic Achievement

Academic Achievement in Adults with a History of Childhood Attention-Deficit/Hyperactivity Disorder: A Population-Based Prospective Study

- Young adults with research-identified childhood ADHD were invited to participate in a follow up study and were administered an academic achievement battery consisting of the basic reading component of the Woodcock-Johnson III Tests of Achievement (WJ-III) and the arithmetic subtest of the Wide Range Achievement Test—Third Edition (WRAT-3).
- This is the first prospective, population-based study of adult academic outcomes of childhood ADHD.
- Data provide evidence that childhood onset ADHD is associated with long-term underachievement in reading and math that may negatively impact ultimate educational attainment and occupational functioning in adulthood. Voigt, Jan 2017, Journal of Developmental & Behavioral Pediatrics.

Discussion: Vocational and Educational Impact

3- ADHD and Sleep Regulation

ADHD and Sleep: EDS in Adults with ADHD

- Arousal dysregulation has been speculated to be involved in the pathological mechanism of attention deficit/hyperactivity disorder (ADHD).
- However, there has been no epidemiological study assessing the real condition of excessive daytime sleepiness (EDS) in adults with ADHD. This study investigated the prevalence of EDS and the relationship between sleepiness and ADHD symptoms in adults with possible ADHD.
- The rates of having moderate and severe sleepiness in the possible ADHD group were higher than those in the non-ADHD group. Hierarchical logistic regression analyses revealed that the presence of ADHD symptoms was independently associated with EDS even after adjusting for factors related to the presence of sleepiness. Oct 2016, Wakako et al.

Discussion: Treatment Options

4- ADHD and Functional Impairments in Pregnant Women

Associations Between ADHD Symptoms and Occupational, Interpersonal, and Daily Life Impairments Among Pregnant Women

-Past research links symptoms of depression and anxiety with functional impairments among pregnant women. However, no prior research has examined the impact of ADHD symptoms among this population.

-The current study examines associations between ADHD symptoms and impairment in several life domains.

-Self-report measures of ADHD symptoms, impairment, and demographic information were collected from 250 pregnant women.

-Inattentive symptoms were significant predictors of professional life impairment, daily life impairment, and relationship impairment. Impulsivity uniquely predicted variability in professional life impairment and relationship impairment. Hyperactivity was not a significant predictor.

Eddy et al, Jan 2017, Attention Disorders

Discussion: Treatment Options and risks for fetal development

5- EEG: A Helpful Diagnostic Tool? Yes but..

- A neurodevelopmental Disorder but diagnosis does not include biomarkers
- Diagnostic validity and comorbidity issues
- Snyder et al. Brain and Behavior. 2015.
- Used TBR (Theta/Beta Ratio). 275 Children and adolescents, ages 6-17. Clinician, EEG team, multidisciplinary team (as reference)
- High TBR correlated with reference standard closely
- Aimed to integrate an EEG biomarker with clinician's assessment (rather than a stand alone diagnostic tool)
- Diagnostic improvement from 60% to 87%

Thank you!

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