Pediatrics teleECHO
ADHD: History, Diagnosis and Treatment

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A Brief History of ADHD . . .

- 1870's George Bradley, Rhode Island businessman, helped a young Alexander Graham Bell develop the precursor to the telephone – became a millionaire. His daughter Emma contracted encephalitis at 7 years of age and he never was able to find a treatment for her
- At the time there were mostly only adult institutions for maladies such as these
- Upon his death in 1906, he left his entire fortune to establishing a facility to care for children who had mental health challenges. . .

Emma Pendleton Bradley Home, Rhode Island

A Brief History of ADHD . . .

- 1931 – Emma Pendleton Bradley Home is opened for children who are demanding and difficult to control
- Led by nurses and Dr. Charles Bradley, a young Harvard medical school graduate who was devoted to children's mental health. . .
- Did spinal taps to try to find out what was wrong with the children
- To treat the subsequent headaches he used an over the counter sinus medication called Benzedrine
- Headaches remained, but behaviors improved dramatically! Staff were amazed at the results.
- The children were able to focus, pay attention and learned for the first time in their life. . .

A Brief History of ADHD . . .

- 1937 – Bradley writes up the results of his study in the American Journal of Psychiatry
- Bradley continues to treat children with Benzedrine, emphasizes that social therapies were still important and not all children improved. . .some had nausea, increased anxiety and insomnia
- 1938 - Food, Drug and Cosmetic Act, precursor to the FDA, power to keep a drug off the market until it was deemed safe. . .
- 1940 – Swiss company develops a new molecular formation of amphetamine – calls it Ritaline

A Brief History of ADHD

- 1950's – Young clinician named Keith Conners, PhD, reads Bradley's study, wants to reproduce his findings in a more scientific method . . .
- 1956 – Ritaline chemical formulation termed methylphenidate, comes to market as "Ritalin" for narcolepsy, chronic fatigue and depression
- Conners receives permission from Johns Hopkins and NIMH agrees to fund his study, one of the 1st times the federal government subsidizes a trial of psychotropic medication in children

A Brief History of ADHD . . .

- 1962 – Trial of Ritalin for children who had a condition termed "Hyperkinetic Impulse Disorder"
- Again dramatic changes improving alertness and children's ability to learn; some lost their appetite and could not sleep, some more anxious
- Study was seen as a success and published in the American Journal of Psychiatry . . .
- What to call the new disorder? . . . "Minimal Brain Dysfunction"

A Brief History of ADHD . . .

- 1969 – Conners wants a more reliable tool to measure the symptoms of MBD, develops a Teacher Rating Scale, allows doctors everywhere to diagnosis MBD
- 1971 – Dr. Virginia Douglas describes her work with hyperactive children who had insufficient attention, changed the discourse of the disorder. . .
- 1980 – DSM "Attention Deficit Disorder", accommodates girls with the diagnosis
- 1987 – DSM III "Attention Deficit Hyperactivity Disorder" to count kids (mostly boys) who had hyperactivity as dominant feature
- 1994 – DSM IV keeps "ADHD" but adds subtype "without hyperactivity"

A Brief History of ADHD . . .

- 1994 – Adderall comes to market, had been a weight control drug that a Utah physician was using for children with ADHD who had failed Ritalin
- Many parents were looking for alternative treatments for their children . . .
- NIMH sponsors study to look at the best treatment for ADHD.
- Researchers spent years coming up with the details of the Multimodal Treatment of Children with ADHD or MTA. 14 month trial
- MTA published in 1999 . . .
- Same year a new drug formulation is produced for once a day dosing of methylphenidate – Concerta. . .

Utah Connection . . .

- Keith Conners, PhD

- Born and Raised in Ophir, Utah (near Tooele)
- 1st clinical studies on Ritalin
- Developed the Conner's Rating Scale which was used as the basis for the DSM description of ADHD
- Conner's Rating Scale still used widely today

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ADHD Diagnosis. . .

- DSM V criteria for ADHD, changed in 2013
- Combined Type, Predominantly Inattentive, Predominantly Hyperactive-Impulsive
- Must have symptoms in more than one setting for at least 6 months
- Report from parents, guardians and teachers
- Adolescents may report their symptoms differently; hyperactivity may not be reported or observed as much as with younger children
- Consider other diagnoses when considering ADHD or concurrent disorders. . .
  - Depression, Anxiety, Oppositional Defiant Disorder, conduct disorder, other mood disorders
- Consider risk of abuse . . .risks of not treating. . .
- Rating scales can guide diagnosis . . .

DSM V ADHD Diagnostic Criteria. . .

Inattention – Six or more

Often fails to give close attention to details

Often has trouble holding attention on tasks or play activities.

Often does not seem to listen when spoken to directly.

Often does not follow through on instructions and fails to finish schoolwork, chores, or duties

Often has trouble organizing tasks and activities.

Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time

Often loses things necessary for tasks and activities

Is often easily distracted

Is often forgetful in daily activities.

Hyperactivity/Impulsivity – Six or more

Often fidgets with or taps hands or feet, or squirms in seat.

Often leaves seat in situations when remaining seated is expected.

Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).

Often unable to play or take part in leisure activities quietly.

Is often "on the go" acting as if "driven by a motor".

Often talks excessively.

Often blurts out an answer before a question has been completed.

Often has trouble waiting his/her turn.

Often interrupts or intrudes on others (e.g., butts into conversations or games)

Concerns about Over Diagnosis . . .

- ADHD affects about 9% of children, used to be around 5% . . .most common neurobehavior disorder in childhood
- CDC estimates that it's now up to 11% or more (has been rising over the past 10 years) in certain parts of the country . . .Boys 2x as likely to be diagnosed as girls
- Addiction concerns are real
- High School/College Students . . . Adderall on the rise
- Athletes using stimulants for performance
- Banned by MLB, NFL, NBA, NCAA . . .requires special medical waiver
- Need to be judicious and screen appropriately . . .

ADHD . . .

- Estimate approximately 45% to 85% of children who have ADHD will move into adolescence with the diagnosis
- Approximately 50% to 60% continue to show symptoms into adulthood
- ADHD in childhood is associated with many psychiatric co-morbidities . . .

  -Disruptive Behavior Disorders

  -Addictions

  -Anxiety

  -Depression

  -Social, Educational, Cognitive Difficulties in school

ADHD Treatment. . .

- Large Scale Comparative Treatment Trials Now Guide Treatment Options
  - Multimodal Treatment of ADHD Study
  - Treatment of Adolescent Depression Study (TADS)
  - Pediatric OCD Treatment Study (POTS)
  - Child/Adolescent Anxiety Multimodal Treatment Study (CAMS)

Key Neurotransmitters. . .

- Dopamine - important in the regulation of movement, cognitive processes such as attention and working memory and motivational behavior

  -Main neurotransmitter in reward system

  -Excess Dopamine can cause psychotic symptoms

- Norepinephrine - involved in mediating cardiovascular effects, arousal, concentration, attention, learning and memory

Stimulant Medications

- **Benefits:**
- Improve focus and concentration
- Motivation and drive
- Social interactions
- Academic efficiency and accuracy
- Reduce hyperactivity, impulsivity, and fidgety behaviors

- **Side effects:**
- May cause irritability,
- GI distress & headache
- Dysphoria
- Appetite suppression
- Sleep problems
- Growth and weight concerns
- Possible Hallucinations

ADHD Medication Options

- Established Treatments
  - Stimulants – 1st line
    - Methylphenidate/Amphetamines
  - Atomoxetine – 1st line
  - Alpha-2 agonists – 1st/2nd line
    - Extended release Clonidine/Guanfacine
  - Bupropion – 2nd line
  - Tricyclic Antidepressants – 3rd line, rarely used anymore

Multi-Modal Treatment of ADHD Study

- MTA study: *Arch Gen Psychiatry* 56: 1073-1086, Dec 1999
- 579 children with ADHD-CT; 7-10 yrs; 6 sites; 14 month parallel-design (followed at various intervals up to 16 years after baseline)
- 4 different treatment groups:
  - Medication management (immediate release methylphenidate)
  - Intensive behavior treatment (parent, school, child components)
  - Methylphenidate + Behavior Treatment
  - "Usual" community care – parents sought whatever treatment they could find. . .
  - In the study, average dose of methylphenidate was 30 mg/day

Multi-Modal Treatment of ADHD Study

- <u>What is Behavior Treatment?</u>

- Modifications in the physical and social environment
- Positive reinforcement, time-outs, withdrawing rewards or privileges or token economy
- Parent-child behavioral therapy works at improving parent-child relationships via improved parenting techniques
- Behavioral interventions are most effective if parents understand the principles of behavior therapy and there is consistency
- Teachers can play a large role as well. . .

ADHD Treatment. . .

- MTA study:
  - All 4 groups showed sizable reduction in symptoms over time
  - *Core ADHD symptoms*: Combination group and med-only groups had significantly greater improvement than those given just intensive behavioral treatment or "usual" community care - Ritalin, but likely fewer visits
  - The children receiving medication management, either alone or in combination with behavior therapy, generally showed the greatest improvement.

ADHD Treatment. . .

- MTA study: cont'd.
- Combined behavioral intervention and stimulant medication--(multimodal treatment), yielded no statistically significantly greater benefits than medication management "alone" for the core symptoms of ADHD

- The children who received intensive medication treatment (seven days a week) over the 14 month study grew 4.25 cm (1.7 inches) on average and gained 1.64 kg (3.6 lbs) on average
- Children who received behavior therapy only (no medication) grew 6.19 cm (2.5 inches) on average and gained 4.53 kg (10 lbs).

ADHD Treatment. . .

- MTA study: cont'd.
  - *Non-ADHD symptoms*: (social skills, parent-child relations, oppositional-aggressive behavior, internalizing symptoms, academic achievement)
    - The 3 MTA-delivered treatments were very similar, with the combined treatment arm being consistently superior to UCC.
    - Behavior component important in reducing these non-core ADHD symptoms
    - Combined treatment kids took lower doses of medications than those in the med only group which is noteworthy

ADHD Treatment. . .

- MTA study: 2 year follow-up (*PEDIATRICS*,113 (4); April 2004)
  - Consistent use of stimulant medication was associated with maintenance of effectiveness but continued “mild growth suppression” (1 cm per year over 2 years).

MTA at 8 years

-Treatment effects wore off over time when the intensity of treatment was relaxed – still improved however from baseline

-Approximately 62% of those taking medications at the 14 month mark had stopped at the 8 yr mark . . .

-The patient's initial behavioral symptoms and severity of ADHD better predicted future outcome regardless of the initial type of treatment

-Patients with relative sociodemographic and behavior advantage seemed to have a better trajectory

-Children with ADHD did poorer than 91% their peers without ADHD in the variables tested

- Test scores, teacher ratings, higher rate of grade retention, delinquency, arrest and psychiatric hospitalizations were more common

-Average daily dose at the 8 yr mark 40 mg/day

-JAACAP. 2009;48(5):484-500

Pre-School ADHD Treatment Study (PATS), 2006

- 1st Long-term (70 weeks), large-scale study designed to determine the safety and effectiveness of treating preschoolers who have ADHD
- Low doses of methylphenidate “effective and safe” however, children this age are more sensitive to side effects compared to older children
- Doses varied from 3.75 mg three times daily to 22.5 mg per day; average was 14 mg per day
- Children grew about half an inch less in height and weighed about 3 pounds less than expected
- ** Recommend behavior therapy rather than medication as the initial treatment for pre-school aged children, with parents and/or teachers support

Methylphenidate Formulations

- Methylphenidate/Ritalin (IR, 3-5 hour duration, usually dosed 2-3 times per day)
- Methylphenidate ER (Concerta, 20% IR, 80% continuous release; 10-12 hour duration, do not crush or break)
- Methylphenidate ER (Metadate CD, Biphasic release; 30% IR/70% ER; similar to 2 IR doses given 2 hrs apart; duration 6-9 hours; may sprinkle)
- Methylphenidate ER (Metadate ER, delayed onset with continuous release over 3-8 hours; may need twice daily dosing)
- Ritalin LA (biphasic release; 50% IR/50% ER; similar to 2 IR doses given 3 hours apart; 6-9 hrs duration; may sprinkle)
- Methylphenidate Transdermal (Daytrana; apply 1 patch daily for 9 hrs; 10 hr duration; apply 2 hours before desired effect; lasts 2-3 hours after patch is removed; **be aware of skin color loss, not reversible**

Methylphenidate Formulations

- Aptensio XR (biphasic release, 40% IR/60% ER, 12 hour duration, may sprinkle; do not crush or chew)
- Methylin (IR, comes in tablet, chewable and oral solution)
- Quillichew ER (chewable, biphasic release, 30%IR 70% ER; 8 hour duration)
- Quillivant XR (extended release oral solution, 20% IR/80% ER; 5mg/ml; 12 hour duration) – good if you need to dial in an exact dose
- Focalin (Dexmethylphenidate; 4-5 hour duration; start at 50% of methylphenidate daily dose, more potent)
- Focalin XR (50/50 IR/ER multi-phase release; 8-12 hour duration; convert from IR use same total daily dose)

Amphetamine Formulations

- Adderall is a combination of 4 different amphetamine salts
  - 1/4 dextroamphetamine saccharate
  - 1/4 dextroamphetamine sulfate
  - 1/4 (racemic) amphetamine aspartate monohydrate
  - 1/4 (racemic) amphetamine sulfate
  - Adderall (IR, 2-3 times per day dosing; 5-8 hour duration; divide doses at 4-6 hour intervals)
  - Adderall XR (10-12 hour duration; convert from IR to ER at same total daily dose)
  - May sprinkle

Adderall XR Warning

•FDA warning in 2005, sudden deaths reported; Health Canada suspended the medication

•FDA evaluated the cases and advises that children should not take Adderall if they have:

- A heart defect
- Other heart problems, including high blood pressure, and heart or blood vessel disease
- Overactive thyroid
- Glaucoma
- A history of drug abuse
- Depression and are taking, a Monoamine Oxidase Inhibitor (MAOI)

Managing Side Effects

- Consider Periactin (cyproheptadine) for persistent insomnia or anorexia.
- Monitor cardiac side effects closely
- Consider an alpha-2 agonists for significant insomnia, residual ADHD symptoms, aggressive/disruptive behaviors, or tics.
- Tics can be a side effect, would cautiously still use stimulants with patients who have preexisting tics or Tourette Syndrome.
- Addiction: small but real risk. Greater risk of misusing drugs if ADHD is not treated. Treating may help prevent self-medicating

Amphetamine Formulations

- **Vyvanse** (Lisdexamphetamine)
- **Prodrug** – chemical compound consists of dextroamphetamine coupled with the amino acid L-lysine. Lisdexamphetamine is inactive until the lysine portion of the molecule is cleaved.
- After oral ingestion, Lisdexamphetamine is broken down by enzymes to L-lysine and dextroamphetamine.
- The conversion of Lisdexamphetamine to dextroamphetamine is not affected by gastrointestinal pH level. Duration 10-12 hours
- - Also approved for binge eating disorder in adults

Amphetamine Formulations

- Adzenys XR ODT (once daily dextroamphetamine-amphetamine, oral disintegrating tablet; 50% IR/50% ER; first and only FDA approved ER orally disintegrating tablet for ADHD)
- Dyanavel XR (once daily ER amphetamine based oral suspension; biphasic release 50% IR/50% ER; duration of up to 13 hours)
- Mydayis (once daily dextroamphetamine/amphetamine) – for 13 years and over, half life 9-14 hours

Non-Stimulant ADHD Treatments

- Atomoxetine - FDA approved for 6 years and older
  - Potent Norepinephrine reuptake inhibitor
    - highly selective
    - inhibits presynaptic NE transporter
- Clonidine ER - FDA approved for ADHD 6-17 yrs old in ER form (Kapvay); twice daily dosing
  - Alpha-2 adrenergic agonist
  - Decreases sympathetic tone peripherally
  - Increases release of norepinephrine in the pre-frontal cortex
  - Helps with hyperactivity/impulsivity, aggression, insomnia
  - May help with co-morbid tic disorders or Tourette's
  - Side effects often limit its usefulness - especially sedation, dizziness
  - Stop gradually, monitor for rebound hypertension

Non-Stimulant ADHD Treatments

- Guanfacine ER
  - FDA approved for ADHD in the ER form (Intuniv); once daily dosing
  - Similar mechanism of action as Clonidine, but more selective targeting alpha 2A receptors
  - Less sedating and longer duration compared to Clonidine
  - Can help with co-morbid tic disorders or Tourette's
  - Often helpful in the early/late afternoon and evening as stimulant medication is wearing off for irritable/anxious moods and impulsivity
  - Taper gradually to avoid rebound hypertension

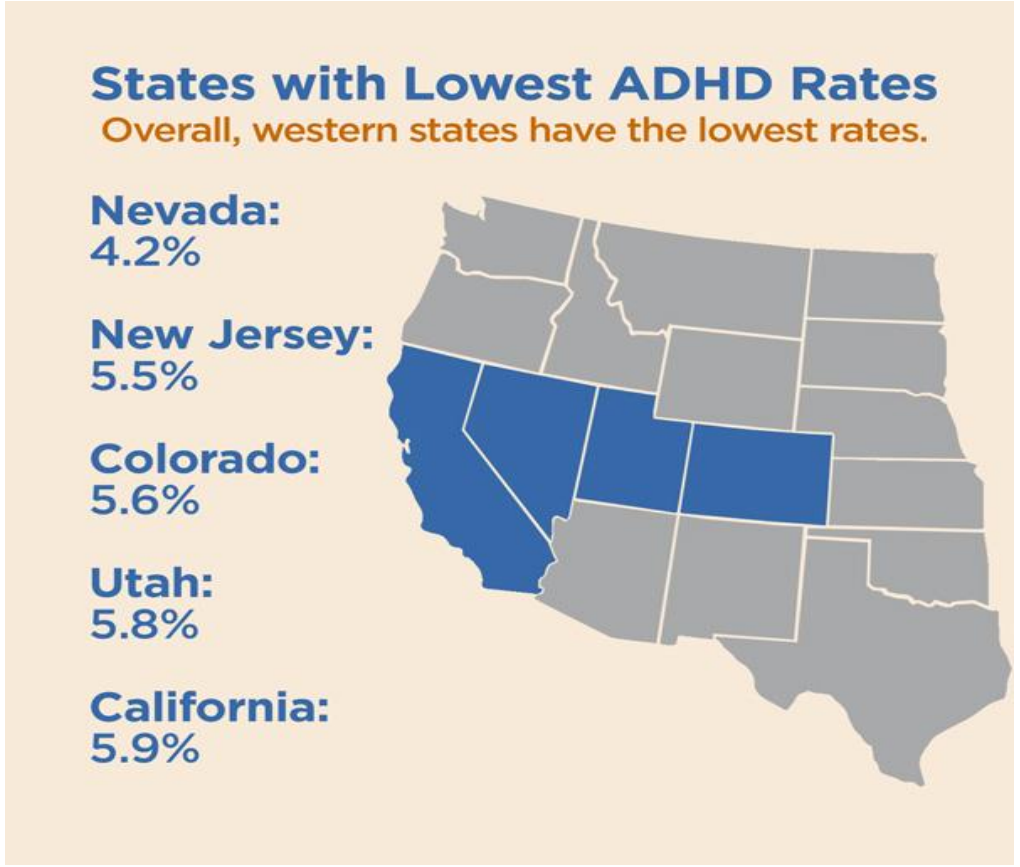
Utah ADHD by the Numbers . . .

- In 2007, 7.2% of US children and 4.8% of children in Utah had ADHD, by parent report.
- **Utah ranked 45th highest**

- In 2011, 8.8% of US children and 5.8% of children in Utah had ADHD, by parent report.
- **Utah ranked 48th highest**

- In 2007, 4.8% of US children were taking ADHD medications
- 3.1% of children in Utah, which ranked **46th highest**

- In 2011, 6.1% of US children were taking ADHD medications
- 3.5% of children in Utah which ranked **47th highest**



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Thank U

Questions/Comments?