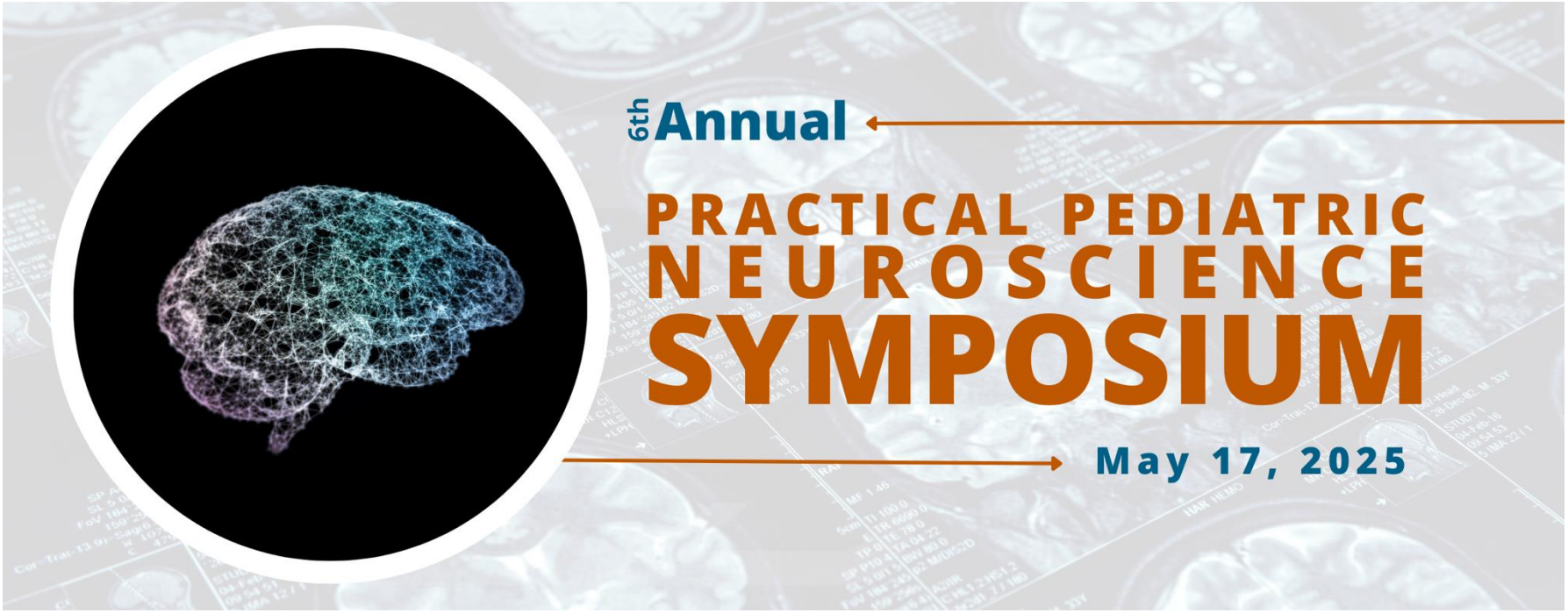

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ADHD Medication Management

6th Annual Pediatric Neurosciences Symposium

Stephen Deputy, MD, FCNS

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Stephen Deputy, MD

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Background of ADHD

Sir Alexander Crichton, a Scottish physician who practiced in western Europe in the late 18th century, provides some of the earliest descriptions of attention deficit disorder (ADD). In his chapter titled “On Attention and Diseases,” Crichton writes,

- *"It may be either born with a person, or it may be the effect of accidental diseases.”*
- *“When born with a person it becomes evident at a very early period of life and renders him incapable of attending with constancy to any one object of education.”*
- *“It is generally diminished with age.”*
- *"The barking of dogs, an ill-tuned organ, or the scolding of women, are sufficient to distract patients of this description to such a degree, as almost approaches to the nature of delirium.”*

Chrichton, 1798

Atten Defic Hyperact Disord. 2010

Background of ADHD

Sir George Frederick Still ("Stills disease") in the early 20th century described ADHD as "… children with a defect of moral control" but without a "general impairment of intellect."

- He further subcategorized two populations of children with this condition as those having underlying physical disease and those who do not.
- This differentiation became the basis for later concepts of brain damage, minimal cerebral dysfunction, and hyperactivity.
- Still also recognized the male:female ratio of children with ADHD as being 3:1. He also recognized this group of children as having the onset of symptoms before the age of 7 years.

Atten Defic Hyperact Disord. 2010

DSM-V Criteria

- A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning
- Six or more symptoms of inattentiveness **and/or** six or more symptoms of hyperactivity/impulsivity (five or more if age 17 or older)
- Symptoms present before the age of 12 years.
- Symptoms present in two or more settings.
- Symptoms interfere with social, school, or work functioning.
- The symptoms are not solely a manifestation of or better explained by other disorders.
- Specify if combined, predominantly inattentive, predominantly hyperactive-impulsive, or unspecified presentation.

National Library of Medicine 2016

Background of ADHD

Epidemiology of ADHD

- 9.4% of children in the US have ever had a diagnosis of ADHD. Mean age of diagnosis is 7 years.
- Boys are more than twice as likely as girls to receive a diagnosis of ADHD, likely due to disruptions caused by hyperactive behaviors.
- Boys tend to have comorbid externalizing behaviors, and girls tend to have comorbid internalizing conditions.
- ADHD is the most common neurobehavioral disorder of childhood.
- The number of children with this condition is far greater than can be managed by the mental health system. **There is evidence that appropriate diagnosis and management can be accomplished in the primary care setting for children and adolescents.**

Pediatrics 2019

Treatment of ADHD (AAP Guidelines)

- Parent training in behavioral management (PTBM) and/or behavioral classroom interventions are the recommended primary intervention for preschool-aged children with ADHD or with ADHD-like behaviors. (*Grade A*)
- Methylphenidate (MPH) may be considered if behavioral interventions do not provide significant improvement and there is moderate-to-severe continued disturbance of functioning in 4- to 5-year-olds. (*Grade B*)
- For children (6-12 years) with ADHD, **primary care clinicians (PCCs) should prescribe FDA-approved medications for ADHD**, along with PTBM and/or behavioral classroom intervention. (*Grade A*)
- For adolescents (12-18 years) with ADHD, the **PCC should prescribe FDA-approved medications for ADHD** with the adolescent's assent. (*Grade A*)
- Educational interventions and individualized instructional supports are a necessary part of any treatment plan and often include an IEP or 504 plan. (*Grade A*)

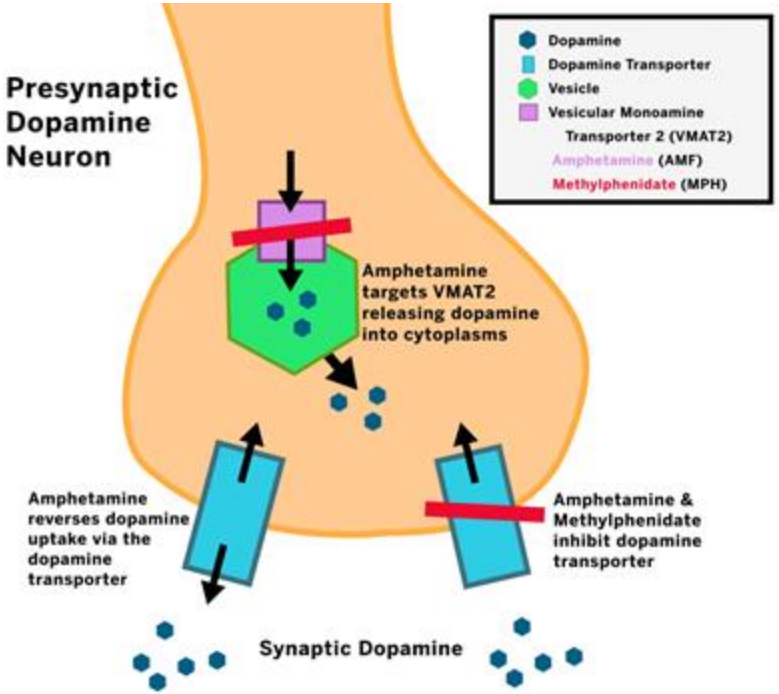
Pediatrics 2019

Treatment of ADHD

- The first medication treatment for ADHD was in 1937 when Charles Bradley reported a positive effect of Benzedrine on institutionalized children with “emotional problems” and major difficulties with learning and behavior. (Bradley 1937)
- Benzedrine is the first brand name for amphetamine.
- By the late 1940s it was widely recognized that amphetamine derivatives were successful for improving cognition, depression, and weight loss through appetite suppression.
- Benzedrine was widely used as a recreational drug from the 1930s to the 1960s before the FDA stepped in.
- It is a schedule II drug (defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.).

Steinbuchel 2002

Mechanism of Action for Stimulants



Amphetamines and MPH

- Both increase presynaptic cytosolic DA by VMAT2 interactions and by MAO inhibition
- Increase synaptic cleft DA by inhibition of DAT
- Increase synaptic cleft NE by inhibition of NET

Amphetamines

- Promote presynaptic release of DA and NE through reversal of DAT and NET

Think of MPH as a reuptake blocker and amphetamine as both a reuptake blocker and releaser of DA and NE.

Stimulant Medications

- Approximately 75% of children with ADHD will have at least a 50% reduction in the severity of core symptoms along with a noticeable improvement in their academic performance.
- Stimulant medications do not directly improve executive function skills (consider recommendation for family to visit CHADD (Children and Adults with ADD) website for more information/resources for managing ADHD).

<u>Potential Side Effects of Stimulants</u>

- Loss of appetite
- Insomnia
- Mood changes and irritability
- Tachycardia and hypertension
- Controversy surrounds reduced height in children

Stimulant Medications

Management of side effects of stimulant medications

1. Anorexia/weight loss
    1. Drug holidays
    2. Weekly weight chart at home, long-term weight monitoring by PCP
    3. Lower dose or change “class” of stimulants
    4. Cyproheptadine
2. Insomnia
    1. Take a good pre-medication sleep history as many children with ADHD combined type have insomnia at baseline.
    2. Determine time medication wears off
    3. Encourage good sleep hygiene +/- melatonin
3. Emotional blunting/irritability
    1. Peak side effects
    2. Lower dose or change “class” of stimulants
4. Tachycardia (check HR on vs off medication)

Remember that the effects of stimulants wear off by the end of the day. A trial of holding the stimulant may sort out if the perceived adverse side effect is due to the stimulant or not.

What stimulant medication to use?

Table 1. Stimulant Medications

Methylphenidate (MPH) for ADHD					
Medication	**Starting Dose**	**How Supplied**	**Dosage Form**	**Duration of Medication Effects**	**Given how many times a day?**
Adhansia XR	25 mg	25, 35, 45, 55, 70, 85 mg	capsules	Up to 16 hours	Once
Aptensio XR	10 mg	10, 15, 20, 30, 40, 50, 60 mg	capsules	12 hours	Once
Azstarys XR	26.1/5.2 mg	26.1/5.2, 39.2/7.8, 52.3/10.4 mg	capsules	12 hours	Once
Concerta	18 mg	18, 27, 36, 54 mg	capsules	12 hours	Once
Contempla XR	8.6 mg	8.6, 17.3, 25.9 mg	disintegrating tablets	12 hours	Once
Daytrana	10 mg	10, 15, 20, 30 mg	patch	6–16 hours	Once
Focalin	2.5 mg	2.5, 5, 10 mg	tablets	4–5 hours	Two to three times
Focalin XR	5 mg	5, 10, 15, 20 mg	capsules	10–12 hours	Once
Jornay PM	20 mg	20, 40, 60, 80, 100 mg	delayed-release capsules	12 hours	Once
Metadate CD	20 mg	10, 20, 30, 40, 50, 60 mg	capsules	8 hours	Once
Quillivant	<10 mg	25 mg	suspension	12 hours	Once
Quillichew	<10 mg	20, 30, 40 mg	chewable tablets	8 hours	Once
Ritalin IR	5 mg	5, 10, 20 mg	tablets	3–4 hours	Two to four times
Ritalin LA	20 mg	10, 20, 30, 40 mg	capsules	8 hours	Once
Amphetamine (AMPH) for ADHD					
Medication	**Starting Dose**	**How Supplied**	**Dosage Form**	**Duration of Medication Effects**	**Given how many times a day?**
Adderall	2.5–5 mg	5–30 mg	tablets	6 hours	Once to twice
Adderall XR	2.5–5 mg	5, 10, 15, 20, 25, 30 mg	capsules	12 hours	Once
Adzenys XR	6.3–12.5 mg	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg	disintegrating tablets	12 hours	Once
Dexedrine Spansule	5 mg	5, 10, 15 mg	spansules	6 hours	Once to twice
Dexedrine Tablets	2.5–5 mg	5, 10, 15, 20 mg	capsules	3–5 hours	Two to three
Dyanavel XR	2.5–5 mg	2.5 mg	suspension	13 hours	Once
Evekeo	2.5–5 mg	5, 10 mg	tablets	3–5 hours	Two to three
Mydayis	12.5 mg	25, 50 mg	capsules	Up to 16 hours	Once
Vyvanse	30 mg	20, 30, 40, 50, 60, 70 mg	capsules	12–14 hours	Once

AACAP ADHD Parents' Medication Guide

Stimulant Medication

- Short-acting (immediate release) vs long-acting (delayed release)
  - Shorter duration of action (3-4 hrs) requires multiple dosing, including in school administration.
  - Short-acting is more prone to diversion for recreational purposes (can be crushed for injection, inhalation, smoking).
  - Short-acting is sometimes useful to help with wearing off of a long-duration stimulant or when additional duration of efficacy is needed.
  - Otherwise, use only delayed-release stimulants.
- Age of child
  - Per the FDA, MPH preparations are approved for children 6 years and older, though guidelines recommend its use in children 4-6 years.
  - Per the FDA, amphetamines are approved for children aged 3-5 years, but there is limited trial evidence in this age group.
  - Liquid preparations, opening delayed-release capsules
- Types (“classes”) of stimulants
  - Amphetamine-based stimulants
  - Methylphenidate-based stimulants
  - Dexmethylphenidate-based stimulants
- Insurance denials

Stimulant Medication Treatment Strategies

- No practice parameters or evidence-based medicine guidance available
- For children with combined type or predominantly hyperactive-impulsive type ADHD
  - Amphetamine preparations are more potent than MPH preparations
  - It takes a higher dose or a more potent stimulant to “capture” hyperactivity-impulsivity symptoms than inattentive symptoms
  - Recommend starting with an amphetamine-based stimulant for ADHD combined type
- For children with predominantly inattentive type ADHD
  - Generally, do not need as high of dose or potency of stimulant for inattentiveness symptoms
  - MPH or dexmethylphenidate
  - Fewer side effects than amphetamine-based stimulants

Stimulant Medication Treatment Strategies

- Starting dosage/changing “class” of stimulants
  - Start low and titrate upwards to effect and duration of effect
  - If reach peak side effects (emotional blunting or crashing and burning when medication is wearing off) before efficacy or duration goals met, need to try another stimulant in same class or move down in class
  - If efficacy remains a problem despite dose escalations, move up in class
  - If side effects are a problem, then move down in class
  - Consider cyproheptadine (2 mg in a.m. and 2 mg in the afternoon) for poor weight gain

Non-Stimulant Medications

- Consider the use of non-stimulant medications (NSM) for children who cannot tolerate stimulant medications due to:
  - Ongoing anorexia despite medication holidays, use of MPH or DexMPH, trial of cyproheptadine, addition of high-calorie/protein shakes
  - Increased irritability or anxiety with stimulants
  - Targeting hyperactive and aggressive behaviors, especially in younger children
  - Targeting anxiety and ADHD in patients with tic disorders (note, evidence does not support stimulants cause or exacerbate tics!)
- Potential side effects from NSMs
  - Sedation (start low and go slow) and dizziness (alpha-2 agonists)
  - Insomnia, headaches, nausea, irritability/aggression (atomoxetine, viloxazine)
- Four NSMs are approved by FDA
  - Selective presynaptic NE reuptake inhibitors
    - Atomoxetine (Strattera)
    - Viloxazine (Qelbree)
  - Alpha-2 agonists
    - Kapvay (extended-release clonidine)
    - Intuniv (extended-release guanfacine)

My Approach to Pharmacological Management of ADHD

- Children between 3 and 6 years:
  - Use guanfacine (0.5 mg bid up to 1.5 mg bid) for hyperactive and impulsive behavior and consider using clonidine (0.1 to 0.3 mg qHS) for insomnia. Start with sleep first!
- ADHD combined type:
  - Start with an extended-release amphetamine stimulant. I start with lisdexamfetamine but will move to extended-release amphetamine/dextroamphetamine salts if I need better efficacy and vice versa if side effects are a problem (insurance may dictate what is available to use).
  - Determine duration of action and amount of time needed to get hyperactivity under control (during school hours for younger children, through school hours and into homework time for older children).
  - The duration of control of hyperactivity dictates the duration of control for inattentiveness symptoms.
  - Hyperactivity and impulsivity generally improve with age and development of better internal self-regulation, though inattentiveness remains.
- Predominantly inattentive type of ADHD:
  - Start with extended-release dexmethylphenidate and titrate to duration.
  - Duration can be determined by return of appetite (if there is anorexia) or by efficiency with homework after school.
  - If efficacy remains a problem, change to extended-release MPH preparation.

My Approach to Pharmacological Management of ADHD

- For all children with ADHD, think about medication management as a “bridge” to help with symptom relief while ongoing efforts to improve executive function skills (organization, time management, prioritization, structure of homework time, written notes, weekly calendar, etc.) continue.
- Consider not starting stimulants at the beginning of the school year in adolescents to see if the child can manage and compensate for their inattentiveness through improved executive function skills.
- Stimulants can be stopped and started at will. There is low risk of addiction, though tolerance may develop in some. Consider giving 7 days per week when starting to make direct observations at home. Continue to use 7 days per week (especially in combined type ADHD) unless there are weight gain concerns. Consider school days only for inattentive subtype.
- Start with low-dose extended-release stimulants and escalate dose to efficacy and duration of efficacy needed. Stop if reach peak effects of emotional blunting (looking like a zombie or “crash and burn” as the medication wears off). Move to a lower “class” of stimulants.

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Questions?

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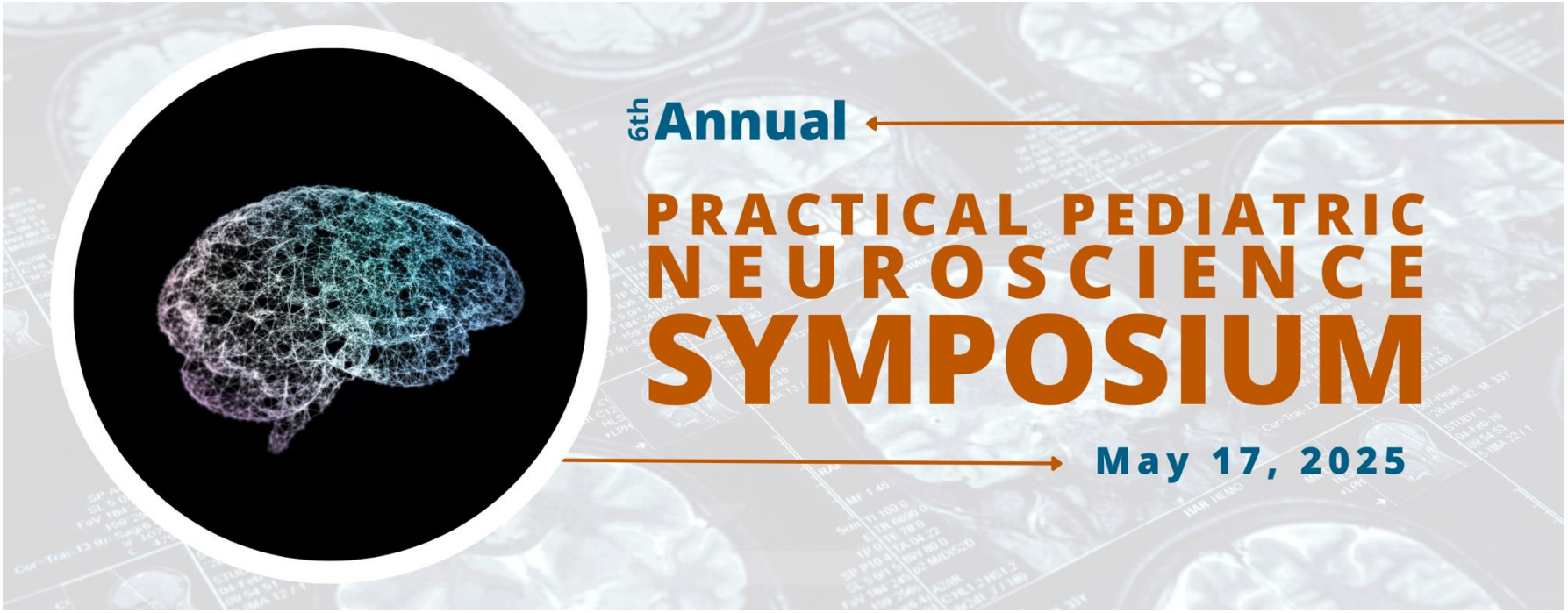

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