

Medication Management of ADHD in Pediatrics

Andrea Chouinard, PharmD, AE-C
Pediatric Pharmacist
Chickasaw Nation Medical Center

Disclosure

- Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months
- I have no relevant financial relationships or affiliations with commercial interests to disclose

Learning Objectives

- At the completion of this activity, pharmacists will be able to:
 - Review guidelines on diagnosis and treatment of Attention-Deficit/Hyperactivity Disorder
 - Identify pharmacologic and non-pharmacologic treatment options and appropriate place in therapy
 - Describe pharmacist's role for providing education, training and counseling to providers, patients and caregivers
 - Discuss opportunities to enhance medication adherence

Pre-Assessment Question

1. Which of the following has the greatest impact on determining susceptibility to ADHD?
 - a) Genetics
 - b) Parenting
 - c) Social environment
 - d) Education System
 - e) Divorce

Pre-Assessment Question

2. Which of the following is recommended for first-line treatment for preschoolers according to the AAP guidelines?
- a) Adderall
 - b) Methylphenidate
 - c) Behavioral therapy
 - d) Referral to psychiatrist
 - e) Strattera

Pre-Assessment Question

3. True or False: The metabolism of methylphenidate is slower in preschool children than in older children and adolescents?
- a) True
 - b) False

Pre-Assessment Question

4. David, a 9 year old boy, is currently taking Amphetamine Salts 10mg tablets. He takes 1 tablet in the morning and 1 tablet at lunch. Mother is requesting him to be switched to long acting Adderall. What should his starting daily dose of Adderall XR be?
- a) 5mg
 - b) 10mg
 - c) 15mg
 - d) 20mg
 - e) 25mg

Epidemiology

Attention deficit hyperactivity disorder (ADHD)

is a mental disorder that most often occurs in children.



6.4 Million American children ages 4-17 have been diagnosed with ADHD.

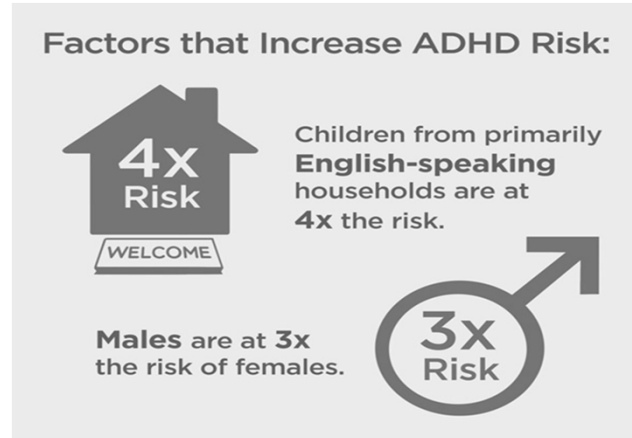
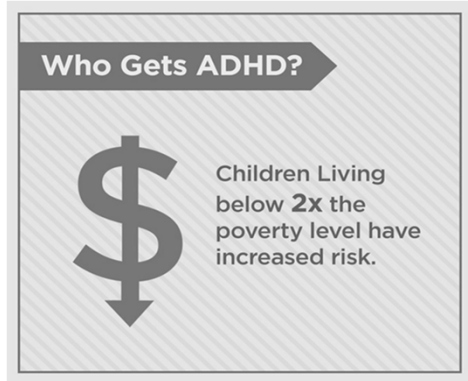
Average age of ADHD diagnosis: **7**

Age when symptoms of ADHD typically first appear: **3-6**

6.1% of American children are being treated for ADHD with medication.

42% increase in ADHD diagnoses over the past 8 years

Demographics



Holland, K., Riley, E., & Krucik, G. T. (2017, October 24). ADHD Numbers: Facts, Statistics, and You. Retrieved from <https://www.addrc.org/adhd-numbers-facts-statistics-and-you/>

What is ADHD?

Key Symptoms

- Inattention
- Hyperactivity
- Impulsivity





ADHD Classifications

- Combined presentation
- Predominantly inattentive
- Predominantly hyperactive/impulsive


Symptoms of ADHD

Boys and girls display very different ADHD symptoms.

Boys' symptoms are obvious and "external":

- Impulsivity or "acting out" 
- Hyperactivity, such as running and hitting 
- Lack of focus, including inattentiveness 
- Physical aggression 

Girls' symptoms are less obvious, and more "internal":

- Being withdrawn 
- Low self-esteem and anxiety
- Impairment in attention that may lead to difficulty with academic achievement
- Inattentiveness or a tendency to "daydream"
- Verbal aggression: teasing, taunting, or namecalling

Holland, K., Riley, E., & Krucik, G. T. (2017, October 24). ADHD Numbers: Facts, Statistics, and You. Retrieved from <https://www.addrc.org/adhd-numbers-facts-statistics-and-you/>

DSM-5 Diagnostic Criteria

Inattention	Hyperactivity/Impulsivity
Often fails to give close attention to details or makes careless mistakes	Often fidgets with or taps hands/feet or squirms in seat
Often has difficulty sustaining attention in tasks or play	Often leaves seat in situations when remaining in seat is expected
Often does not seem to listen when spoke to directly	Often runs about or climbs in situations where it is inappropriate
Often does not follow through on instructions and may fail to finish tasks	Often unable to play or engage in leisure activities quietly
Often has difficulty organizing tasks and activities	Is often "on the go" acting as if "driven by a motor"
Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort	Often talks excessively
Often loses things necessary for tasks or activities	Often blurts out answer before a question has been completed
Is often easily distracted	Often has difficulty waiting his/her turn
Is often forgetful in daily activities	Often interrupts or intrudes on others

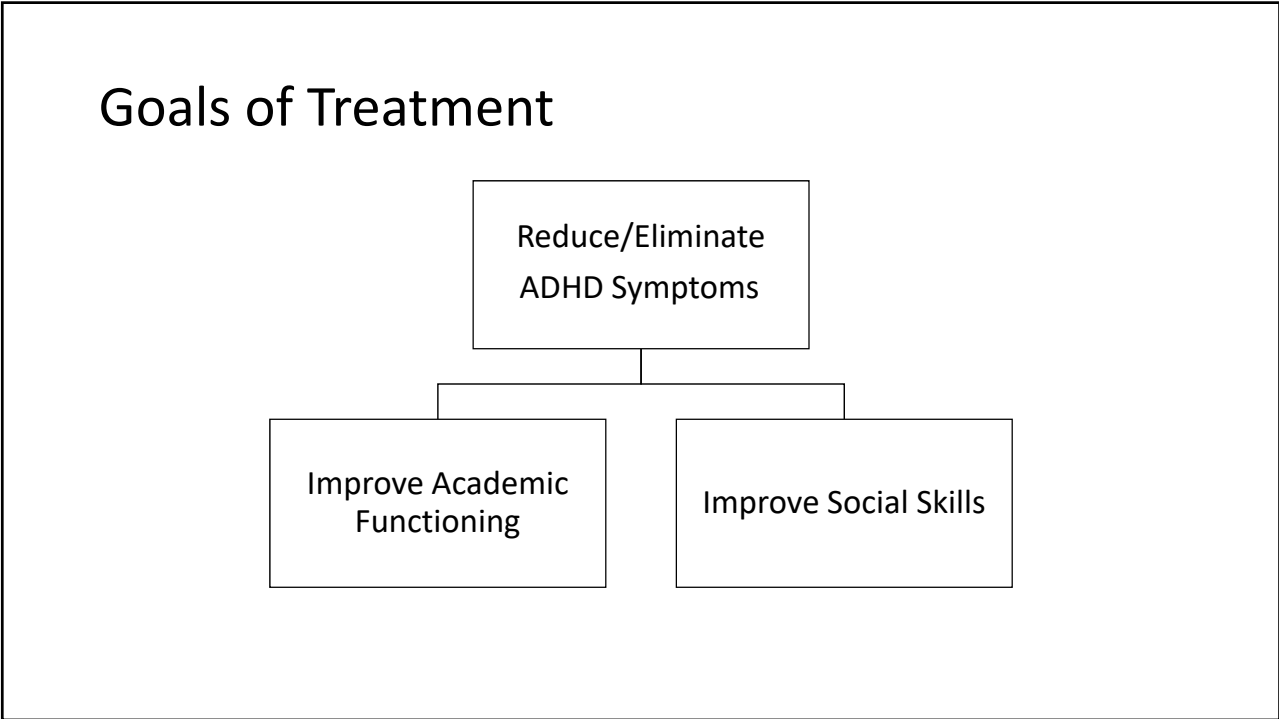
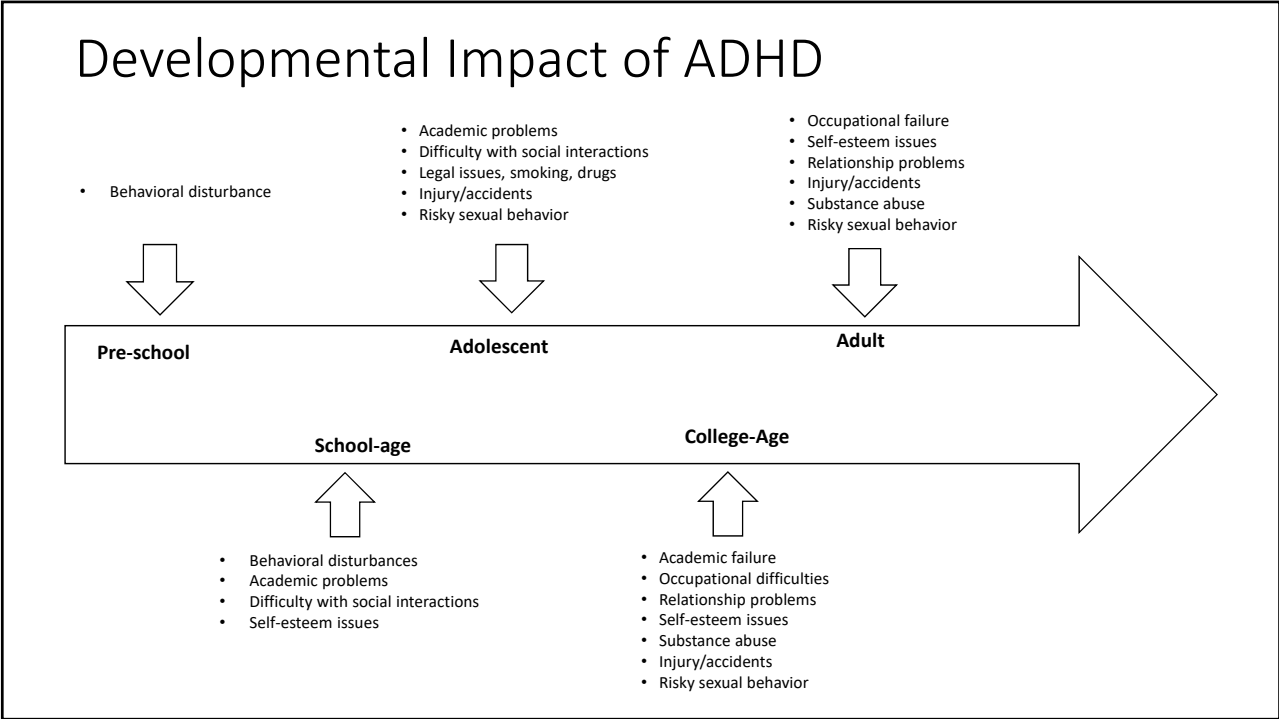
DSM-5 Criteria

- 6 or more symptoms for children up to 16 years of age
- 5 or more symptoms for adolescents 17 years and older and adults
- Symptoms must be present for at least 6 months

Etiology

- Genetics
 - High heritability
- Neurobiological
 - Perinatal stress and low birth weight
 - Severe early deprivation
 - Traumatic brain injury (TBI)
 - Prenatal exposure to alcohol and tobacco
 - Exposure to environmental toxins, such as levels of lead, at a young age
- Environmental
 - Diet?





Guideline Recommendations

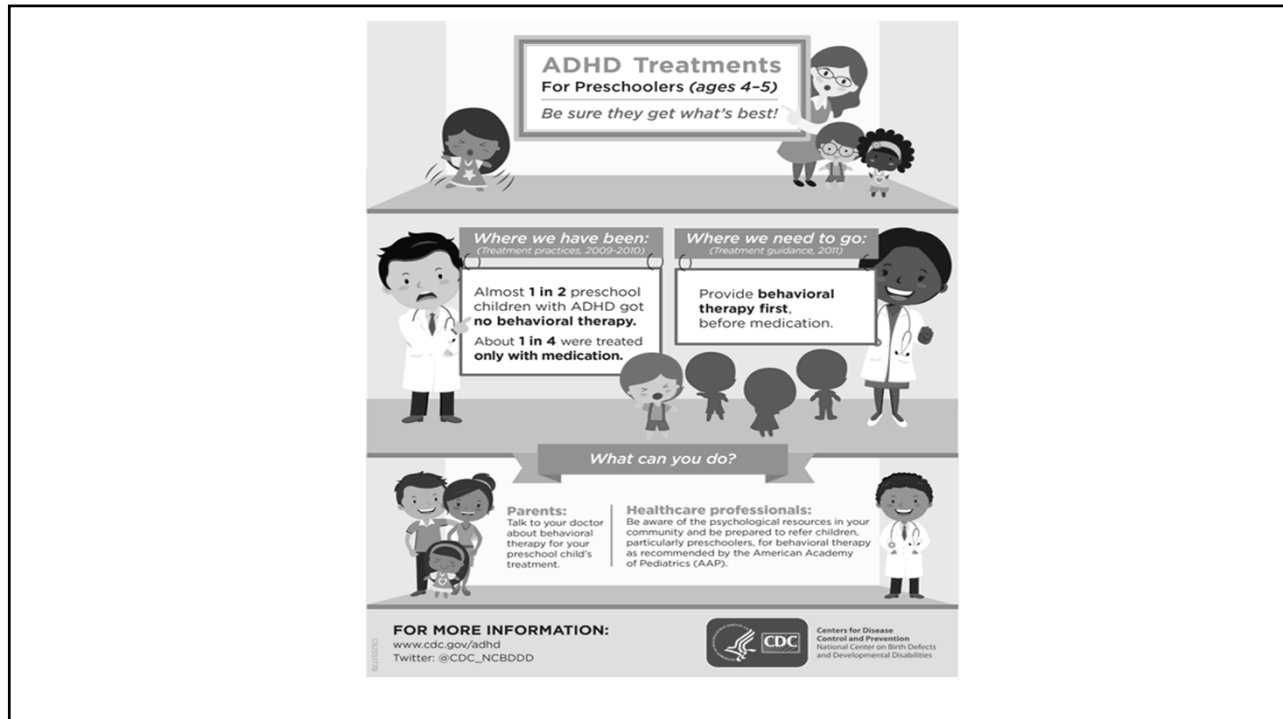
AAP – Clinical Practice Guideline

- Initiate evaluation for ADHD in children 4-18 years of age if behavior or academic problems and ADHD symptoms
- Determine if DSM criteria are met in more than one setting (teacher questionnaires)
- Rule out other causes
- Assess for co-existing conditions
 - Emotional/Behavioral (anxiety, depression, ODD)
 - Developmental (learning, language, etc.)
 - Physical (sleep apnea, tics, etc.)

Guideline Recommendations Cont'd

AAP – Clinical Practice Guideline for Preschoolers

- Addresses evaluation and management of 4 and 5 year olds with ADHD symptoms
- **First line treatment:** Evidence-based parent and/or teacher-administered behavior therapy
- May move to second line if behavior interventions do not provide significant improvement
- Only second-line treatment recommended: Methylphenidate



Guideline Recommendations Cont'd

AAP – Clinical Practice Guideline

- **Preschool aged children with ADHD (age 4-5)**
 - 1st line: Evidence based behavior therapy
 - Methylphenidate if behavior interventions insufficient or moderate to severe continued disturbance in child's function
 - If no satisfactory response, review diagnosis and consider behavioral therapy and/or use of non-FDA approved medications
- **Elementary school aged children (age 6-11)**
 - 1st line: FDA-approved medications for ADHD - strong evidence for stimulants and/or
 - Parent and/or teacher administered behavior therapy
 - Evidence weaker for non-stimulant medication
- **Adolescents (12-18 years)**
 - 1st line: FDA-approved medications for ADHD with adolescent agreement
 - May prescribe behavior therapy

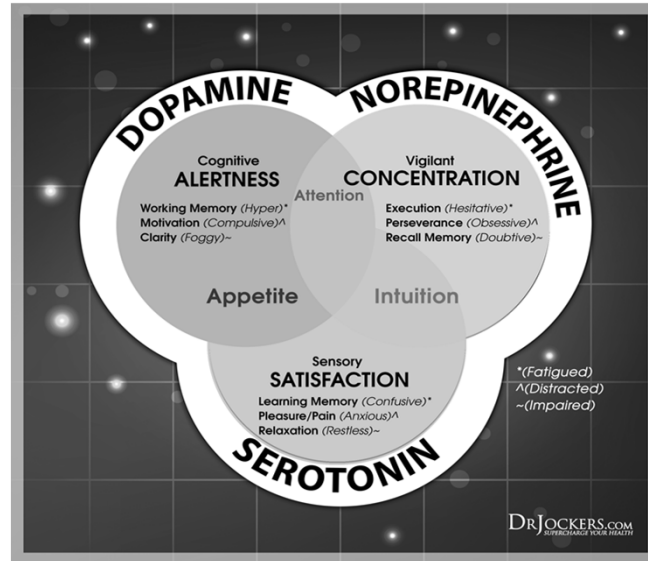
ADHD Medications

- Two Classes of Medication
 1. Stimulants
 2. Non-stimulants
 - Selective Norepinephrine Reuptake Inhibitor
 - Alpha Adrenergic Agonists

Why Do Doctors Stimulate Hyper Kids?

<https://www.youtube.com/watch?v=Fh2ZGAlpkug>

Neurotransmitter effect on ADHD



Stimulants

- Impact the dopaminergic and noradrenergic systems
- MOA is not completely understood
 - Thought to result from the presynaptic blockade of the re-uptake of catecholamines (dopamine and norepinephrine) which prevents their degradation
 - Amphetamine compounds increase the release of catecholamines
 - Specifically, affect dopamine and NE levels in the brainstem, midbrain and frontal cortex

Pharmacokinetics

- Rapid absorption
- Low plasma protein binding
- Rapid extracellular metabolism
- Absorption and bioavailability may increase after a meal

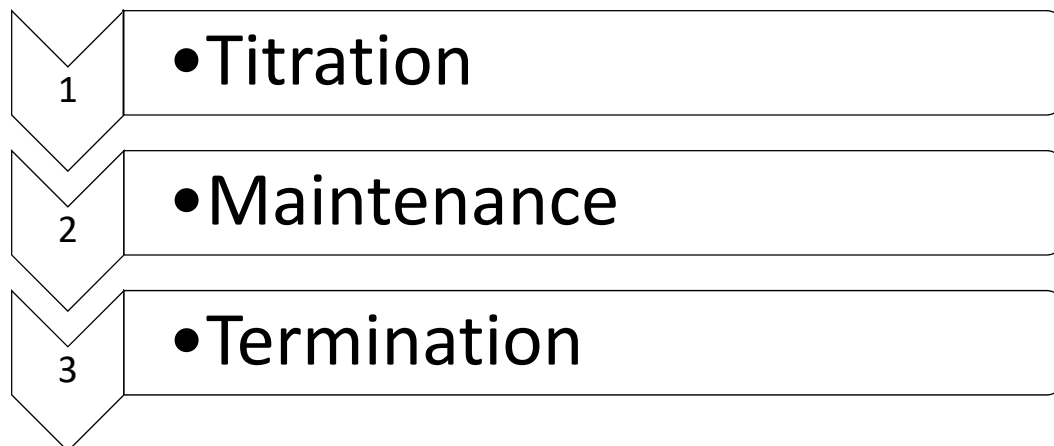
Adverse Drug Reactions

- Feeling restless and jittery
- Difficulty sleeping
- Loss of appetite
- Headaches
- Upset stomach
- Irritability, mood swings
- Depression
- Dizziness
- Racing heartbeat
- Tics

FDA-Approved ADHD Medication Table

Stimulants		
Class	Trade Name	Generic Name
<i>Amphetamines</i>	Adderall	mixed amphetamine salts
	Adderall XR	extended release mixed amphetamine salts
	Dexedrine	dextroamphetamine
	Dexedrine Spansule	dextroamphetamine
	Vyvanse	Lisdexamfetamine (extended release)
<i>Methylphenidate</i>	Concerta	methylphenidate
	Daytrana	methylphenidate (patch)
	Focalin	dexmethylphenidate
	Focalin XR	extended release dexmethylphenidate
	Metadate ER	extended release methylphenidate
	Metadate CD	extended release methylphenidate
	Methylin	methylphenidate hydrochloride (liquid & chewable tablets)
	Quillivant XR	extended release methylphenidate (liquid)
	Ritalin	methylphenidate
	Ritalin LA	extended release methylphenidate
	Ritalin SR	extended release methylphenidate
Non-stimulants		
Class	Trade Name	Generic Name
<i>Norepinephrine Uptake Inhibitor</i>	Strattera	Atomoxetine
<i>Alpha Adrenergic Agents</i>	Intuniv	extended release guanfacine
	Kapvay	extended release clonidine

Pharmacotherapy Stages



Titration Stage

- Optimal dose and frequency are determined
- Target outcomes achieved with minimal to no ADRs
- Usually lasts from 1 to 3 months
- Requires close monitoring (sometimes weekly)
- Start medication on weekend

Titration Stage Continued

- Treatment failure may occur if:
 - Lack of satisfactory improvement in core symptoms at maximum dose
 - Occurrence of intolerable adverse effects
 - Lack of adherence
 - Medication diversion
 - Unrealistic expectations
 - Possible comorbid psychiatric diagnosis

Maintenance Stage

- Begins once optimal dose has been determined
- Regular monitoring is necessary
- Monitor ADRs of therapy
- Review child's understanding of medication as he/she matures

Termination Stage

- Stable improvement of ADHD symptoms
- Closely monitored trial of core symptoms
- Alpha-2 adrenergic agonists should follow taper

Methylphenidate IR

- AAP first line therapy
- Children ≥ 6 years and adolescents:
 - Initial: 2.5mg BID before breakfast and lunch
 - Increase by 5 to 10mg/day at weekly intervals
 - May require 3 doses/day
 - Usual max dose: 60mg/day

Methylphenidate Cont'd

Dose Titration for Preschoolers

- Begin at 2.5mg PO twice daily – Increase as necessary up to 7.5mg three times daily over the course of one week (PATS study)
- Usually started at lower dose and increased in smaller increments
- Metabolism is slower in preschool children than in older children and adolescents

Methylphenidate ER

- Only approved for ≥ 6 years and older
- Initial dose varies with specific product
- Suggested dosing when switching from IR products
- Multiple dosage forms

Methylphenidate Dosage Forms

<i>Stimulants</i>		
Class	Trade Name	Generic Name
<i>Amphetamines</i>	Adderall	mixed amphetamine salts
	Adderall XR	extended release mixed amphetamine salts
	Dexedrine	dextroamphetamine
	Dexedrine Spansule	dextroamphetamine
	Vyvanse	lisdexamfetamine (extended release)
<i>Methylphenidate</i>	Concerta	methylphenidate
	Daytrana	methylphenidate (patch)
	Focalin	dexmethylphenidate
	Focalin XR	extended release dexmethylphenidate
	Metadate ER	extended release methylphenidate
	Metadate CD	extended release methylphenidate
	Methylin	methylphenidate hydrochloride (liquid & chewable tablets)
	Quillivant XR	extended release methylphenidate (liquid)
	Ritalin	methylphenidate
	Ritalin LA	extended release methylphenidate
Ritalin SR	extended release methylphenidate	
<i>Non-stimulants</i>		
Class	Trade Name	Generic Name
<i>Norepinephrine Uptake Inhibitor</i>	Strattera	Atomoxetine
<i>Alpha Adrenergic Agents</i>	Intuniv	extended release guanfacine
	Kapvay	extended release clonidine

Amphetamine

- IR tablets: FDA approved ≥ 3 years and older
- XR capsules: FDA approved ≥ 6 years and older
- Children eliminate amphetamine faster than adults
- Weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range
- Duration of action is longer than methylphenidate

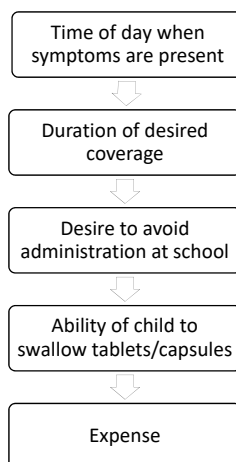
Amphetamine Cont'd

- Current AAP guidelines do not recommend in children ≤ 5 years old
- Initial dose for ≥ 6 years: 5mg once or twice daily
- Usual max dose: 40mg/day
- Conversion from IR to XR \rightarrow Use same total daily dose
- Elimination may decreased with hepatic impairment

Lisdexamfetamine

- Prodrug - Lower risk for abuse
- FDA approved for children ≥ 6 years and adolescents
- Initial dose: 20mg/day
- Capsules can be opened and mixed with water
- Chewable tablet available
- Increase in increments of 10 to 20mg at weekly intervals
- Max dose of 70mg

Selection of Stimulant



Stimulant Safety Concerns

Effect on the
Developing Brain

Heart-Related
Problems

Psychiatric
Problems

Potential for
Abuse

Tactics to Combat ADRs

- Appetite loss → Give with meals and high-calorie drink
- Difficulty falling asleep → Lower last stimulant dose of the day or move to earlier in the day
- Sadness → Reevaluate diagnosis
- Behavioral rebound → Overlap stimulant dosing pattern, switch to long-acting, combine IR and ER
- Irritability → Evaluate when occurs

Non-stimulant: Atomoxetine

- Second-line
- MOA: Enhances norepinephrine activity by selectively inhibiting norepinephrine reuptake
- Cannot crush, chew or open capsule
- Drug interaction: CYP2D6
 - Initiate at lower doses
- Boxed Warning: Suicidal ideations
- Continue stimulant when changing to Atomoxetine

Titration of Atomoxetine

Children and Adolescents \leq 70kg

- Initial: 0.5 mg/kg for minimum of 3 days
- Titrate up to daily dose of ~1-2 mg/kg in one or two divided doses
- Max dose: 1.4 mg/kg or 100mg (whichever is less)

Children and Adolescents $>$ 70kg

- Initial: 40mg for minimum of 3 days
- Increase to approximately 80mg
- After 2 to 4 weeks: May increase to max of 100mg if needed

Non-Stimulant: Alpha Adrenergic Agonists

- Guanfacine
- Clonidine

Guanfacine

- FDA approved in ages 6 to 17 years
- MOA: Preferentially binds postsynaptic α_{2A} -adrenoreceptors in the prefrontal cortex and has been theorized to improve delay-related firing of prefrontal cortex neurons
- IR: Take at bedtime to minimize somnolence
- ER: Take at same time every day (AM or PM)
 - Not with high-fat meal
- Discontinuing medication – Tapering may be warranted
- A more selective alpha agonist than clonidine

Clonidine

- FDA approved for ADHD
- MOA for ADHD: Unknown
- IR dosing:
 - $\leq 45\text{kg}$, initial 0.05mg HS (max dose: weight dependent)
 - $> 45\text{kg}$, initial 0.1mg HS (max 0.4mg/day)
- XR dosing: initial 0.1mg HS
- Increase in increments every 3-7 days until desired response
- Do not discontinue abruptly

Active Monitoring of ADHD Medication

Presentation of
side effects

How does the
patient feel?

Patient and family
satisfaction with
treatment

Are efficacy goals
being met
throughout the
day?

Adherence to
treatment regimen

Effective Tips for Parents/Guardians

- Refill reminders
- Automated refills
- Blister packaging
- Once-daily dosing with one alarm reminder
- Using a medication chart
- Reminder App



Pharmacist Intervention

- If return of ADHD symptoms:
 - Was the dose or medication formulation changed?
 - Has the patient been adhering to treatment?
 - Were medication dosages inadvertently missed?
 - Has patient been taking amphetamine containing products with acidic juice?

Pharmacist Intervention Cont'd

- Potential for abuse with stimulants
 - Extended release formulations due to lack of rapid uptake
- Increasing focus on sleep hygiene, stress management, diet and exercise
- Optimize therapy
- Provide counseling and education

Factors Influencing Adherence

- Effectiveness
- Tolerability
- Ease of use
- Simplified dose regimen
- Cost
- Negative perceptions of ADD/ADHD diagnosis by patient or family
- Patient/parent distrust of provider

Virtual Visits

- CNMC Pediatrics adopted virtual visits for stable ADHD patients
- Prevents taking patient out of school
- Allows for more active monitoring every 3 months

New - Breakthrough Treatment?

- FDA cleared first medical device for treating ADHD
- At-home nerve stimulation system
- Delivers mild electrical pulse while patient is sleeping
- Placebo-controlled trial of 62 children – Significant improvements after 4 weeks
- Adverse effects
- Contraindications

https://www.fiercebiotech.com/medtech/fda-clears-first-device-treatment-for-childhood-adhd?mkt_tok=eyJpIjoiT0dZNVpEQTV0amd3TW1VM5isInQioiI0UpDTmM3UGIFUFI0aWVxbTV1VlwwTHROR0NOWXFpdjhYdzVCRDlpbktPanRwcUp6bXhWQKRScklXWFRJSHF5UkpURUxQVHVpWVJcL1RnVXN4VIRwYjRj

Post-Assessment Question

1. Which of the following has the greatest impact on determining susceptibility to ADHD?
 - a) Genetics
 - b) Parenting
 - c) Social environment
 - d) Education System
 - e) Divorce

Post-Assessment Question

2. Which of the following is recommended for first-line treatment for preschoolers according to the AAP guidelines?
 - a) Adderall
 - b) Methylphenidate
 - c) Behavioral therapy
 - d) Referral to psychiatrist
 - e) Strattera

Post-Assessment Question

3. True or False: The metabolism of methylphenidate is slower in preschool children than in older children and adolescents?
- a) True
 - b) False

Post-Assessment Question

4. David, a 9 year old boy, is currently taking Amphetamine Salts 10mg tablets. He takes 1 tablet in the morning and 1 tablet at lunch. Mother is requesting him to be switched to long acting Adderall. What should his starting daily dose of Adderall XR be?
- a) 5mg
 - b) 10mg
 - c) 15mg
 - d) 20mg
 - e) 25mg

Conclusion

- Use guidelines for recommending treatment for Attention-Deficit/Hyperactivity Disorder
- Select pharmacologic agents based on patient specific variables and treatment needs
- Enhance compliance by providing pharmacist education and counseling
- Discuss opportunities to improve treatment goals and patient knowledge of disease state

Questions?



References

1. Holland, K., Riley, E., & Krucik, G. T. (2017, October 24). ADHD Numbers: Facts, Statistics, and You. Retrieved from <https://www.addrc.org/adhd-numbers-facts-statistics-and-you/>
2. The National Institute of Mental Health. (2018, March). NIMH » Attention Deficit Hyperactivity Disorder. Retrieved from <https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml>
3. Attention-Deficit / Hyperactivity Disorder (ADHD). (2017, August 31). Retrieved from <https://www.cdc.gov/ncbddd/adhd/diagnosis.html>
4. Overview. (n.d.). Retrieved from <https://chadd.org/about-adhd/overview/>
5. Steering Committee. (2011, November 01). ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Retrieved from <http://pediatrics.aappublications.org/content/1>
6. Attention-Deficit / Hyperactivity Disorder (ADHD). (2018, September 21). Retrieved from <https://www.cdc.gov/ncbddd/adhd/guidelines.html>
7. 12 Strategies to Beat ADHD Naturally. (2018, November 16). Retrieved from <https://drjockers.com/adhd/>
8. Drug information from Lexicomp

Medication Management of ADHD in Pediatrics

Andrea Chouinard, PharmD, AE-C
Pediatric Pharmacist
Chickasaw Nation Medical Center