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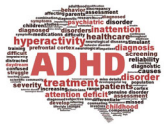
ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)



Renee Robinson, PharmD, MPH, MS Pharm
Associate Professor, UAA/ISU College of Pharmacy

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Objectives

- Recognize signs, symptoms, and behaviors related to ADHD and ADHD therapy.
- Review medications commonly used to treat ADHD, familiarizing oneself with categories and medication characteristics (e.g., pharmacokinetic differences, common side effects, etc.)
- Integrate and apply knowledge to assist patients, families, and providers in identifying unmet therapeutic needs.
- Provide patient-centered care as the medication expert, guiding medication selection, dose management, and side effect management advice to patients, caregivers, and providers

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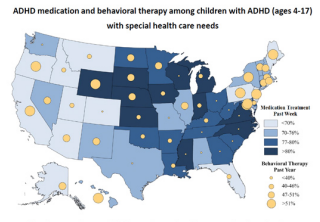

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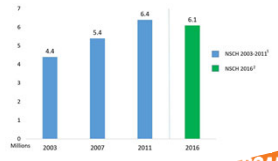
Epidemiology of ADHD

- Most well researched neurodevelopmental disorder in childhood
- 6 – 9% of children and 2 – 3% of adults
  - Globally, prevalence similar
- Males > females
  - 2-4:1 – children
  - 1.6:1 – adults



DiPiro et al. *Pharmacotherapy: A Pathophysiologic Approach*, 10e. New York, NY: McGraw-Hill; 2017.

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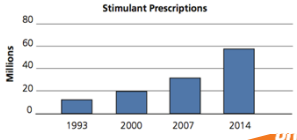
Epidemiology of ADHD

- Increased rate of prescribing – ADULTS
- PBM analysis - 400,000 privately insured age <65 years
  - ADHD med use increased by 54.4% from 2008-2012
  - Children still received higher % of Rx vs. adults
    - 80% stimulants



DiPiro et al. *Pharmacotherapy: A Pathophysiologic Approach*, 10e. New York, NY: McGraw-Hill; 2017.

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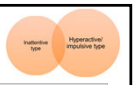
Presentation & Target Symptoms



Inattentive	Hyperactive/Impulsivity
• Frequently forgets daily activities • Easily distracted by external stimuli • Unable to listen when spoken to directly • Loses items necessary for tasks or activities • Trouble organizing schoolwork & other activities • Difficulty maintaining attention in work or play activities • Unable to follow instructions and fails to finish schoolwork and other tasks • Avoids, dislikes, or is reluctant to begin activities that require continuous attention • Fails to focus on details or makes careless mistakes in schoolwork or other activities	• Talks excessively • Difficulty waiting their turn • Impulsively blurts out answers • Runs or climbs in unacceptable situations • Inability to remain seated when necessary • Fidgets with hands or feet or squirms in seat • Unable to play or engage in quiet, leisure activities • Often "on the go" or acts as if "driven by a motor" • Interrupts activities or conversations of others, or intrudes or takes over for others

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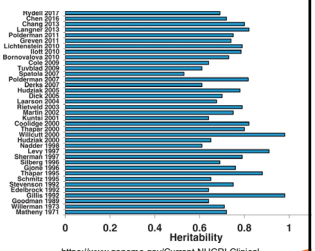
Etiology/Pathophysiology

- DSM-5
  - Minimum of 6 months, persistent pattern inattention and/or hyperactivity/impulsivity
  - >6 symptoms (or >5 symptoms if age >17 years)
  - Symptoms present before age 12 years and occur in >2 settings (home, work, school)
  - No manifestation of other psychiatric disorder



https://www.genome.gov/Current-NHGRI-Clinical-Studies/ADHD-Genetic-Research-Study-at-NIH
https://www.nature.com/articles/s41380-018-0070-0

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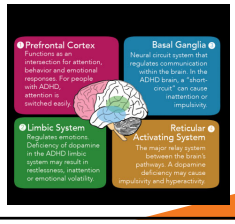
Etiology/Pathophysiology

- Norepinephrine (NE) and dopamine (DA) dysfunction in Prefrontal Cortex (PFC)
- Executive functioning deficits
  - Focus
  - Organization
  - Prioritization
  - Memory



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Adult ADHD: Comorbidities

- Rule out competing psychiatric diagnoses with similar presentation
  - *Inattention* more associated with withdrawal and depressive symptoms
    - Anxiety
    - Mood
    - Substance abuse disorders
    - Maladjustment
  - *Hyperactivity-impulsivity* more associated with externalizing disorders
    - ODD
    - CD
    - Substance use disorders (SUD)

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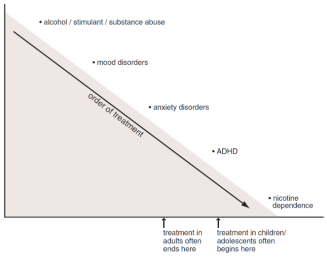
What should be treated first?



Stahl's Psychopharmacology, Fourth Edition 2013

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TREATMENT

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Nonpharmacologic Options

- Behavioral therapy
- Cognitive behavioral therapy (CBT)
  - Insufficient evidence for children, most effective for adults
- Other interventions:
  - School-focused
  - Family-focused
  - Child-focused

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Treatment Guidelines

1. Behavior therapy, methylphenidates (MPH), amphetamines (AMP)
2. Atomoxetine
3. Bupropion or guanfacine
4. TCA or clonidine
5. Venlafaxine

https://pediatrics.aappublications.org/content/144/4/e20192528

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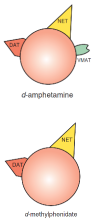
Stimulant Mechanism of Action



- Increase NE and DA signaling in prefrontal cortex
- Amphetamines (AMP)
  - Competitively inhibit (DAT) transporters AND stimulate direct release of NE and DA
  - Disrupt presynaptic vesicles that contain monoamines, including NE and DA, so more is released into the synapse
    - Also enhance release of NE in periphery
- Methylphenidate (MPH)
  - Competitively inhibit (DAT) transporters, selectively inhibits presynaptic reuptake of DA and NE (DA > NE)
    - Minimal effects in periphery
- Both inhibit MAO (amphetamine > methylphenidate)
  - Higher doses may act as release 5-HT agonist

Stahl's Essential Psychopharmacology: Fourth Edition. 2013.

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CNS Stimulants

- Amphetamine Derivatives (AMP)
  - Amphetamine Salts
  - Dextroamphetamine (d-AMP)
- Methylphenidates (MPH)
  - Methylphenidate
  - Dexmethylphenidate (d-MPH)

General Potency Ratio	
Stimulant	Approximate Equivalent Dose (mg)
Methylphenidate	2
Dexmethylphenidate	1
Amphetamine	1
Amphetamine Mixed	1
Dextroamphetamine	1
Lisdexamfetamine	2.5

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Clinical Use of Stimulants

- Start with IR formulation and assess efficacy and tolerability
  - May transition to long-acting stimulant if effective
- Equal Efficacy between both stimulant types
- Other factors:
  - Duration of acting, PK profiles, patient response
- Failure of one stimulant → switch to the other class

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CNS Stimulants: AMP-Containing Products

Duration	Generic Name	Brand Name	Adult Dose
Short acting	Dextroamphetamine IR	Dexedrine Zenzedi ProCentra	10-60mg (2-3x/day)
	Mixed AMP salts	Adderall	10-60mg (2-3x/day)
	Racemic AMP sulfate	Evekeo	10-60 (1-2x/day)
	Racemic AMP sulfate susp	Dyanavel XR	5-20mg once daily
Intermediate acting	Dextroamphetamine	Dexedrine spansules	10-40mg (1-2x/day)
Long acting	Mixed AMP salts	Adderall XR	20-60mg once daily
	Lisdexamfetamine	Vyvanse	30-70mg once daily

*AMP = amphetamine
*IR = immediate release
*XR = extended release

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CNS Stimulants: MPH-Containing Products

Duration	Generic Name	Brand Name	Adult Dose
Short acting	MPH IR	Methylin Ritalin	10-60mg (2-3x/day)
	Dexmethylphenidate IR	Focalin	5-20mg (2-3x/day)
Intermediate acting	MPH ER	Metadate ER, Methylin ER Ritalin SR	10-60mg (1-2x/day)
Long acting	MPH CD	Metadate CD	20-60mg
	MPH LA	Ritalin LA	10-60mg
	MPH XR suspension	Quillivant XR	20-60mg
	MPH OROS	Concerta	18-72mg
	MPH MLR	Aptensio XR	10-60mg
	MPH transdermal patch	Daytrana	10-30mg
	Dexmethylphenidate XR	Focalin XR	10-40mg

*IR = immediate release, ER = extended release, XR = extended release, OROS = osmotic release oral system, MLR = extended release multilayer bead

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Differentiating Stimulants

Amphetamine derivatives/ Methylphenidates

- Short-acting
- Intermediate-acting
- Long-acting

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Short-Acting Amphetamines (AMP)

Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Short-Acting			
Adderall ® (Mixed AMP salts)	~ 3-4 hr	4-5	Often requires BID-TID dosing If dose is taken late in the day, can cause insomnia d-AMP also comes as a liquid solution (ProCentra®)
Dextrostat/Dexedrine® (d-AMP)			
Procentra® (d-AMP)			

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Intermediate-Acting AMP

Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Intermediate Acting			
Dexedrine Spansules ® (d-AMP)	6-8	8	Once or BID dosing Spansules contains 50:50 mix of short and delayed release

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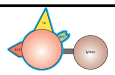
Long-Acting AMP



Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Long-Acting			
Adderall XR® (mixed AMP salts)	7	10	Once daily bead-filled caps, contains 50:50 mix of immediate and delayed release
Vyvanse® (lisdexamfetamine)	3-4		Once daily formulation Pro-drug of dextroamphetamine -Activated in gut, so cannot be snorted or injected, possibly less "high"

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Methylphenidates (MPH)

Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Short-Acting			
Ritalin® (MPH)	1-3	4	Often requires BID-TID dosing If dose is taken late in the day, can cause insomnia MPH also comes as a solution or chewable tablet
Focalin® (d-MPH)			
Intermediate-Acting			
Ritalin SR® (MPH)	4-5	6-8	Wax-based matrix Commonly dosed BID
Metadate ER® (MPH)			

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Long-Acting MPH

Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Long-Acting			
Ritalin LA® (MPH)	2 peaks: 1-3 hr, then 5-6 hr	8-12	Once-daily bead-filled cap, 50:50 mix of immediate and delayed release
Metadate CD® (MPH)			Once-daily bead-filled cap, 30:70 mix of immediate and delayed release (option for worsened afternoon sxs)
Quillivant XR® (MPH-XR suspension)	4	12	Only extended-release solution: 20:80 mix of immediate and delayed release
Aptensio XR® (MPH-MLR)			

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Long-Acting MPH

Brand/Generic	Peak (hr)	Duration (hr)	Special Info
Long-Acting			
Concerta® (MPH)	2 Peaks: 2 hrs, then 3-4 hrs, then slow release phase	8-12	Once-daily OROS formulation Ghost tablet in feces Avoid in those with bowel obstruction
Focalin XR® (d-MPH)	2 Peaks: 1.5 hr, then 6 hrs	10	Once-daily bead-filled cap, 50:50 mix of immediate and delayed release
Daytrana® (MPH)	10-30 mg	8	Delayed onset of 2 hrs Remove after 9 hours for 12 hour duration

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SPECIAL FORMULATIONS

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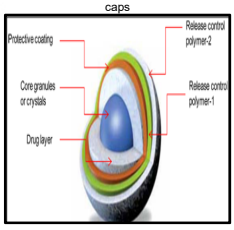
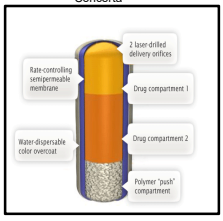
Special formulations

Spheroidal oral drug absorption system (SODAS)- bead-filled caps



Osmotic-controlled release oral delivery system (OROS)- Concerta



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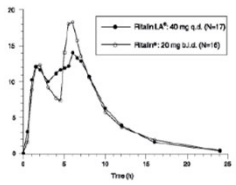
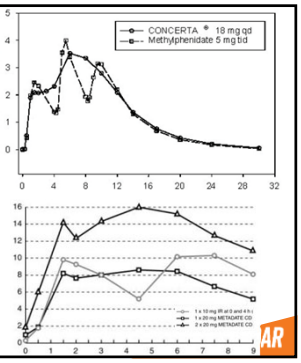
Pharmacokinetics





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Pharmacokinetics: MPH Patch

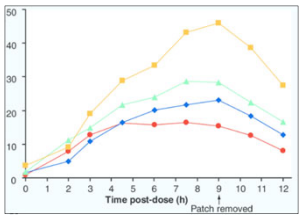

Image adapted from: https://www.researchgate.net

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Patient Case

- JD is a 9 YO female referred by her pediatrician and recently started on the long-acting methylphenidate transdermal patch (Daytrana®).
- Applied 8am and removed prior to bedtime
- After 1 week on the medication, both her teachers and her parents note improvement in JD's symptoms. However, JD's mother notes that JD is not sleeping as well and is now taking 1-2 hours longer than normal to fall asleep.

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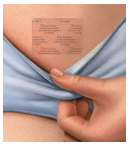
Special formulations

- Proper disposal necessary to avoid abuse/toxicity



Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch** (mg)
10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55
30	3.3	37.5	82.5

Package Insert [Daytrana]. Noven Pharmaceuticals. Miami, Fl 2010.

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Adverse Effects/Precautions

- Emotional / jitteriness
- Insomnia
- New-onset tics
- Headache
- Increased HR/BP
- Weight loss
- Decreased appetite/GI distress
- Psychiatric /seizures

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Without proper treatment for ADHD symptoms, a patient is at higher risk for developing

A. Cardiovascular disease
B. Substance use disorder
C. Bipolar Disorder
D. Insomnia

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Monitoring

- Baseline and at each follow-up
  - Appetite
  - BP
  - HR
  - Height
  - Weight
  - Mood

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Safety Concerns

- Black box warning for abuse!
  - Drug dependence (high potential for abuse/misuse)
  - Misuse may lead to sudden cardiac death/serious CV events
  - Caution in patients with cardiovascular contraindications
    - Advanced arteriosclerosis, symptomatic CV disease, moderate to severe HTN, cardiac arrhythmias, HF, recent MI
- Other contraindications
  - Hyperthyroidism, thyrotoxicosis, glaucoma, agitated states, history of drug abuse, during or within 14 days of MAOI administration

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Other Pharmacologic Options

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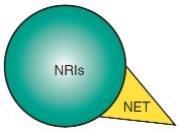
Atomoxetine (Strattera®)

- Non-stimulant FDA approved in 2002
- Mechanism: inhibits pre-synaptic NE reuptake (NR
- Pharmacokinetics
  - CYP 2D6 metabolized, active metabolite
  - Increased exposure with CYP 2D6 inhibitors
- Delayed therapeutic effect up to 4 weeks
  - Adjust dose once monthly
- Niche: Contraindication/poor candidate for stimular
  - Active/history substance use disorder
  - Comorbid anxiety disorder
  - Tic disorder



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Atomoxetine (Strattera®)

- Dose: 40 – 100mg daily
- Black Box Warning: Increased suicidality
- Warnings/Precautions
  - Potential for severe liver injury, priapism?, hostile or aggressive behaviors
- Adverse Effects (dividing dose BID may help)
  - GI discomfort, HA, irritability, low appetite, nausea, dizziness (take in PM), insomnia (take in AM)
  - Increased HR/BP less likely but possible

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Extended-release Alpha2 Agonists

- Monotherapy or adjunct to stimulants
- Mechanism of Action:
  - α-2 adrenergic agonist at the postsynaptic receptor
  - Inhibit presynaptic NE release
  - Increase blood flow in prefrontal cortex
- Immediate/extended-release formulations
  - Higher bioavailability and peak concentrations with IR formulation
  - Caution when converting!
- Niche: ADHD with tic disorder, persistent aggression or impulsivity

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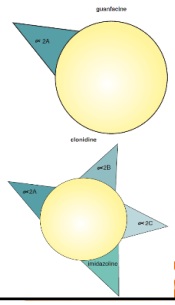
Extended-release Alpha2 Agonists

- Dosing
  - Extended-release clonidine 0.1mg BID or higher
  - Extended-release guanfacine once daily
  - Titrate to effective dose, taper to discontinuation
- Adverse Effects
  - Sedation and hypotension (dose-limiting)
    - Clonidine > guanfacine



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Images: Stahl's Psychopharmacology; Fourth Edition 2013

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2nd Line Treatments

Brand/Generic	Side Effects/Precautions
Strateera® (atomoxetine)	• GI, insomnia, dizziness • BBW: increased risk of _____
Catapres®/ Kapvay® (clonidine immediate/extended release)	• Common adverse effects: somnolence, dry mouth, dizziness, hypotension, headache • Taper when discontinuing due to _____ _____ • If sedation is a problem during the day with IR, use lower dose during the day or switch to ER • Maximal effects may take 2-4 weeks
Tenex®/Intuniv® (guanfacine immediate/extended release)	

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Alternative Agents (3rd line)

- Bupropion
  - 3rd line
  - Niche: CI to stimulants, comorbid depression, nicotine dependence
- Tricyclic Antidepressants (TCAs)
  - Imipramine, desipramine, nortriptyline with most data
  - 3rd/last-line due to CV risks, OD risks
  - Niche: CI to stimulants, comorbid depression/anxiety
- Modafanil (Provigil)
  - Only modest efficacy in studies in school-aged children
  - Risk for Stevens Johnson Syndrome, exacerbations of psychosis or mania

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Natural Products

- Polyunsaturated fatty acids
  - Omega-3 and omega-6 may be decreased in ADHD
  - May be used as adjunct in children
  - Doses up to 1 gram/day (EPA-based) have been studied
- Iron supplementation
  - May be used as adjunct for children at risk for iron deficiency
  - Ferrous sulfate 80mg/day studied in children with ADHD with low serum ferritin
- Others – St. John's wort, Gingko biloba, magnesium, and zinc supplementation have been studied by require further research before recommendations can be provided

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Pharmacotherapy for ADHD

- Duration of Therapy
- If symptom-free for >1 year,
  - Need for medication re-assessed
- After discontinuation, if deterioration reported, restart medication

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Pharmacotherapy for ADHD

- Pregnancy
  - Stimulants results in increased risk of premature birth and low birth weight, newborns may experience withdrawal effects. Avoid if possible.
  - Atomoxetine unknown in pregnancy, use with caution
- Lactation
  - Simulants:
    - AMP may decrease milk production, infant may experience irritability, agitation, crying. Avoid if possible.
    - MPH should be used with caution, crosses into breastmilk in low quantities
  - Atomoxetine (unknown), clonidine, guanfacine should be used with caution. Monitor for sedation with guanfacine
  - Bupropion (per LactMed) relatively safe and well-tolerated, use IR formulation and give dose immediately after feeding

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Take Home Points

- ADHD is a psychiatric disorder characterized by symptoms of inattention, hyperactivity, and/or impulsivity
- Stimulants are first-line therapy
- Agents such as atomoxetine, alpha agonists, or bupropion may be appropriate alternatives for patients who have failed or had partial response to stimulant therapy

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