All About ADHD in Pediatric Patients: Pharmacologic Approaches

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April 2024

Introduction

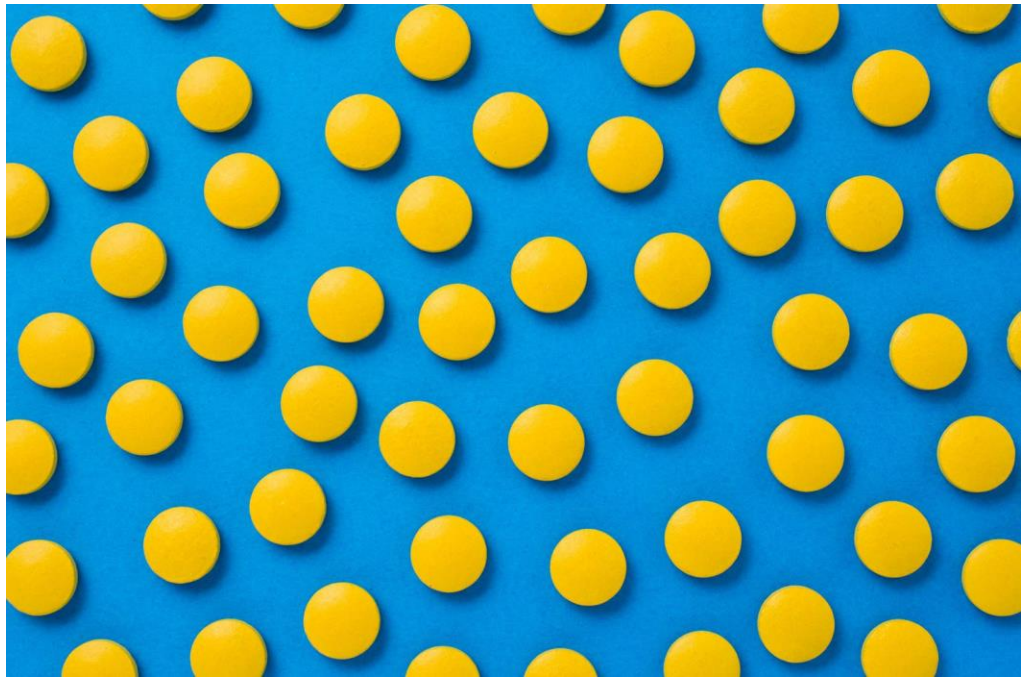
- No conflicts of interest to disclose

- Generic names will be used whenever possible, but the brand name drug may be referenced if appropriate. Inclusion of a brand name drug in this presentation does not represent endorsement

- There will be no mention of off-label use of medications in this presentation

Preface

- Treatments, not diagnosis
  - Based on proper diagnostic assessment & ongoing evaluation and adjustments
- Therapy or Psychotherapy



Learning Objectives

1. Describe one similarity between three ADHD guidelines for pediatric patients: CADDRA, NICE, AAP

2. Identify specific qualities in methylphenidate and amphetamine-based dosage forms that may benefit certain patients

3. Explain one strategy to help navigate drug shortages

Outline

- ADD/ADHD
  - DSM V TR Criteria
  - Review of guidelines and landmark trials
  - Current formulations and medications available
- Navigating shortages
- Case Presentation

DSM-5-TR Criteria

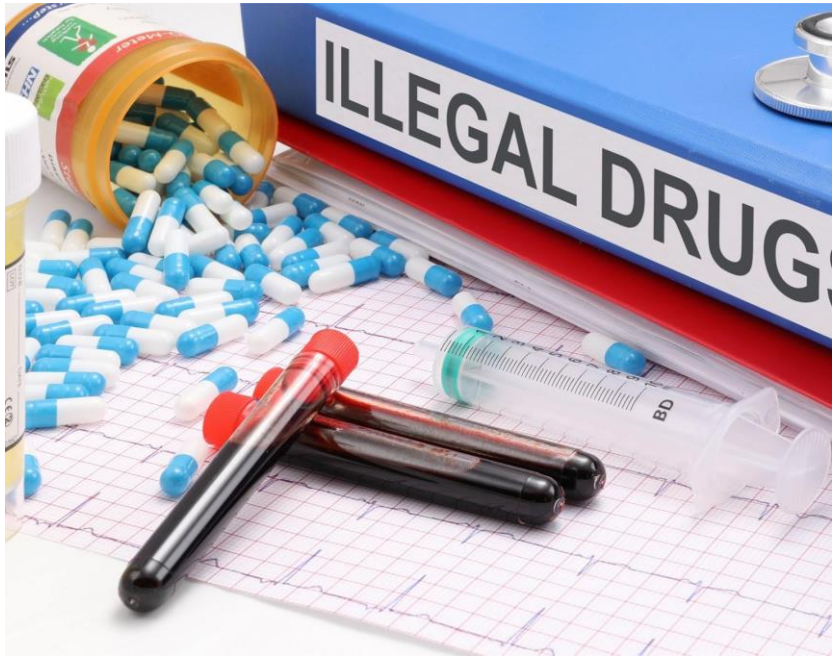
- A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2),
  1. Inattention
  2. Hyperactivity and impulsivity
- Several symptoms present before age 12 and in 2+ settings
- Symptoms are not better explained by another mental disorder

ADHD Guidelines & Trial

- Canadian ADHD Resource Alliance (CADDRA) (2018)
  - 1st line: Long-acting psychostimulants (stronger evidence), atomoxetine, GXR, and short-acting psychostimulants (weaker evidence)
- National Institute for Health and Care Excellence (NICE) (2018)
  - Recommend stimulant use (methylphenidate or lisdexamfetamine) 2nd line
- American Academy of Pediatrics (AAP) (2019)
  - Recommend “FDA Approved Medication” and parent/caregiver training in behavior management (PTBM)

Treatment >>>>> no treatment

MTA: Multimodal Treatment Study of Children with ADHD (1999-2017)



Medication or Medication + Behavioral Therapy >> Behavioral Therapy or Community Care

Taking medication slowed growth by about three-fourths of an inch and 6 pounds. Growth rates were slower at the beginning of therapy but normalized by the end of 3 years

Children with ADHD showed significantly higher-than-normal rates of delinquency (27.1 percent vs. 7.4 percent) and substance use (17.4 percent vs. 7.8 percent) after three years **independent of treatment**

Molina BS, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S; MTA Cooperative Group. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry. 2013 Mar;52(3):250-63

Methylphenidate & Derivatives

Amphetamine & Derivatives

OR

Atomoxetine

Viloxazine

+/-

Guanfacine ER

Clonidine ER

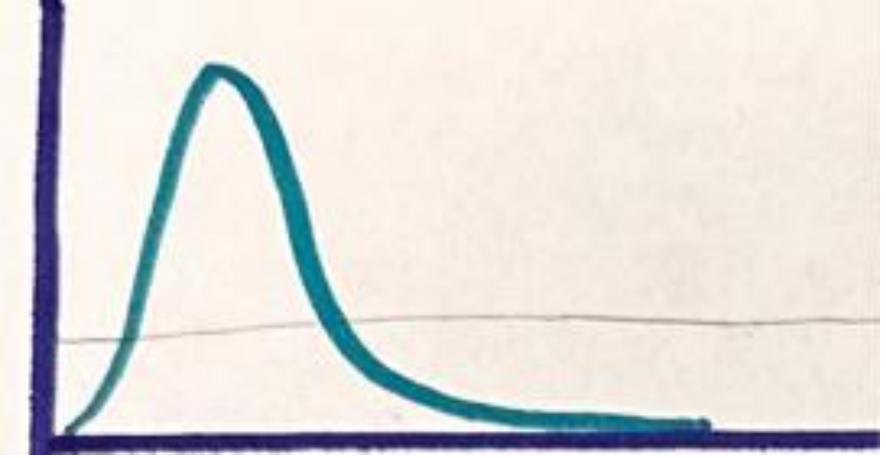
Severe and Most Common Risks of Treatment

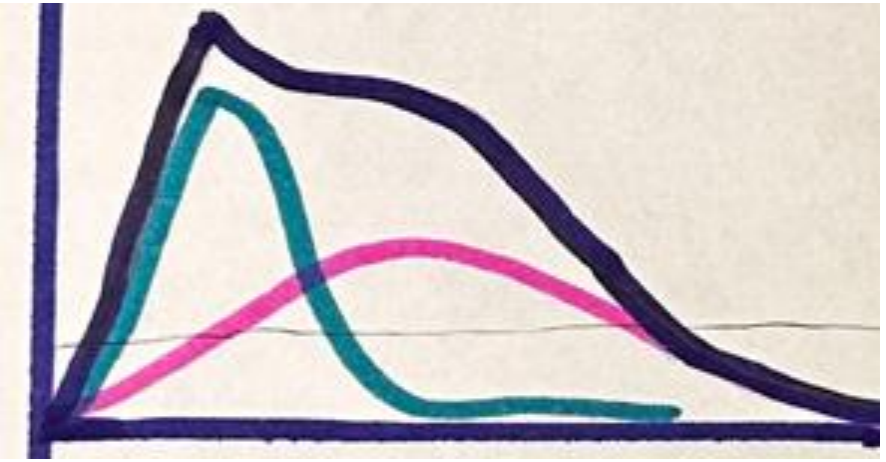
Methylphenidate & Derivatives

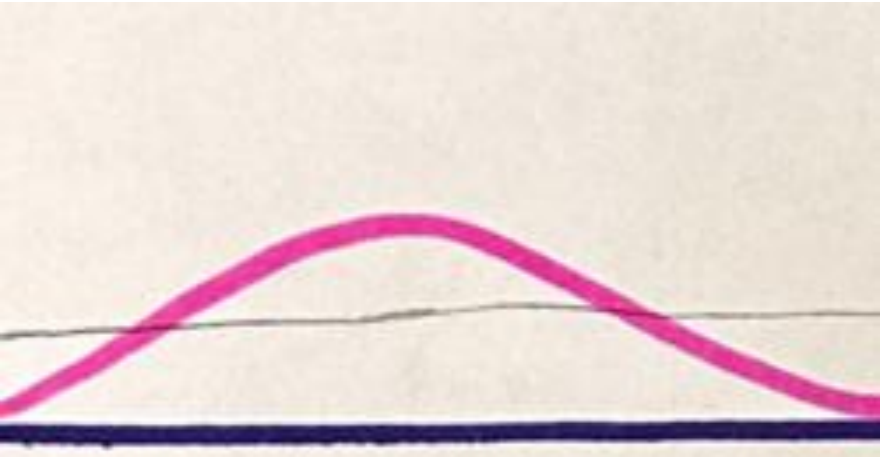
Amphetamine & Derivatives

- Boxed Warning: abuse, misuse, and addiction
- Cardiovascular effects – caution if pre-existing cardiac abnormalities
- Growth suppression
- Priapism
- Psychiatric & Behavioral Effects
- Common: Insomnia, Decreased Appetite, Headache, Dry Mouth

Harstad EB, Weaver AL, Katusic SK, et al. ADHD, stimulant treatment, and growth: a longitudinal study. *Pediatrics*. 2014;134(4):e935-e944. doi:10.1542/peds.2014-0428





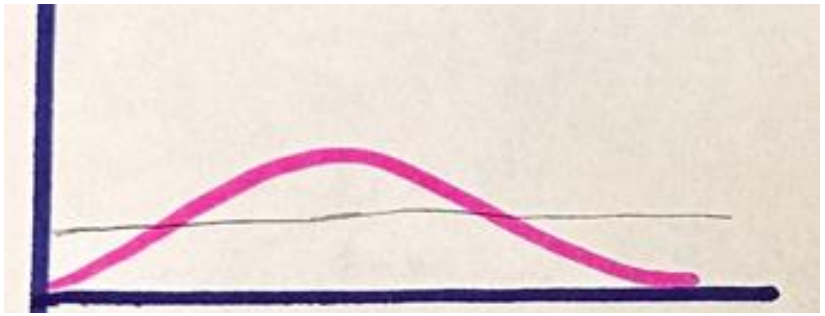


Methylphenidate (MPH)

- Immediate release (IR) – tablets, can all be cut/crushed, added to food
  - Ritalin ©, Methylin ©
  - Onset at 20-60 minutes, duration of 3-6 hours
- Extended release (ER or XR) – all capsules can be poured out onto food, ER tablets cannot

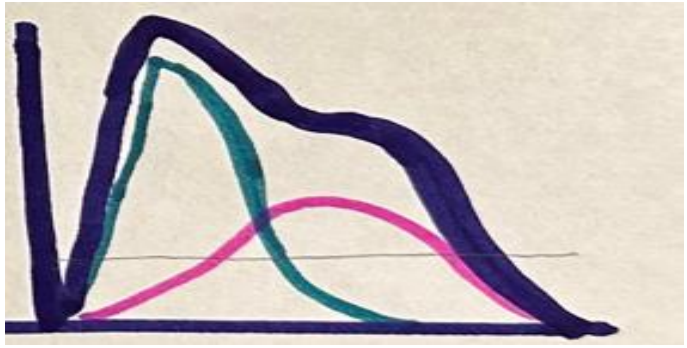
***Most MPH-ER drugs are a combination of IR and ER

MPH-ER

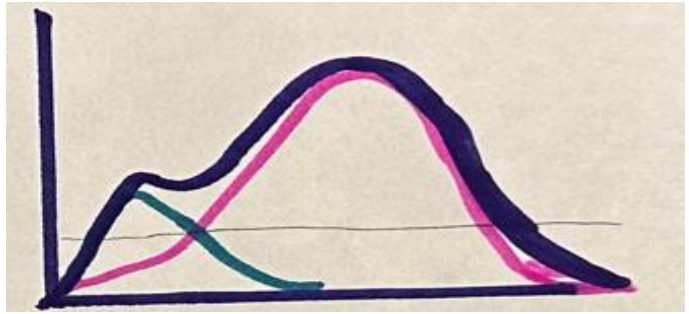


- Monophasic: Metadate ER ©
  - Onset at 90 minutes, duration 3-8 hours
  - NO IR component

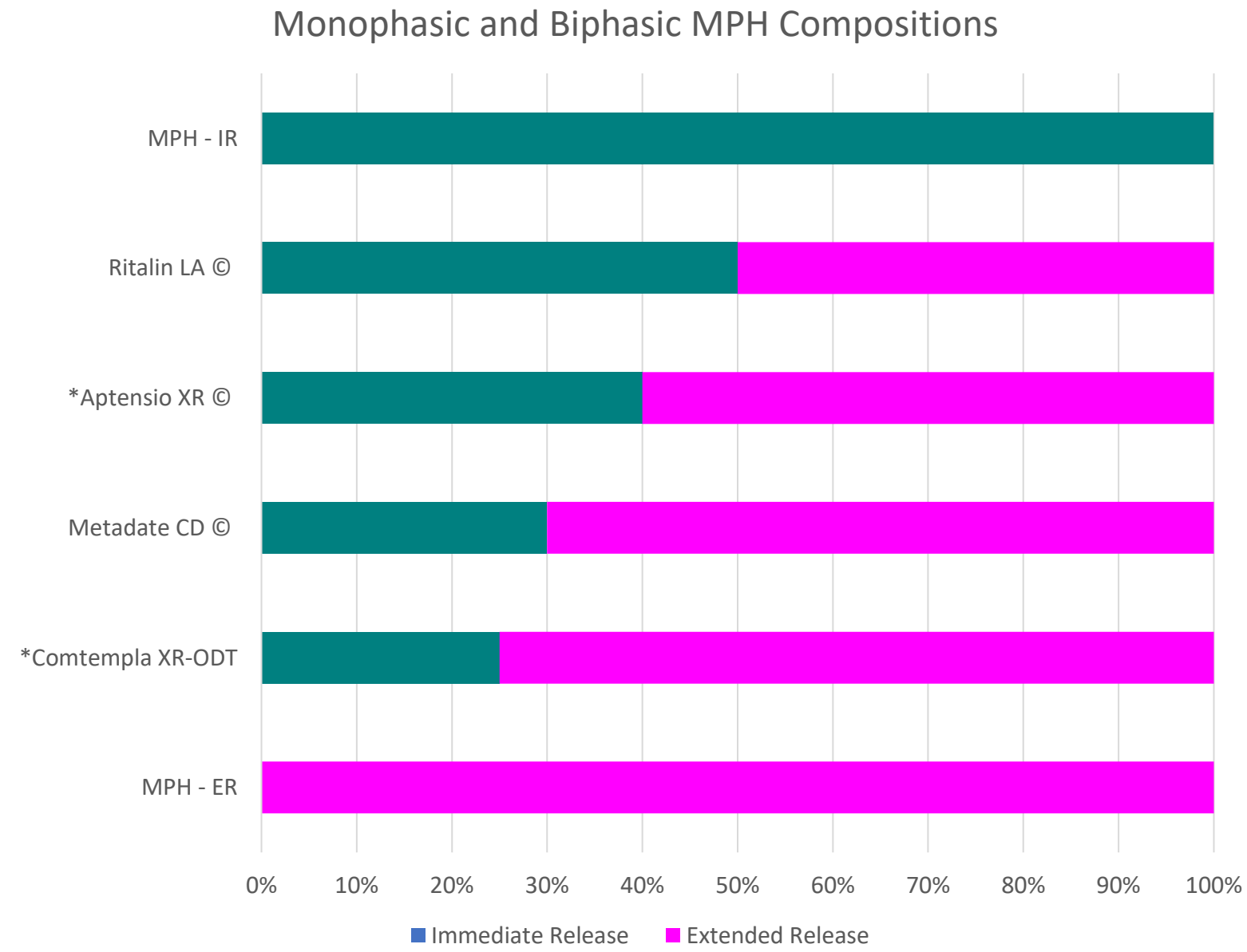
- Biphasic (IR:ER): Metadate CD © (30:70), Ritalin LA © (50:50), *Aptensio XR © (40:60) capsules, Contempla XR-ODT © (25:75)
  - Onset at 20-60 minutes, duration ~8 hours

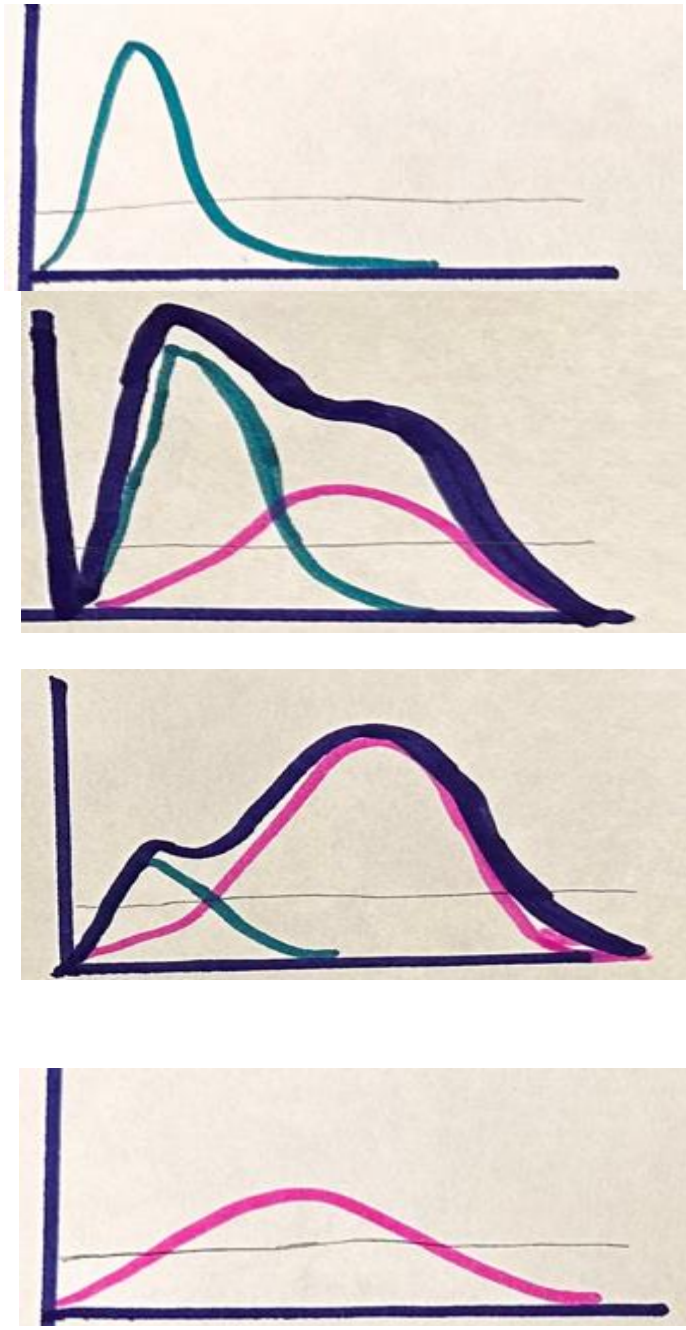


IR:ER 50:50



IR:ER 30:70

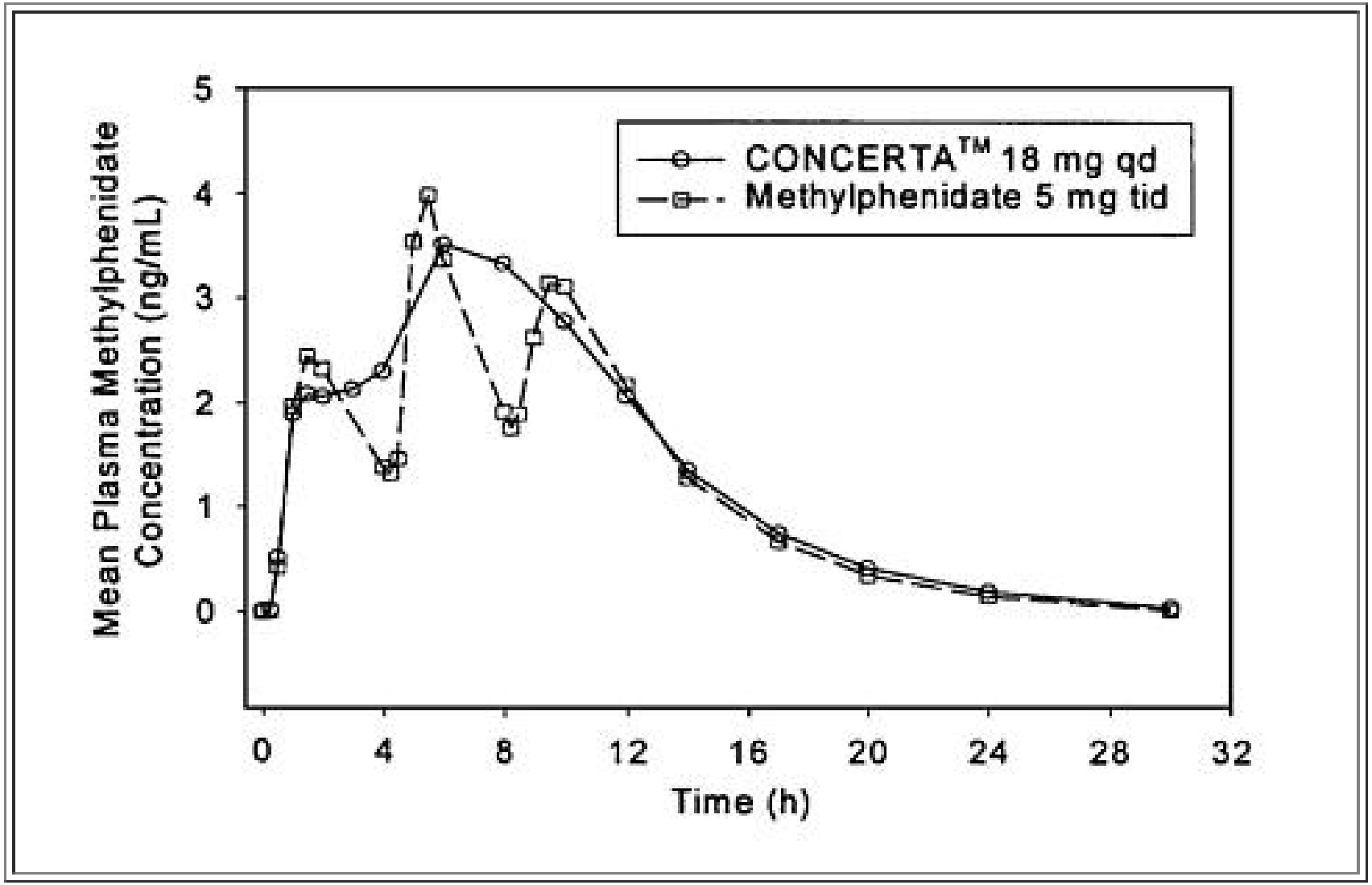




*Dose is not equivalent to the oral MPH dose

Triphasic MPH-ER

- Mimics BID-TID dosing (i.e. Concerta © 18mg dose is the same as 5mg BID-TID)



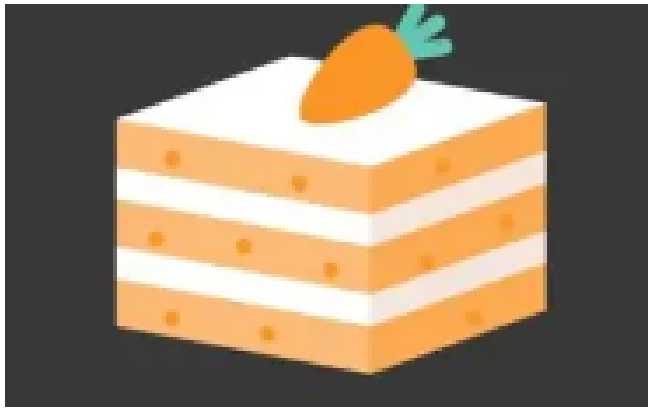
Rafael Maldonado (2013) Comparison of the pharmacokinetics and clinical efficacy of new extended-release formulations of methylphenidate, Expert Opinion on Drug Metabolism & Toxicology, 9:8, 1001-1014, DOI: 10.1517/17425255.2013.786041

MPH-ER

- Daytrana © Patch
  - Apply 2 hours before school/work/start of the day, can be worn up to 9 hours, lasts up to 10
- Liquid formulation: Quilivant XR © liquid (IR:ER 20:80)
  - Need to reconstitute an entire bottle
- Jornay PM © capsule
  - 5% of drug released in first 10 hours

MPH-ER

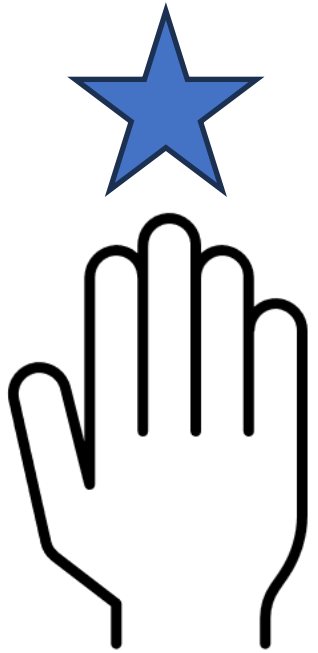
- CTX-1301 in development
  - Triphasic dexmethylphenidate tablet
  - 3 different release layers
  - Duration up to 16 hours



Dextro - & Levo -

- When discussing dextro and levo forms:

Levo = Left



Dextro = Right

Dexmethylphenidate (D-MPH)

- Focalin © tablets & Focalin XR © capsules (D-MPH)

- Serdexmethylphenidate (SDX) and dexmethylphenidate (D-MPH) (Azstarys ©)
  - SDX is a prodrug that gives the drug its ER component and abuse deterrence, similar to Lisdexamfetamine

Amphetamine-based (AMP) Drugs

- Mixed Amphetamine Salts (D-AMP:L-AMP 3:1)
  - Adderall ® IR tablets, Adderall XR ® capsules
- Mixed salts of a single-entity amphetamine (D-AMP:L-AMP 3:1)
  - Mydayis ® ER capsules (16h duration)
- Amphetamine sulfate (D-AMP:L-AMP 1:1)
  - Evekeo ® tablets, Evekeo ODT ®, Dynavel XR ® suspension, Adzenys ER ® suspension, Adzenys XR-ODT ®
- Lisdexamfetamine (converts to D-AMP)
  - Vyvanse ® capsules
- Dextroamphetamine (D-AMP)
  - Dexedrine ® tablets and ER capsules, Dexedrine Spansule ®, Zenzedi ® tablets, ProCentra ® liquid

Mixed Amphetamine Salts (Adderall © IR and XR)

- Most prescribed agents from this group
- All generic
- Predictable kinetics
- ER formulation has an IR component
- Easy to dose, titrate
- Can pour capsules into food, crush tablets
- Abuse and diversion potential

Lisdexamfetamine (Vyvanse ©)

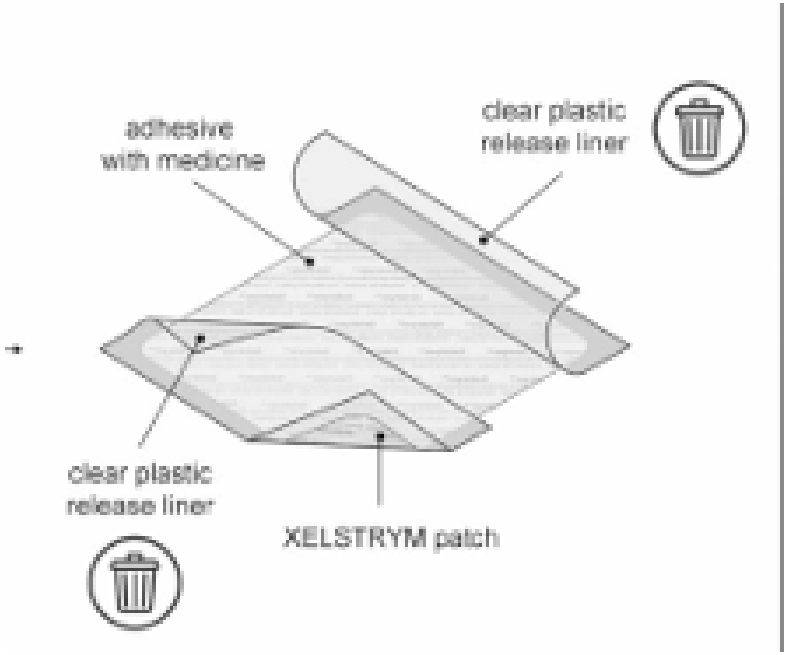
- Several generic companies approved to produce, but demand >> supply
- Unique mechanism of action means it has LOW abuse potential
  - Absorbed through GI tract into blood
  - Blood enzyme cleaves Lysine and releases D-AMP throughout the day
  - May pour capsule into food
- Divide dose by 2.5 to get equivalent D-AMP
  - E.g. 70mg of lisdexamfetamine = 30mg of dextroamphetamine

Dextroamphetamine (D-AMP)

- Half the dose of typical mixed salt amphetamine products
  - E.g. If someone is taking Adderall © 10mg, switch to D-AMP 5mg
- May be better tolerated in some patients and may need a lower equivalent Adderall© dose
- Same abuse and diversion potential as mixed salt amphetamine formulations

D-AMP patch

- Xelstrym ©
- Newest formulation
- Patch is worn for up to 9 hours



Methylphenidate & Derivatives

Amphetamine & Derivatives

OR

Atomoxetine

Viloxazine

+/-

Guanfacine ER

Clonidine ER

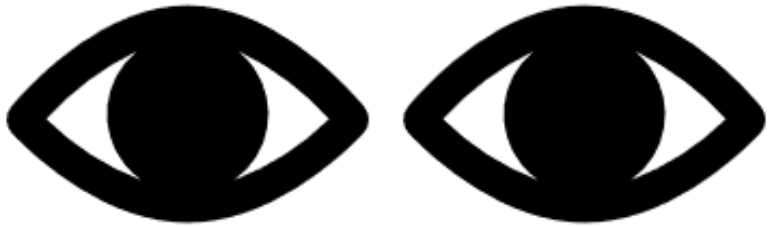
Severe and Most Common Risks of Treatment

Atomoxetine

Viloxazine

- Cardiovascular effects – caution if pre-existing cardiac abnormalities
- Boxed Warning: Suicidal ideation
- Drug-Drug Interactions: CYP2D6 (fluoxetine, bupropion)
- Atomoxetine only: Growth Suppression, Hepatotoxicity, Priapism, Psychosis/Mania
- Common: Drowsiness, Insomnia, Decreased Appetite, Nausea, Headache, Dry Mouth

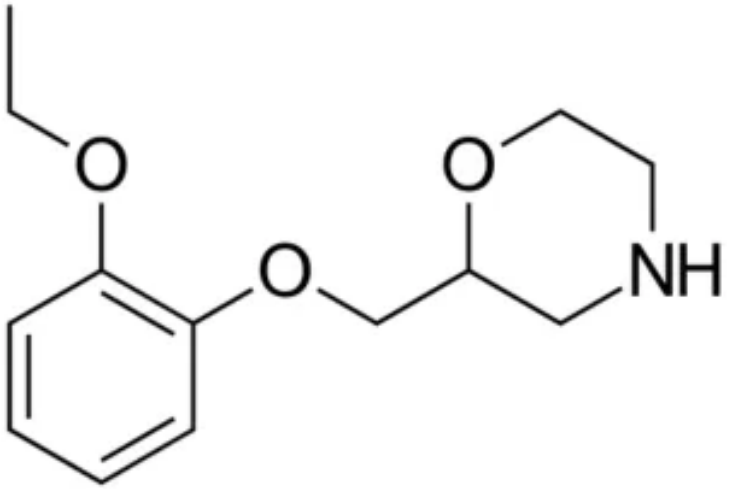
Atomoxetine



- Non-stimulant; SNRI
- Delayed onset of action
  - 2-4 weeks, although some may see effects sooner
- CANNOT open capsule – ocular irritation
- Dosing – 0.5mg/kg/day to 1.2mg/kg/day if <70kg, otherwise start at 40mg
  - 10mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg

Viloxazine

- Non-stimulant; SNRI
- Brand name only – manufacturer coupon on website
- Newest ADHD agent
- Similar place in therapy as atomoxetine, but may have a quicker onset and favorable side effects
- May sprinkle capsule into applesauce



Price MZ, Price RL. Extended-Release Viloxazine Compared with Atomoxetine for Attention Deficit Hyperactivity Disorder. CNS Drugs. 2023 Jul;37(7):655-660.

Methylphenidate & Derivatives

Amphetamine & Derivatives

OR

Atomoxetine

Viloxazine

+/-

Guanfacine ER

Clonidine ER

Severe and Most Common Risks of Treatment

Guanfacine ER

Clonidine ER

- Cardiovascular effects – Opposite of the other ADHD Meds
- Common: Lowered BP & HR, Dizziness/Drowsiness, Headache

Guanfacine ER

- Generic available
- May be mildly sedating
- Can be used as monotherapy or as adjunct
- Peripherally acting
- Duration of action ~18-24 hours
- Dosed once daily
- 1mg-4mg daily dose
- CANNOT take a drug holiday

Clonidine ER

- Generic available
- Transdermal patch available
- May be moderately-severely sedating
- Can be used as monotherapy or as adjunct
- Centrally acting
- Duration of action ~12 hours
- Dosed twice daily
- 0.1mg-0.4mg daily dose
- CANNOT take a drug holiday

Planning Ahead

- Plan for drug destruction in the event of discontinuation
- Keep medication in a secure location

Drug Shortages

Demand >>> Supply

Increased Demand during COVID19

- Increased prescriptions for C II stimulants (14%) and nonstimulant ADHD drugs (32%) for two main groups:
  - Adults ages 20-39: 30% & 81%
  - Female patients: 25% & 59%
- Increased ADHD symptoms in children and adolescents
  - Virtual schooling, household economic stressors, quarantine orders
- Increased access due to flexibility to prescribe to patients via telehealth, without in-person evaluations, out-of-state prescriptions
- Amphetamine-based prescriptions >>> Methylphenidate

*Decreased prescriptions from Psychiatry for C II stimulants (-1%)

Chai G, Xu J, Goyal S, et al. Trends in Incident Prescriptions for Behavioral Health Medications in the US, 2018-2022. *JAMA Psychiatry.* Published online January 10, 2024. doi:10.1001/jamapsychiatry.2023.5045

Decreased Supply

- DEA & FDA blame manufacturers for not maximizing production for the quotas allowed
- Insurance companies may require "step therapy" and restrict members to certain pharmacies or require brand vs. generic
- Shortage of active/raw ingredients
  - E.g. ZenZedi contaminated with an antihistamine recently
  - E.g. Lisdexamfetamine
    - Multiple generic companies approved to make over the last year, but largely unavailable except as brand name product

Possible solutions until supply can meet demand

- Electronic prescribing
- Allowing for partial fills when available
- Mail order pharmacies
- Look at the patient's formulary
- Therapeutic equivalents

Conclusion

- Guidelines largely recommend medication as a part of ADHD treatment, specifically stimulants

- Overall, ADHD medication options haven’t changed
  - Formulations have multiplied
  - Generic availability has eased ability to access
  - Increased flexibility in dose timing

- Shortages are an ongoing problem, and you may have to try multiple strategies to get your patients their drugs

Questions?

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Product Information: fluoxetine oral tablets, fluoxetine oral tablets. Edgemont Pharmaceuticals, LLC (per FDA), Austin, TX, 2011

Product Information: Lexapro(R) oral tablets, oral solution, escitalopram oxalate oral tablets, oral solution. Forest Pharmaceuticals, Inc. (per FDA), St. Louis, MO, 2014

Product Information: ZOLOFT oral tablets, oral solution, sertraline HCl oral tablets, oral solution. Roerig (per manufacturer), New York, NY, 2019.

Product Information: CYMBALTA(R) oral delayed-release capsules, duloxetine oral delayed-release capsules. Lilly USA LLC (per FDA), Indianapolis, IN, 2020

Product Information: PAXIL CR(R) oral extended-release tablets, paroxetine oral extended-release tablets. Apotex Corp (per FDA), Weston, FL, 2019.

Product Information: Citalopram oral capsules, citalopram oral capsules. Almatica Pharma LLC (per FDA), Morristown, NJ, 2022.

Product Information: EFFEXOR XR(R) extended-release oral capsules, venlafaxine hydrochloride extended-release oral capsules. Wyeth Pharmaceuticals Inc, Philadelphia, PA, 2008.

Product Information: WELLBUTRIN(R) XL oral extended-release tablets, bupropion hydrochloride oral extended-release tablets. Valeant Canada LP (per Health Canada), Laval, QC, Canada, 2016.

Product Information: Daytrana(TM) transdermal patches, methylphenidate transdermal system transdermal patches. Shire US Inc, Wayne, PA, 2009.

Product Information: JORNAY PM(TM) oral extended-release capsules, methylphenidate HCl oral extended-release capsules. Ironshore Pharmaceuticals & Development Inc (per manufacturer), Chesterbrook, PA, 2018.

Product Information: QUILLICHEW ER(TM) extended-release chewable tablets, methylphenidate HCl extended-release chewable tablets. Tris Pharma, Inc. (per manufacturer), Monmouth Junction, NJ, 2015.

Product Information: APTENSIO XR(TM) oral extended-release capsules, methylphenidate HCl oral extended-release capsules. Rhodes Pharmaceuticals L.P. (per FDA), Coventry, RI, 2015.

14. Product Information: QUILLIVANT XR(R) oral extended-release suspension, methylphenidate HCl oral extended-release suspension. NextWave Pharmaceuticals Inc (per FDA), Mommouth Junction, NJ, 2021.

Product Information: Metadate CD(R) oral extended release capsules, methylphenidate HCl oral extended release capsules. UCB, Inc. (per FDA), Smyrna, GA, 2013.

Product Information: CONCERTA(R) oral extended release tablets, methylphenidate HCl oral extended release tablets. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2017.

Product Information: Ritalin LA(R) oral extended-release capsules, methylphenidate HCl oral extended-release capsules. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2013.

Product Information: RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, methylphenidate hcl oral tablets, sustained-release oral tablets. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2006.

Product Information: QUILLIVANT(TM) XR oral extended release suspension, methylphenidate HCl oral extended release suspension. NextWave Pharmaceuticals, Inc. (per FDA), New York, NY, 2013.

Product Information: VYVANSE(R) oral capsules, oral chewable tablets, lisdexamfetamine dimesylate oral capsules, oral chewable tablets. Shire US Inc. (per FDA), Lexington, MA, 2017.

Product Information: ADDERALL XR(R) oral capsules, dextroamphetamine sulfate dextroamphetamine saccharate amphetamine aspartate monohydrate amphetamine sulfate oral capsules. Shire US Inc. (per FDA), Lexington, MA, 2017.

Product Information: ADDERALL(R) oral tablets, dextroamphetamine saccharate amphetamine aspartate monohydrate dextroamphetamine sulfate amphetamine sulfate oral tablets. Barr Laboratories, Inc. (per FDA), Pomona, NY, 2015.

Product Information: MYDAYIS(R) oral extended-release capsules, dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate oral extended-release capsules. Shire US Inc (per manufacturer), Lexington, MA, 2017.

Product Information: METADATE(R) ER extended-release tablets, methylphenidate hydrochloride . Celltech Pharmaceuticals, Inc, 2002.

Product Information: Focalin(R) oral tablets, dexmethylphenidate HCl oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2019.

Product Information: FOCALIN XR(R) oral extended-release capsules, dexmethylphenidate HCl oral extended-release capsules. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2019.

Product Information: EVEKEO ODT(TM) orally disintegrating tablets, amphetamine sulfate orally disintegrating tablets. Arbor Pharmaceuticals LLC (per FDA), Atlanta, GA, 2019.

Product Information: EVEKEO(R) oral tablets, amphetamine sulfate oral tablets. Arbor Pharmaceuticals, LLC (per DailyMed), Atlanta, GA, 2016.

Product Information: DEXEDRINE(R) SPANSULE(R) oral sustained release capsules, dextroamphetamine sulfate oral sustained release capsules. Amedra Pharmaceuticals LLC (per FDA), Horsham, PA, 2017.

Product Information: INTUNIV(R) oral extended-release tablets, guanfacine oral extended-release tablets. Shire US Inc. (per FDA), Wayne, PA, 2015.

Product Information: KAPVAY(R) oral extended-release tablets, clonidine HCl oral extended-release tablets. Concordia Pharmaceuticals Inc (per FDA), Bannockburn, Il, 2014

Case Presentation: AB

AB is a 12yom with a ADHD diagnosis based on the following symptoms present for the last 2 years:

- Difficulty remaining focused during class
- "Mind in the clouds"
- Often turns in work late or doesn't complete projects at all
- Easily distracted, makes careless mistakes
- Gets in trouble in class
- Avoids homework and chores
- "Ants in his pants"
- Often blurts out answers in class
- Interrupts the teacher and his classmates
- "Motor Mouth"

AB

- AB received early intensive behavioral intervention services and has weekly check-ins with his parents and teachers to address any classroom concerns. His parents had been leaning on behavioral therapies and avoiding stimulant use, but his symptoms worsened at the beginning of the school year, and he's fallen behind in most of his classes

- He was started on MPH-ER (IR:ER 30:70) 40mg once every morning

AB's School Schedule: Fall

0700: Breakfast

- Take MPH-ER (IR:ER 30:70) 40mg before leaving for school

0755-1114: Math, Geography, Biology

1117- 1147: Lunch

1150-1437: Language Arts, Gym

1445: Ride the bus home, have a snack, and start homework

AB's School Schedule: Spring

0700: Breakfast

- Take MPH-ER (IR:ER 30:70) 40mg before leaving for school

0755-1114: **Gym**, Geography, Biology

1117- 1147: Lunch

1150-1437: Language Arts, Math

1445: Ride the bus home, have a snack, and start homework

AB’s Schedule

- His new schedule has Gym as the first class of the day, and he has been struggling to focus during his last class, Math. He is disruptive, fidgety, and often needs reminders to stay on task during individual work time. He is falling farther and farther behind as the semester continues, and he is embarrassed to ask questions for fear of being made fun of by his classmates. His teachers have brought up these concerns at the last 3 weekly check ins.

- His parents are open to making a change and would like options from which to choose

Which of the following medication options would you present to AB's parents?

What other information would you want to know before making a change?

1. Switch to an amphetamine-based product, such as amphetamine-dextroamphetamine extended release, 10mg capsule every morning
2. Add MPH-IR 10mg at lunchtime
3. Change to MPH-ER (Triphasic) 36mg every morning, equivalent to 10mg TID
4. Change to Jornay PM, starting with a 20mg capsule at 8pm every night
5. Add guanfacine ER 1mg every morning to help with hyperactivity /impulsivity
6. Switch to atomoxetine (weight based dosing and titration)

Thank you!

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