ADHD:
A Focus On Drug Therapy

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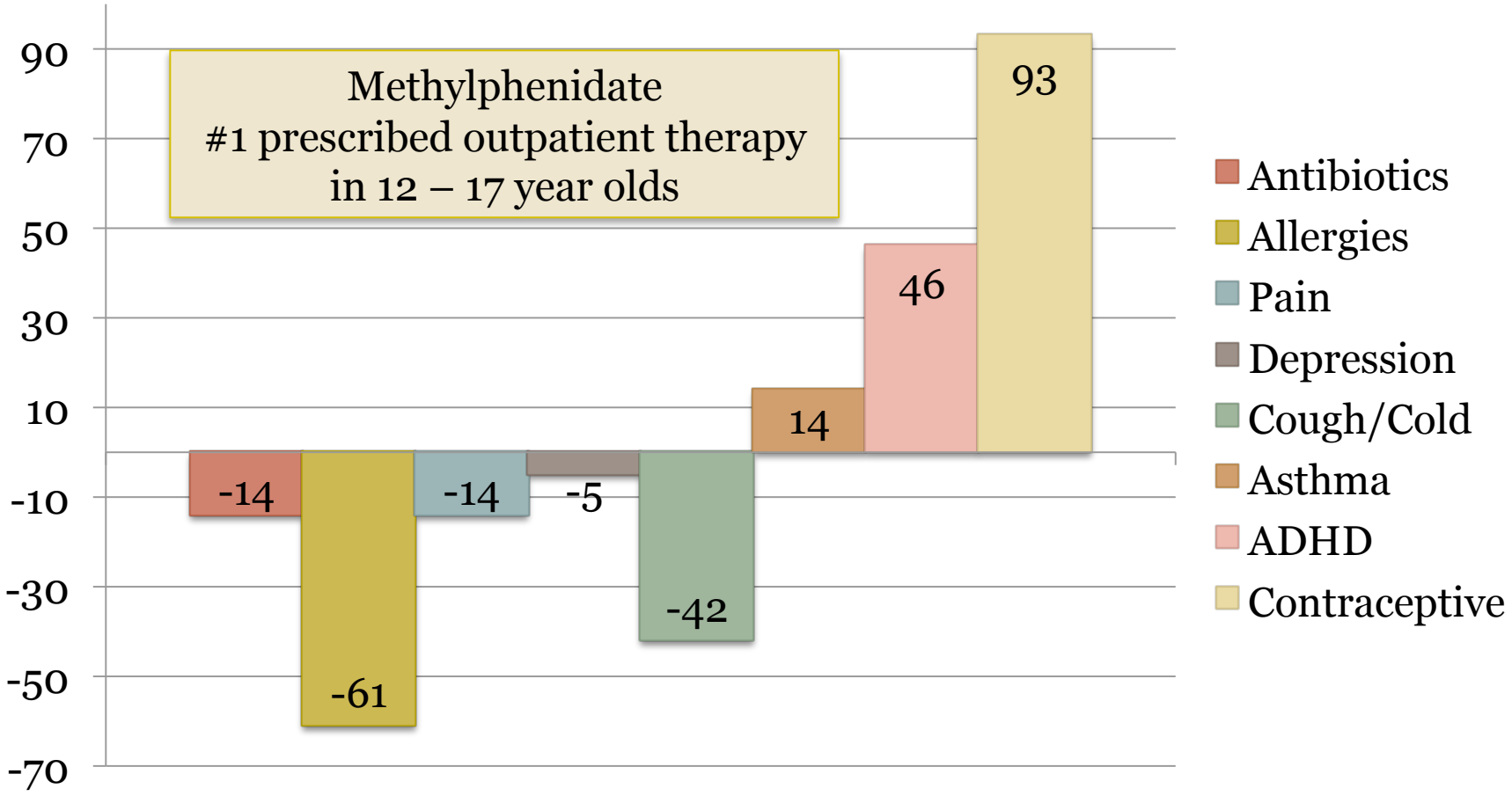
SEPTEMBER 13, 2013

Outpatient Prescription Drug Utilization in US Children, 2002-2010

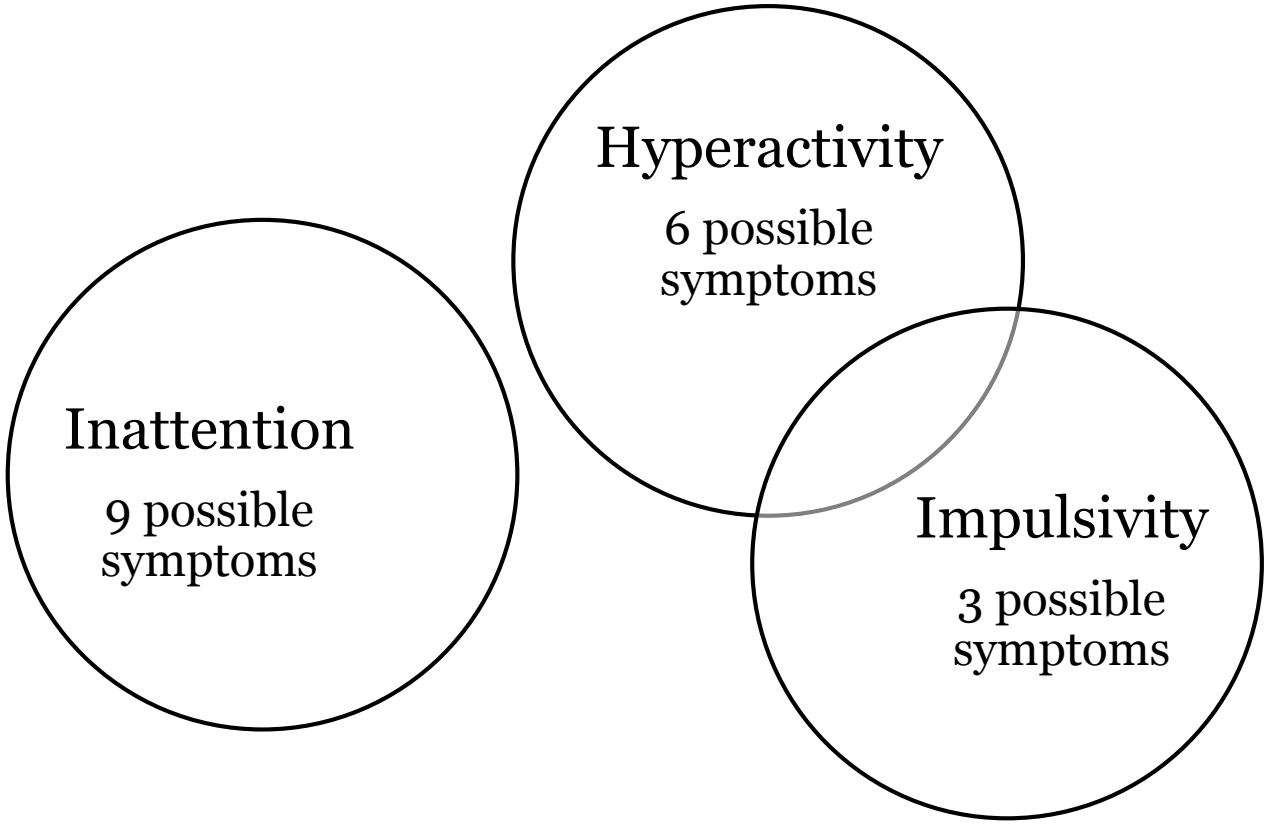


Chai G, et al. *Pediatrics.* 2012;130:23-31.

Benji is a 6 yo male recently diagnosed with ADHD. His mother notes he is very energetic and in constant motion. His history is + for disruptive episodes at home and in school. His teacher reported he has constant fidgeting, frequently interrupts others, becomes bored easily and rushes through assignments. He has kicked other children in the classroom and has difficulty making friendships. His parents have completed a 7 week behavioral training program for parents of children with ADHD. They feel that Benji's behavior is better, but still difficult. It is decided to begin Benji on medication therapy.

Family history + father with ADHD as child, negative for cardiac disease

ADHD Symptoms



ADHD Clinical Diagnosis – **DSM V**

- Persisted for at least 6 months
- Clear evidence symptoms interfere with or reduce the quality of social, academic, or occupational functioning
- Some symptoms were present prior to **age 12 years**
- Symptoms are present in $\geq$ 2 settings
- Symptoms can not be better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)

www.dsm5.org

ADHD Genetics

- Estimated 75% heritability
- 4 – 8 x increase if first degree relative with ADHD
- 2 x risk of defective 7-repeat allele in type 4 dopamine receptor gene (DRD4)
  - Results in deficits in translating dopaminergic signal to second messenger systems
  - Also affected by norepinephrine and epinephrine
- Variations in presynaptic dopaminergic transport protein (DAT1) may also be present
  - Linked to response to methylphenidate and atomoxetine – questionable clinical significance*

*McGough JJ. *Pharmacogenomics.* 2012;13:365-8.

AAP ADHD Guidelines – Initial Treatment
Action Statement Five

4 – 5 years old

- First Line
  - Parent Based Behavior Therapy
  - Teacher Based Behavior Therapy
- Methylphenidate
  - **IF** inadequate response from behavior therapy with moderate – severe continuing disturbance

6 – 11 years old

- Preferred
  - FDA – approved medications + behavior therapy
- Alternative
  - FDA – approved medications alone
  - Behavior therapy alone
- Stimulants preferred medication

Pediatrics. 2011; 128:1007.

AAP ADHD Guidelines – Initial Treatment
Action Statement Five

12 – 18 years

- Preferred
  - FDA approved medication (with assent of adolescent) + behavior therapy
- Alternative
  - FDA approved medication (with assent of adolescent) alone
  - Behavior therapy alone

Pediatrics. 2011;128:1007

Multimodal Treatment Study of Children with ADHD

Compared 4 treatment strategies of 579 children diagnosed with DSM IV ADHD, combined type

1. Systematic medication management (MedMgt)
2. Multicomponent behavior therapy (Beh)
3. Combination of 1 and 2 (Comb)
4. Usual community care (CC)

Jensen PS, et al. *J Am Acad Child Adolesc Psychiatry.* 2007;46:989-1002.

Multimodal Treatment Study of Children with ADHD

- At 14 months
  - All groups with improvement over baseline
  - Comb and MedMgt significantly greater improvement over Beh and CC
  - Comb but not MedMgt had significantly better outcomes than Beh and CC for internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement
- At 3 years
  - No significant treatment group differences in ADHD symptoms or functioning

Jensen PS, et al. *J Am Acad Child Adolesc Psychiatry.* 2007;46:989-1002.

Question 2

To initiate stimulant therapy in Benji, which of the following treatment regimens is (are) recommended?

A. Methylphenidate (Ritalin) 5 mg PO BID
B. Mixed amphetamine salts (Adderall) 2.5 mg PO BID
C. Atomoxetine 10 mg PO once a day
D. A and B only
E. All of the above

Stimulant Therapy

- Methylphenidate or amphetamine are the most effective drug treatments for ADHD
- Many studies show large effect size ~1

$$\frac{(\text{ADHD rating scale}_{\text{Therapy}} - \text{ADHD rating scale}_{\text{Placebo}})}{\text{Standard deviation of the mean}}$$

0.6 – 1 large effect

0.4 – 0.6 moderate effect

- Stimulant response rate 65-75% versus 4-30% placebo
- If one stimulant ineffective, 20-40% chance response to 2nd

Dopheide J.*Pharmacotherapy*. 2009;29:656-679.

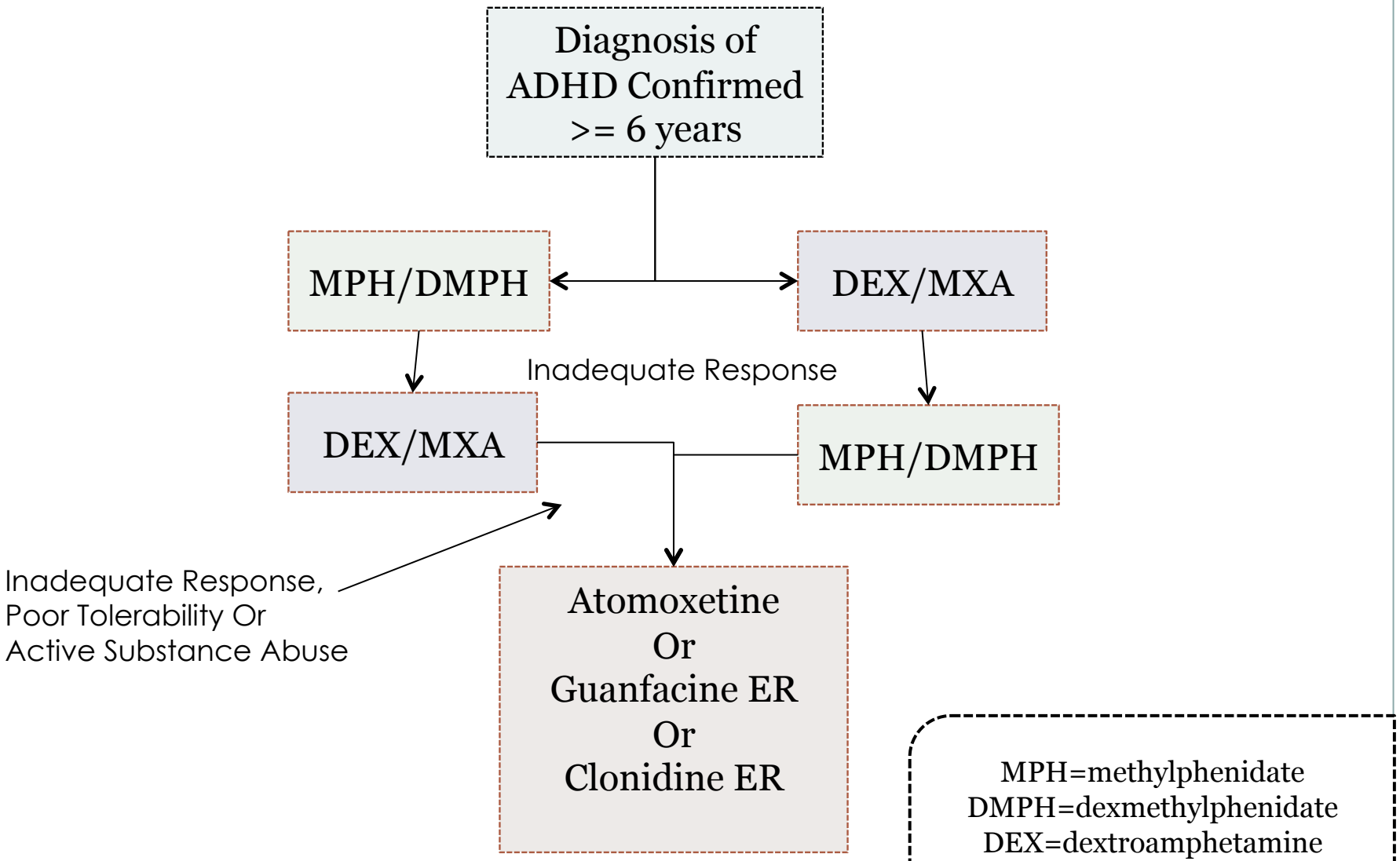


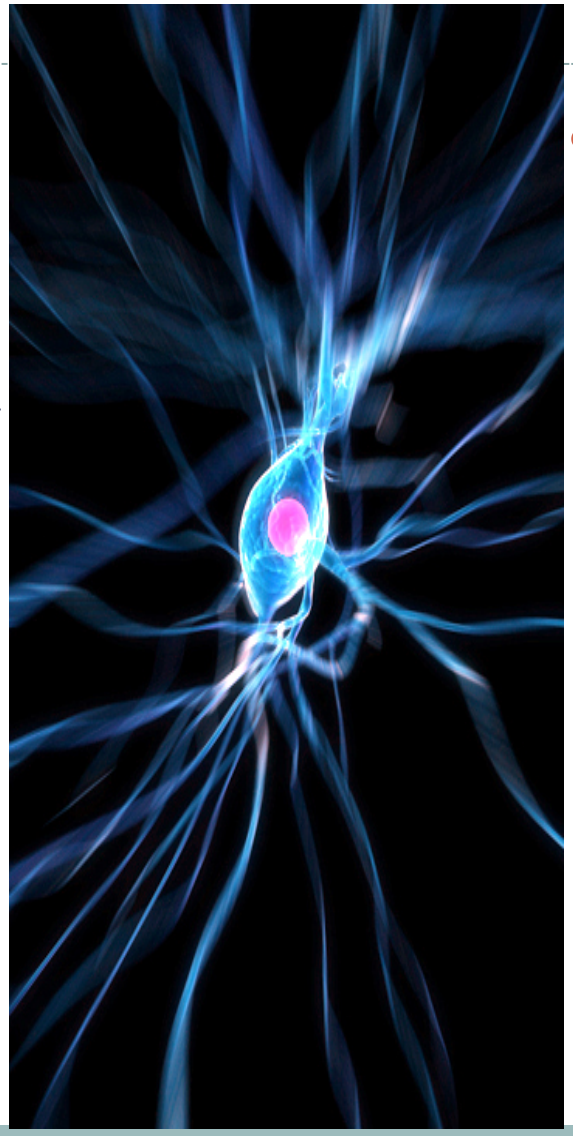
Figure 72-1 *Pharmacotherapy* and *Pediatrics* 2011

Pharmacologic Actions of Stimulants

- Block presynaptic dopamine and norepinephrine reuptake
- Amphetamines increase dopamine release.
- Also inhibit monoamine oxidase
  - Amphetamines > methylphenidate

Catecholaminergic Neurotransmission Relative to ADHD

- Dopamine
  - Striatal-prefrontal
  - Enhances signal
  - Improves attention
    - Focus
    - Vigilance
    - Acquisition
    - On-task behavior
    - On-task cognitive
    - Perception (?)



- Norepinephrine
  - Prefrontal
  - Dampens noise
    - Distractability
    - Shifting
  - Executive operations
  - Increases inhibition
    - Behavior
    - Cognitive
    - Motor

Question 3

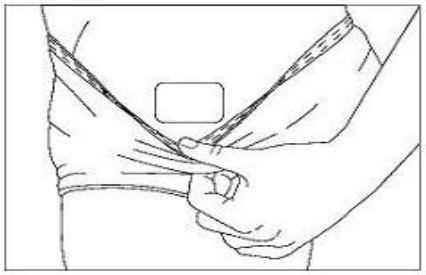
Benji is now 8 years of age and has had a positive therapeutic response to methylphenidate (Ritalin LA). However, he is having difficulty swallowing the tablet. What product could you prescribe for Benji to take the place of Ritalin LA that should work as well with a similar duration of action but less trouble swallowing?

A. Methylphenidate (Concerta)
B. Methylphenidate (Daytrana)
C. Mixed amphetamine salts (Adderall XR)
D. Atomoxetine (Strattera)

Stimulants differ by pharmacodynamics: duration of action

Length of Action	Drugs/Products
Short-acting (4-6 hr)	Dexmethylphenidate (Focalin) Methylphenidate (Ritalin, Methylin) Dextroamphetamine (Dextrostat, Dexedrine, Procentra) Mixed Amphetamine Salts (Adderall)
Intermediate acting (about 8 hr)	Methylphenidate (Ritalin SR, Metadate ER, Methylin ER) Dextroamphetamine (Dexedrine Spansules)
Long-acting (10-12 hr)	Dexmethylphenidate (Focalin XR) Methylphenidate (Metadate CD, Ritalin LA, Concerta, Daytrana, Quillivant XR) Lisdexamfetamine (Vyvanse)
Longer acting (16 hr)	Amphetamine Mixed Salts (Adderall XR)

Daytrana



- Transdermal patch form of methylphenidate
- Good alternative if difficulty swallowing tablets
- Studied in children 6-12 years
- Available in 10, 15, 20 and 30 mg patches worn for 9 hours/day
- Administered topically by placing over alternating hips for 9 hour wear time
- Onset 2 hr after application
- 20 mg patch ~ 20 mg TID IR methylphenidate
- Start low dose and titrate up
- Caution about appropriate disposal

Dopheide JA. *Pharmacotherapy*. 2009;29:656-679.

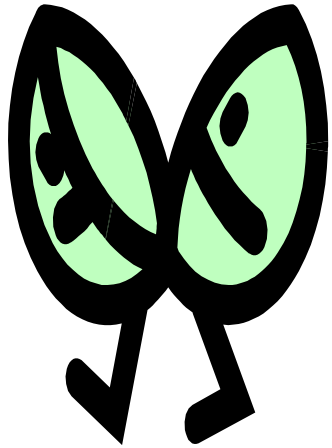
Methylphenidate HCL – Quillivant XR

- Newly approved extended release liquid
- 25 mg/5 ml
- Initial dose > 6 yrs:
  - 20 mg daily

http: Nextwave Pharms Inc.

Dexmethylphenidate

- One isomer of methylphenidate
- Dose is ½ methylphenidate dose
- Short-acting
  - Focalin
  - Duration of effect 3 – 5 hours
  - Initial dose 2.5 mg daily to BID
- Long-acting
  - Focalin XR
  - 50% IR, 50% SR beads
  - Approved for ≥ 6 years



Mixed Amphetamine Salts/Dextroamphetamine

Mixed amphetamine

- Short to intermediate acting (Adderall)
  - Duration of effect 4 – 6 hours
  - Fast onset 15 – 30 min
  - Approved ≥ 3 years
- Long acting (Adderall XR)
  - 50% IR/50% ER beads
  - Duration upto 16 hours

Dextroamphetamine

- Short acting (Dexedrine, Dextrostat, Procentra)
  - Duration of effect 3 – 5 hours
  - Approved ≥ 3 years
- Intermediate acting (Dexedrine Spansule)
  - Duration of effect 5 – 8 hours

Lisdexamfetamine (Vyvanse)

- Prodrug of dextroamphetamine (bound to l-lysine)
- Must be metabolized in the GI system
- Peak effect 3.5 hours
- Duration of effect ~ 10 hours
- Decrease euphoria compared to IR dextramphetamine
  - Possibly decreased abuse potential
- 70 mg lisdexamfetamine ~ 30 mg mixed amphetamine salts

Dopheide JA. *Pharmacotherapy*. 2009;29:656-679

Stimulant Therapy

- No efficacy difference between MPHD and dextroamphetamine or different forms
- Individual children may respond to one stimulant but not another
- Doses not usually weight based, begin with low dose and titrate up
- Reduce dose if adverse effect
  - Overly sensitive
  - Overfocused
  - Dull or restricted

AAP. Pediatrics. 2001;108:1033-1044.

ADHD Treatment Strategies

- Important to explain clearly and objectively
  - Risks
  - Benefits
  - Actions
  - Potential adverse effects
- Many parents may view starting stimulants as an emotional situation
- Stimulant medications should initially be given on a trial basis.

Woodard R. *Pediatric Nursing*. 2006;32:363-370

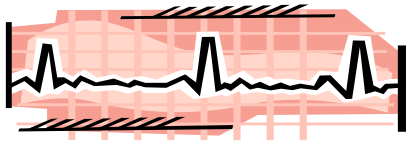
Question 4

Benji is now doing well with ADHD treatment with the Daytrana patch. He is in clinic today, and his mom is concerned because she has heard that stimulants may affect the heart and cause death. She is especially concerned because her father recently had a heart attack. You should:

A. Order an ECG on Benji
B. Taper Benji off the Daytrana and start a non-stimulant
C. Monitor blood pressure and heart rate at each visit
D. Combination of all

Stimulants and Cardiovascular Risk

- Short-term use associated with small increases in HR and BP
- 1999-2003 reports to FDA
  - 25 sudden deaths in children
  - 54 cases serious cardiovascular adverse effects (heart attacks, stroke, hypertension, palpitations, arrthymias)
  - Undiscovered structural cardiac defects found in some cases
  - Advisory committee determined rate not > general population
- ECG in children at risk because of family history or symptoms
- Recent large retrospective cohort studies have not found an association with stimulant use and adverse cardiovascular effects.



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Stimulant Adverse Effects

- Jitteriness
  - 15-30% develop motor tics
  - Contraindicated with seizure disorder per package insert
  - Reduce dose
- Sleep disturbances
  - Adjust dose schedule
    - Take last dose of day earlier or lower last dose of day
  - Consider a sedating medication at bedtime
    - Melatonin, cyproheptadine, clonidine, guanfacine
  - Methylphenidate less insomnia than dextroamphetamine
- Headache
- Stomach ache

Stimulant Adverse Effects on Growth

- Appetite suppression
  - Give child favorite foods when dose level lower
  - Add cyproheptadine
- Growth effects
  - Can cause alterations in growth hormone secretion
  - Effects minimal for most children
    - One study noted 3 kg weight deficit 1st year, 1.2 kg 2nd year
    - MTA study noted 1 – 2 cm decrease (esp. compliant, higher doses)
  - Should assess height and weight at least twice a year
  - Drug holidays may allow for rebound growth in weight/height
    - Also allows for reassessment of therapy need

Additional Points on Initiating Stimulants

- Titration
  - Goal maximum benefit/minimal adverse effects
  - Typically titrate every 3 – 7 days (weekly or bi-weekly during 1st month of therapy)
- Follow-up
  - Repeat assessment by week 4
    - Response, adverse effects, HR, BP and weight
  - Initially continue monthly follow-up until consistent response
  - Every 3 months during 1st year
  - At least twice yearly
- Trial off medicine after several years of control

AAP. Supplement to ADHD Guidelines. *Pediatrics*. Nov 2011.

Stimulant Risk of Substance Abuse

- Diagnosis of ADHD associated with greater risk of adolescent/adult substance abuse
- No studies link CNS stimulants to risk
- May help with focus in treatment programs, but recommended to treat substance abuse first prior to starting stimulants

- Misuse/diversion can occur

Misuse/Diversion of Stimulants

- Survey of 4300 adults found nonmedical use of 2%.
- Misuse in young adults 18 – 25 years has been reported as 4 – 6%.
- Diversion in college students may be significant, one study reported illicit use of 8%.
- Misuse more likely in Caucasian men, history of alcohol or illicit drug use.

Post RE, Kurlansik SL. *Am Fam Physician.* 2012;85: 890-6.

Preventing Misuse/Diversion

- Have patients sign controlled substances agreements
- Perform random urine drug screening
  - Verify patient is taking prescribed medicine
  - Screen for nonprescribed or illicit drugs
- Schedule periodic follow-up to assess medication effectiveness and potential violation of agreement

Post RE, Kurlansik SL. *Am Fam Physician.* 2012;85: 890-6.

Atomoxetine (Strattera)

- Similar structure to SSRI anti-depressants
- Lower efficacy compared to stimulants
  - Mean effect size 0.7
  - Delayed onset of therapeutic effect ~ 2 - 4 weeks
  - 2nd line agent
- Elimination primarily by hepatic metabolism
  - Subset of patients slow metabolizers by CYP2D6 – could have accumulation of drug

Atomoxetine (Strattera)

- Most common adverse effect in studies
  - Modest decrease in appetite
    - Monitor for weight loss
- Additional adverse effects
  - Vomiting
  - Sleepiness
  - Irritability, aggression
- Monitor blood pressure and heart rate
- Recent rare cases of liver dysfunction reported

Atomoxetine (Strattera)

- September 2005 – Black Box Warning on suicidal ideation
- Medication guide available at www.strattera.com
- Risk higher
  - Bipolar illness
  - Family history of bipolar illness
  - Personal or family history of attempting suicide

Alpha$_2$ Agonists

- Clonidine ER (Kapvay)
- Guanfacine ER (Intuniv)
  - Previously used as adjuncts
    - Primarily for disruptive behavior, motor tics, irritability
    - Also anxiety initiated/worsened by stimulants, improve sleep
- ER forms can be alternative to stimulants
- Effect size ~ 0.7

Alpha$_2$ Agonists

- Must monitor blood pressure as these drugs are also utilized as antihypertensives
  - Also other cardiovascular adverse effects
- Constipation common
- Sedation
  - Guanfacine less sedation than clonidine