

# Pharmacological Treatment of ADHD

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# Immediate Release Stimulants

	Onset	Peak	Duration	Daily Doses
MPH (Ritalin <sup>®</sup> , Metadate <sup>®</sup> , others)	20-60 minutes	~2 hours (Range 0.3-4 hours)	3-6 hours	2-3
D-Amphetamine (Dexedrine <sup>®</sup> , Dextrostat <sup>®</sup> )	20-60 minutes	1-2 hours	4-6 hours	2-3
D,L-Amphetamine (Adderall <sup>®</sup> )	30-60 minutes	1-2 hours	4-6 hours	2

# Limitations of Immediate Release Stimulants

- Short half-life
- Multiple daily doses to provide coverage beyond school hours
  - Compliance issues
- Uneven coverage due to short half-life
  - Trough periods between doses
  - ‘Roller coaster effect’
- Administration at school
  - Embarrassment
  - Potential for diversion

# First Generation Sustained-Release Stimulants

	Onset	Peak	Duration	Daily Doses
MPH (Ritalin SR <sup>®</sup> , Metadate <sup>®</sup> ER, Methylin <sup>®</sup> ER)	60-90 minutes	~5 hours (Range 1.3-8.2 hours)	5-8 hours	2
D-Amphetamine (Dexedrine <sup>®</sup> spansules)	60-90 minutes	NA	6-8	2

# Second Generation Sustained-Release Stimulants

- New technology
- Quicker onset than first generation agents
- Allows for once-daily dosing

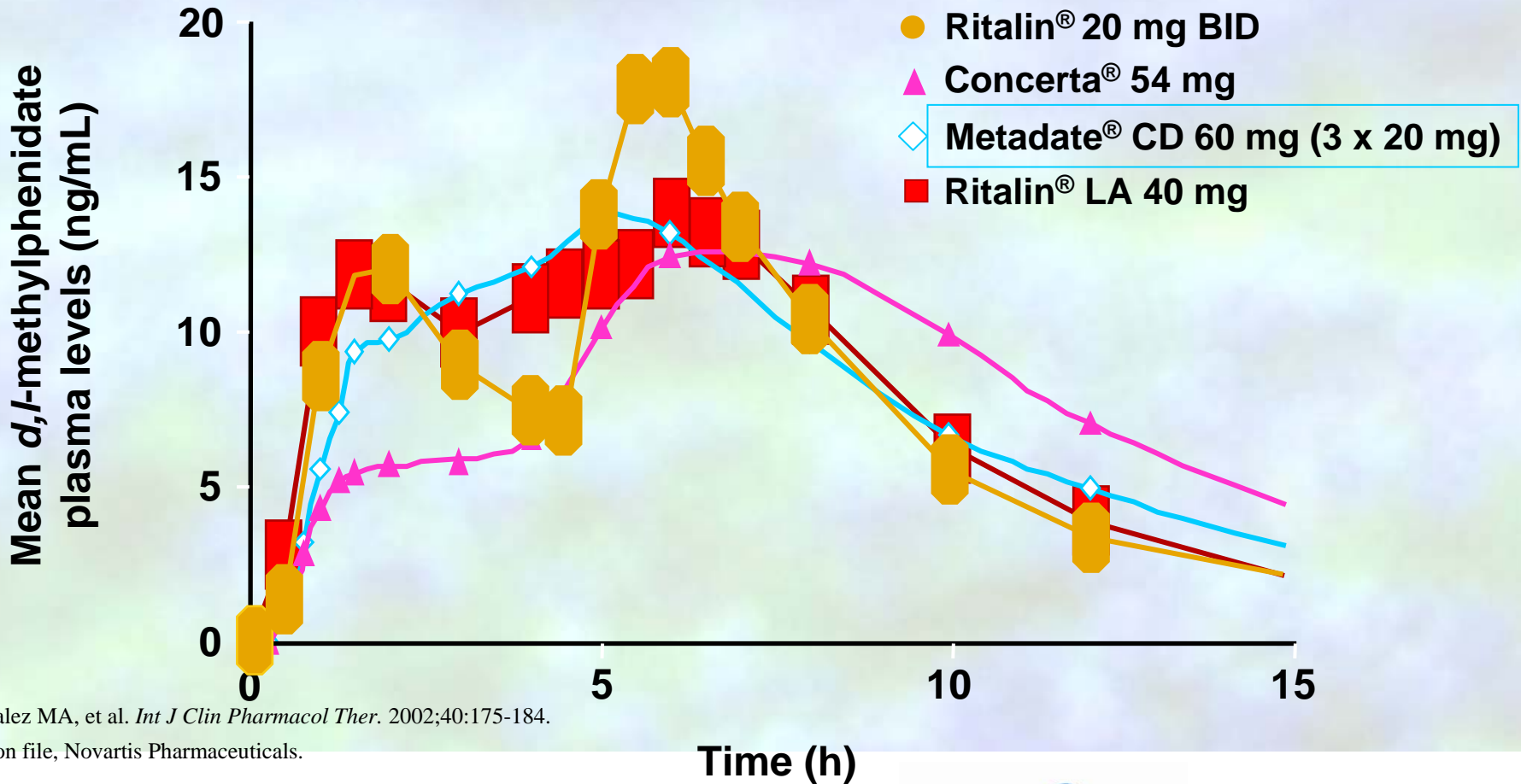
# Long-Acting Methylphenidate Formulations

Products	Concerta®	Metadate® CD	Ritalin® LA
Formulation Technology	OROS®	Diffucaps®	SODAS™
Dose	18mg 27mg 36mg 54mg	10mg 20 mg 30mg 40mg 50mg 60mg	10mg 20mg 30mg 40mg
Immediate Release	<b>22%</b> 4mg 6mg 8mg 12mg	<b>30%</b> 3mg 6mg 9mg 12mg 15mg 18mg	<b>50%</b> 5mg 10mg 15mg 20mg
Sustained/ 2 <sup>nd</sup> release	<b>78%</b> 14mg 21mg 28mg 42mg	<b>70%</b> 7mg 14mg 21mg 28mg 35mg 42mg	<b>50%</b> 5mg 10mg 15mg 20mg

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# Comparison of Extended-Release Methylphenidate Dosage Forms



Gonzalez MA, et al. *Int J Clin Pharmacol Ther.* 2002;40:175-184.  
 Data on file, Novartis Pharmaceuticals.

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# Sustained-Release Amphetamine (Adderall XR®)

- Mimics the action of IR amphetamine given BID
- Alternative to MPH-based stimulants
- Pulse-delivery system
  - Equal portions of IR and XR beads within capsule
  - IR beads release immediately after ingestion
  - XR beads release 4 hours later
- Food delays  $T_{max}$  by 2.5 hours, but not extent of absorption
- Available in 5, 10, 15, 20, 25, and 30mg capsules

# Dexmethylphenidate (Focalin®)

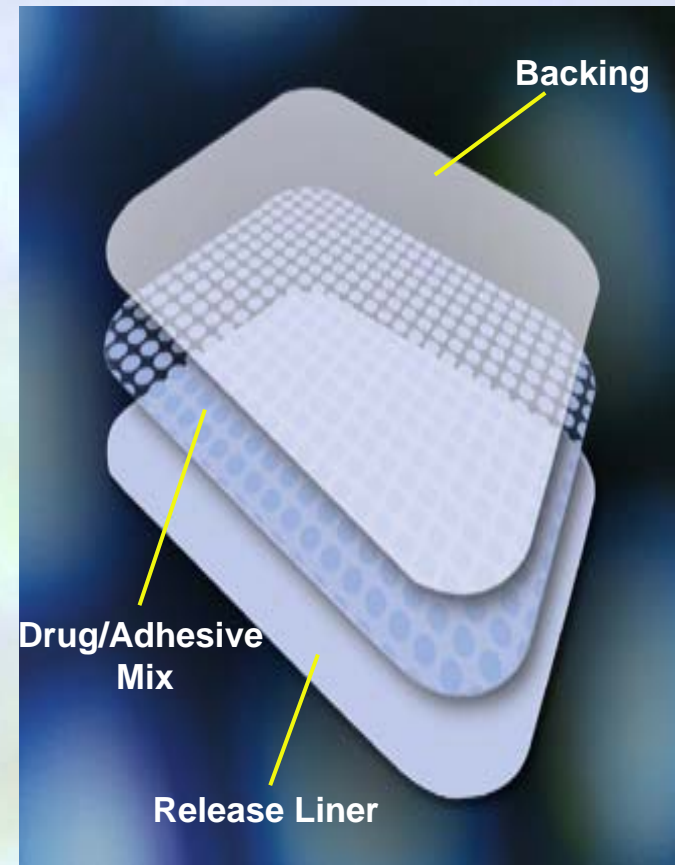
- d-*threo* (active) enantiomer of MPH
- Selectively distributes to CNS striatum
- IR and XR formulations available
- XR formulation similar release mechanism to sustained-release amphetamine
  - 50% IR, 50% XR beads within capsule
- **No real evidence for decreased side effects or better tolerability**
- Weigh cost vs. benefit

# Lisdexamfetamine (Vyvanse®)

- Dextroamphetamine prodrug (inactive until metabolized)
- Hypothesized to have lower abuse potential
  - Still classified as CII
- Recommended starting dose (children and adults) or dose when switching from other agents is 30mg
- Capsule may be taken whole or opened and dissolved in water
- $T_{\max}$  = 3.5 hours, Duration 12 hours
- Lisdexamfetamine 30, 50, 70mg = amphetamine XR 10, 20, 30mg (efficacy and duration)
- Available doses 20, 30, 40, 50, 60, 70mg

# Transdermal Methylphenidate (Daytrana™)

- Approved for use in children aged 6-12 years
- Applied for 9 hours, works for ~12 hours
- Flexible dosing
  - Regulate hours of coverage by taking off or leaving on
  - Symptom improvement in 4-6 hours
- Patch size conversion to MPH dose delivered over 9 hours
  - 12.5 cm<sup>2</sup> = 10 mg
  - 18.75 cm<sup>2</sup> = 15 mg
  - 25 cm<sup>2</sup> = 20 mg
  - 37.5 cm<sup>2</sup> = 30 mg



Methylphenidate transdermal system [Daytrana] Prescribing Information, Wayne, PA, Shire US; 2006

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# Deciding Between Stimulant Formulations

- Immediate-release vs. sustained-release
- Side effect profiles are similar
- Differences in pharmacokinetic profiles
- Cost

# Non-Stimulant Treatment Options

## Atomoxetine (Strattera®)

- Norepinephrine reuptake inhibitor
- Less effective than stimulants
  - Modest effect size with atomoxetine vs. large effect size with stimulants
- No known abuse potential; not a controlled substance
- Approved for >6 years of age, adolescents, and adults
- Duration of action ~ 8 hours
- Dosed QD or BID
  - If dosed BID, give 2<sup>nd</sup> dose late afternoon/early evening to decrease insomnia
- Available strengths: 10mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg capsules
- May take 3-6 weeks for maximum benefit

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# Atomoxetine Dosing

Child's Weight Range (pounds)	Starting Dose (Minimum of 3 days)	Target Dose: Titrate to target dose – either QD or BID
40-62	18 mg	25 mg
63-93	25 mg	40 mg
94-126	40 mg	60 mg
127+	40 mg	80 mg (100 mg Max)

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# Non-Stimulant Treatment Options

- Bupropion
  - Efficacy data for treating hyperactivity and impulsivity
  - Less effective than stimulants with a higher rate of side effects in children than MPH
  - Not FDA-approved for use in children
- Tricyclic Antidepressants
  - Desipramine, imipramine, nortriptyline
    - High rates of adverse events, especially in children

# Non-Stimulant Treatment Options

- Alpha agonists (clonidine, guanfacine)
  - Less effective than stimulants
  - May be used as monotherapy or in combination with stimulants
  - May be beneficial in patients with tics
  - Generally well-tolerated in children
    - Monitor for hypotension and daytime sedation
  - Should be reserved for monotherapy after stimulants, atomoxetine, and antidepressants have failed

# Treatment Resources

- Children's Medication Algorithm Project (CMAP)

- Treatment algorithm for ADHD

- <http://www.dshs.state.tx.us/mhprograms/CMAP.shtm>