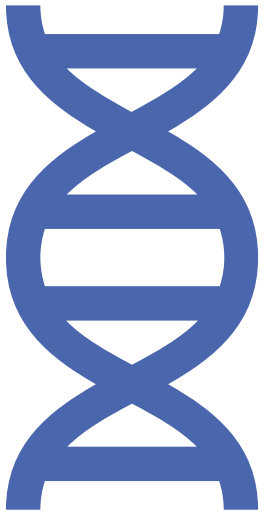





Attention Deficit Hyperactivity Disorder: A Focus on Stimulants

Michelle Blair Reinhardt, PharmD, BCPP

Board Certified Psychiatric Pharmacist

Objectives

- Recall which neurotransmitters are involved in the pathophysiology of Attention Deficit Hyperactivity Disorder (ADHD)
- Review the treatment guidelines for ADHD
- Compare and contrast stimulant medication pharmacotherapy of ADHD
- Identify resources for clinical practice

ADHD Pathophysiology

Dopamine (DA) and **norepinephrine (NE)** are the most widely implicated

Mesocortical

DA deficiency decreases the ability to maintain attention to dull or repetitive tasks, postpone indulgence, regulate mood and arousal, and resist distractions

Prefrontal

NE dysfunction leads to inability to modulate attention, arousal, and mood

Treatment Guidelines for ADHD

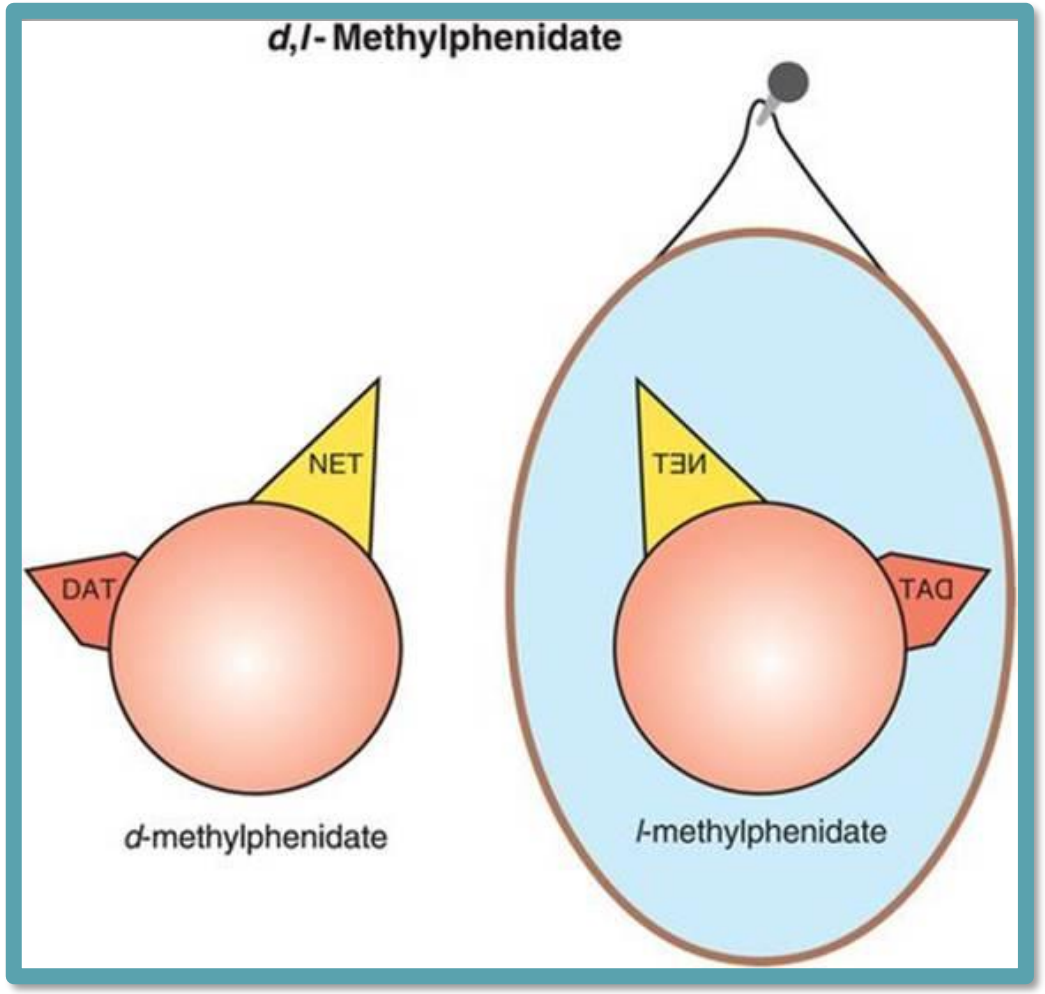
American Academy of Pediatrics (AAP) 2019	
First-line	• Ages 4-5 years: parent training behavior management • Ages 6-18 years: methylphenidate (MPH) or amphetamine (AMP)
Second-line	• Ages 4-5 years: MPH • Ages 6-18 years: atomoxetine, guanfacine XR, clonidine XR

Wolraich ML, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*. 2019;144(4):e20192528

General Differences of Stimulants

- Methylphenidate Products
  - Majority of MPH contain racemic (**50:50**) mixtures of *d*- and *l*-MPH enantiomers
    - *d*-MPH most active
    - *l*-MPH is minimally active

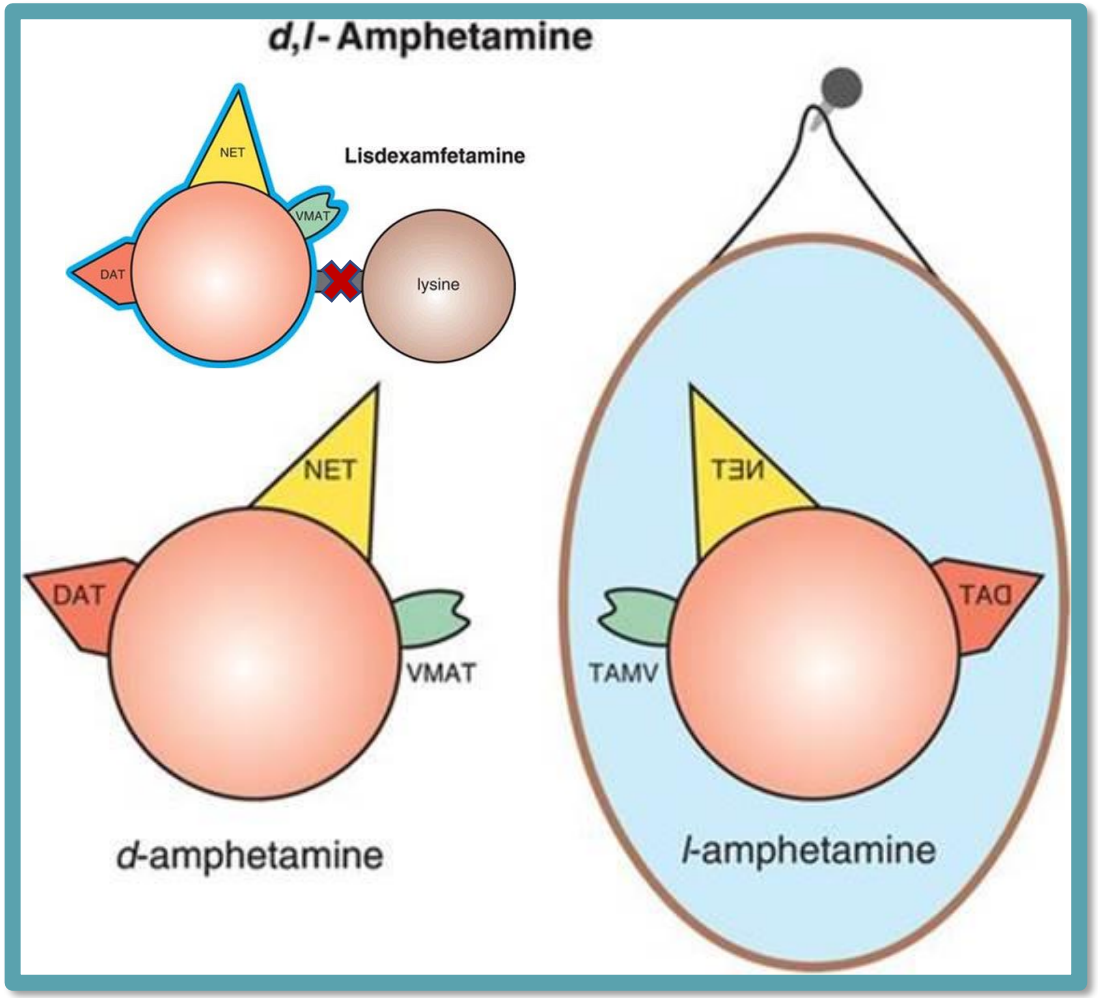
- Dexmethylphenidate (Focalin®)
  - *d*-MPH (enantiopure)



Expert Opinion on Drug Metabolism & Toxicology. 2019;15(11):937-974;
Stahl, S. M. (2008). Essential Psychopharmacology Online. Retrieved February 25, 2020

General Differences of Stimulants

- Amphetamine Products
  - "Mixed amphetamine salts"
    - Mix of *d*- and *l*-AMP enantiomers in a **3:1 ratio**
    - *d*-AMP is 3-5x more potent than *l*-AMP in blocking DA reuptake
    - *d*-AMP = *l*-AMP blocking NE reuptake
- Dextroamphetamine (Dexedrine®)
  - *d*-AMP (enantiopure)
- Lisdexamfetamine (Vyvanse®)
  - *d*-AMP + lysine (prodrug)



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Mechanism of Action

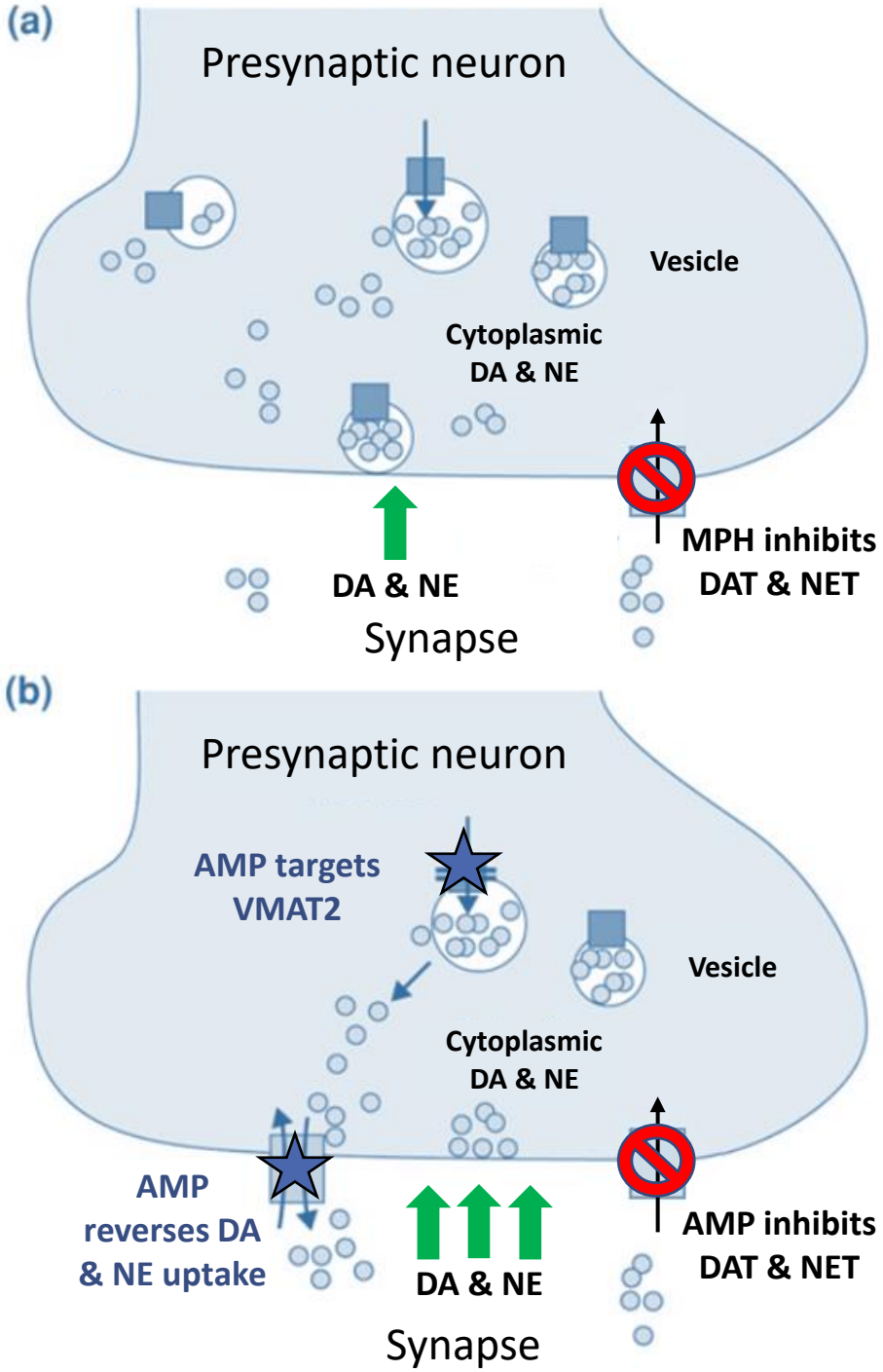
(a) Methylphenidate (MPH)

- Inhibits dopamine transporter (DAT) presynaptic neuron = *increased DA* in synapse
- Inhibits norepinephrine transporter (NET) presynaptic neuron = *increased NE* in synapse

(b) Amphetamine (AMP)

- Inhibits DAT = *increased DA* in synapse
- Inhibits NET = *increased NE* in synapse
- Targets vesicular monoamine transporter 2 (VMAT2) = *increased DA & NE* in cytoplasm
- Reverses DAT & NET transporters = *increased DA & NE* release from cytoplasm into synapse

Eur Child Adolesc Psychiatry (2012) 21:477–492



Stimulant Medications

Methylphenidate Products

- Methylphenidate and dexmethylphenidate
- Advantages:
  - Less likely to suppress appetite, worsen tics, and cause insomnia
- Disadvantages:
  - More erratic pharmacokinetics, greater differences between brand/generic formulations

Amphetamine Products

- Amphetamine, dextroamphetamine, and lisdexamfetamine
- Advantages:
  - More predictable pharmacokinetics, lisdexamfetamine may have less abuse potential
- Disadvantages:
  - Higher rate of causing/worsening tics and growth suppression, drug-drug interactions (CYP450 2D6 substrates)




Immediate & Sustained Release Formulations

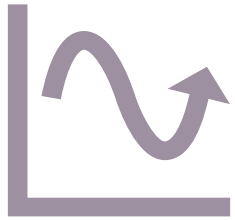
Immediate Release (IR)

First to be FDA approved

Rapid absorption and metabolism

Therapeutic effects wear off within a few hours

BID to TID dosing to achieve symptom control



Sustained Release (SR)

Ritalin SR, Metadate ER, Methylin CD

Not as effective as IR formulations

Release from a wax matrix, causing variable medication onset and duration

Onset	Duration
Rapid: 20-60 minutes	Short: 2-6 hours
Slow: 1-3 hours	Intermediate: 6-8 hours
	Long: 8-12 hours

Long-Acting Methylphenidate Formulations Approved in U.S. for ADHD

Brand Name	Enantiomer /Salt	Drug Delivery	PK Release Profile	IR/ER (%)	Onset (mins)	Tmax (hrs)	T1/2 (hrs)	Duration of action (hrs)
Long-Acting								
Adhansia XR	*d,l*-MPH	Multilayer beaded double-pulse system	Biphasic: mimics BID dosing	IR 20%; ER 80%	20-60	1st peak: 1.5 2nd peak: 11	4-7	10-16
Aptensio XR™	*d,l*-MPH	Multilayer beaded double-pulse system	Biphasic: mimics BID dosing	IR 40%; CR 60%	20-60	1st peak: 2 2nd peak: 8	12	12
Concerta®	*d,l*-MPH	OROS™ osmotically active tri-layer CR system	Compares with TID dosing of IR MPH	IR 22%; CR 78%	30-60	1st peak: 1 2nd peak: 6-10	3.5	10-12
Cotempla XR-ODT™	*d,l*-MPH	Oral dissolvable tablet	Single peak	25% IR; 75% CR	60	5	4	12
Daytrana®	*d,l*-MPH	DOT Matrix® - transdermal patch	Compares with TID dosing of IR MPH but dependent on duration of wear time	N/A	120	8-10	4-5	10-12 – effect can last ≤ 3 hrs after removal
Focalin XR®	***d*-MPH**	SODAS® - beaded double-pulse system	Biphasic: mimics BID dosing	IR 50%; DR 50%	30	1st peak: 1.5 2nd peak: 6.5	P: 2-3; A: 2-4.5	9-12
Jornay PM	*d,l*-MPH	DELEXIS® - DR/ER layered microbeads	QHS dosing – single AM peak	N/A	8-10 hrs	14	5.9-6.5	12
Metadate CD®	*d,l*-MPH	Diffucaps® - beaded double-pulse system	Biphasic: mimics BID dosing	IR 30%; DR 70%	20-60	1st peak: 1.5 2nd peak: 4.5	6.8	6-8
QuilliChew ER™	*d,l*-MPH	Chewable tablet	Single peak	IR 30%; ER 70%	60-120	5	5.2	10-12
Quillivant XR®	*d,l*-MPH	ER oral suspension	Compares with BID dosing of IR MPH	IR 20%; DR 80%	45	P: 2-4; A: 4	P: 5; A: 5.6	12
Ritalin LA®	*d,l*-MPH	SODAS® - beaded double-pulse system	Biphasic: mimics BID	IR 50%; DR 50%	10-60	1st peak: 2 2nd peak: 5.5-6.6	P: 2.5; A: 3.5	6-8

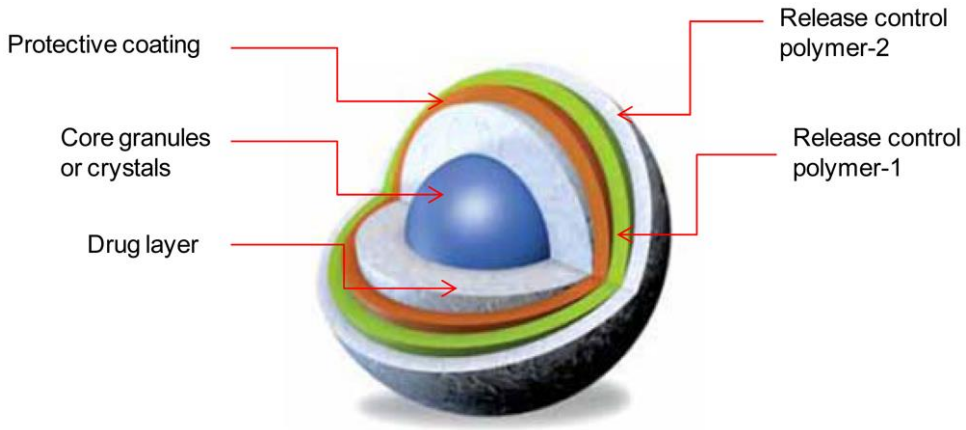
BID: twice daily dosing; CR/CD: controlled release; DR: delayed release; IR: immediate release; LA: long acting; ODT: oral dissolvable tablet; QHS: at bedtime; TID: three times daily; XR/ER: extended release

Expert Opinion on Drug Metabolism & Toxicology. 2019;15(11):937-974; Jann, M. (2016). Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents.

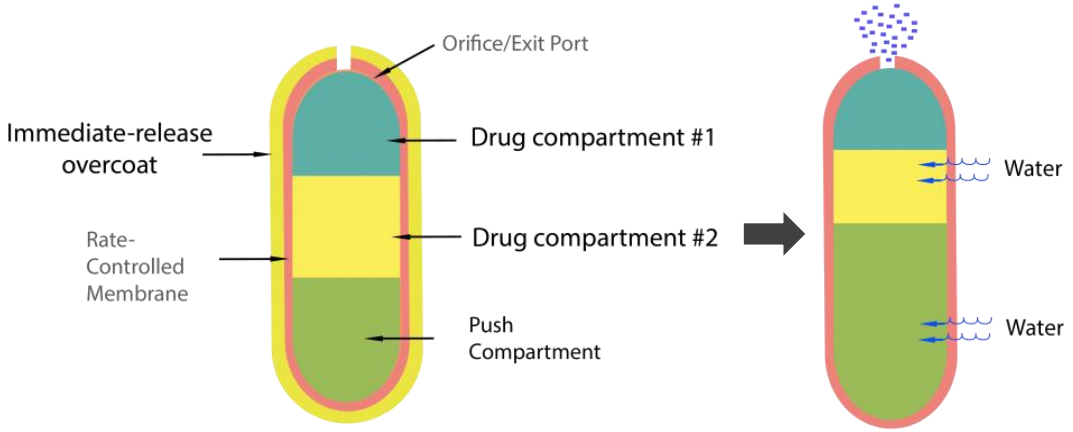
Long-Acting Amphetamine Formulations Approved in U.S. for ADHD

Brand Name	Enantiomer/Salt	Drug Delivery	PK Release Profile	IR/ER (%)	Onset (mins)	Tmax (hrs)	T1/2 (hrs)	Duration of action (hrs)
Long-Acting								
Adderall XR	Mixed salts of *d,l*-AMP (ratio of 3:1)	SODAS® - beaded double-pulse system	Biphasic: mimics BID	IR 50%; DR 50%	30	7	9-14	10-12
Adzenys ER	Mixed salts of *d,l*-AMP (ratio of 3:1)	Liquid oral suspension	Single peak	IR 50%; DR 50%	-	5-6	9-15	10-12
Adzenys XR-ODT	Mixed salts of *d,l*-AMP (ratio of 3:1)	Oral dissolvable tablet	Single peak	IR 50%; DR 50%	-	5-6	9-12	10-12
Dyanavel XR	Mixed salts of *d,l*-AMP (ratio of 3.2:1)	LiquiXR® - liquid oral suspension	Single peak	Not reported	60	~4	10-15	8-10
Mydayis	Mixed salts of *d,l*-AMP (ratio of 3:1)	Triple-bead extended release	Triphasic: mimics TID	Not reported	60	7-10	10-13	16
Vyvanse	***d*-AMP**	Prodrug	Single peak	N/A	-	3.5	9-12	10-12

Spheroidal oral drug absorption system (SODAS®)



Osmotic-controlled release oral delivery system (OROS®)



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Managing Common and Uncommon Side Effects

Adverse Effect	Management Strategy
	Common Adverse Effects
Loss in appetite, weight loss	• When stimulant effects are low (i.e. breakfast, bedtime), give a meal high in calories
Stomachache	• Give stimulant on a "full stomach" • Decrease the dose if possible
Insomnia	• Give the stimulant earlier in the day and/or decrease the last dose of the day • Switch to intermediate duration stimulant
Headache	• Give stimulant with food or divide the dose • May consider analgesic agent (i.e. apap, ibu)
Rebound symptoms	• Trial a longer-acting stimulant
Irritability/Jitteriness	• Decrease dose • Assess for comorbid condition (i.e. anxiety, depression)
	Uncommon/Rare Adverse Effects
Zombie-like state	• Decrease dose or change stimulant
Tics, abnormal movements	• Decrease dose • Consider alternative medication
Hypertension, pulse fluctuations	• Decrease dose • Change medication
Hallucinations	• Stop stimulant and reassess diagnosis

Serious Adverse Events

Growth suppression

~1 cm/yr growth suppression during the 1st 3 years

Black box warning – sudden death & serious cardiovascular adverse reactions

Baseline patient history, cardiac exam and EKG

New-onset/worsening of psychiatric manifestations

Summary & Pearls

- Response to methylphenidate vs. amphetamine is idiosyncratic
- MPH thought to have less adverse drug reactions
- AMP thought to have more favorable pharmacokinetics
- Evaluate when symptoms occur to help identify which medication to use based on onset/duration
- Adverse effects can often be managed without stopping the stimulant
- Start at a low dose and titrate every 1-2 weeks
- Titrate to max dose that controls symptoms without adverse effects




Resources

1) Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Edition) – June 2019
   - https://hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/facilities-regulation/psychiatric/psychotropic-medication-utilization-parameters.pdf

2)

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2019, VOL. 15, NO. 11, 937–974
https://doi.org/10.1080/17425255.2019.1675636

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REVIEW

OPEN ACCESS Check for updates

An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations

Ann C. Childress[a], Marina Komolova[b] and F. Randy Sallee[c]

[a]Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV, USA; [b]Highland Therapeutics Inc., Toronto, ON, Canada; [c]Ironshore Pharmaceuticals Inc., Durham, NC, USA

Questions?