

ADHD - Stimulant treatments

دکتر شاهرخ امیری

فوق تخصص روانپزشکی کودک و

نوجوان

استاد دانشگاه علوم پزشکی تبریز

Stimulant Treatments

- Immediate- release Stimulants
 - Ritalin, Methylin , Dexedrine, Adderall and Focalin
- long acting preparations
 - Concerta
 - Metadate CD
 - Ritalin LA
 - Adderall XR

Stimulant Treatment

- long acting preparations
- Focalin XR
- Methylphenidate transdermal system:MTS (Daytrana)
- lisdextroamphetamine dimesylate :LDX (Vyvanse)
- ER oral suspension MPH

- Used for past 60 + years
- *Stimulants are the first class of compounds reported to be effective in the treatment of ADHD in children*
- Stimulants are FDA approved for the treatment of AD/HD in children and adolescents, but most physicians consider them the first line medication treatment for ADHD in adults too.
- Response rate to stimulants is about 70%, even in adults
- There may be response differences between the stimulants (methylphenidate vs. amphetamine salts)

- Stimulants appear to cause an increase in the availability of dopamine in the nucleus accumbens or the striatum areas of the brain.
- The effect on the nucleus accumbens is believed to cause euphoria and to be responsible for the stimulants' abuse liability.
- Dopamine increases in the striatum may be associated with the risk of motor tics

- A recent study reported in the Jan. 1999 issue of *Science* suggests that methylphenidate elevates levels of serotonin, and that this may account for some of its calming effects

ADHD: Stimulants

Side effects:

- Decreased appetite
- Insomnia
- Headaches
- Stomachache
- Irritability/Moodiness
- Tics
- Changes in sex drive

Side effects:

- Diplopia
- Dizziness
- Edema
- Fluid retention
- Rebound, "Wear-off" effects
- Increased heart rate and blood pressure

Side effects:

- More rarely increased Lethargy and Fatigue
- Stimulant- associated toxic psychosis
- Delays in growth
- Cardiovascular side effects
- Obtaining an ECG??

Substance abuse and Stimulants

- After FDA review, the only black box warning for stimulants concerns their abuse potential
- While misuse for treating fatigue can be accomplished by oral administration, abuse for euphoria typically requires snorting or injecting, and thus there is greater risk in immediate-release formulations that can be crushed.

Substance abuse and Stimulants

- Studies of ADHD patients **do not support the** fear that being prescribed stimulants will lead to substance abuse
- Studies supporting the abuse potential of stimulants have looked at other populations
- Several studies including a 13 year longitudinal study indicate that stimulant treatment of ADHD protects **against future** substance abuse
- Although stimulants can indeed be abused, their use does not seem to cause abuse individuals who do not already have a substance abuse problem

Substance abuse and stimulants

- The Food and Drug Administration (FDA) has classified the stimulants as Schedule II.
- Schedule II medications generally have a higher potential for abuse than most other types of medication.
- If individuals take their medication as prescribed, the potential for addiction to methylphenidate or amphetamine is fairly low.
- Still we are cautious about prescribing stimulants to individuals who are abusing drugs. **Injecting stimulants intravenously, inhaling them or mixing them with illegal drugs** can lead to further substance abuse

- Moreover, the most commonly abused substance in adolescents and adults with ADHD is marijuana, not stimulants

ADHD: Stimulants

Comes in several forms: **Methylphenidate**

- a) **Straight Ritalin** (5, 10, 15 and 20 mg)
- b) **SR Ritalin** (Ciba 20 mg) seems to show inconsistent results
- c) **Metadate CD, ER**, (Celltech 10 & 20 mg)
- d) **Concerta(ER)** (18, 27, 36 and 54 mg) (11- 12)
- h) **Ritalin LA** (5, 10, 15, 20 mg)
- e) **Methylin** (5, 10, 20 mg)
- f) **Daytrana Patch** (10, 20, 30 mg)

Dextro-amphetamines/amphetamines

- 1) Most used straight release are:
 - a) **Dexedrine(Dextroamphetamines)** (Short-acting tablets 5mg, 10 mg), Rapid onset of action 20–30 minutes. Lasts 4-5 hours.
 - b) **Dexedrine spansule (5,10 and 10 mg) (8 hours)**
- **Amphetamine**
- Dextro-amphetamines/amphetamines
 - a) Adderall
 - b) Adderall XR
- **Lisdexamfetamine(Vyvanse)**

New-Generation Stimulants

- **Dexmethylphenidate**
- **Focalin**
- **Focalin XR**

New-Generation Stimulants

- Methylphenidate has four optimal isomers: d-threo, L-threo, d-erythro, L-erythro
- There is stereoselectivity in receptor site binding and its relationship to response.
- The standard preparation is composed of the threo,d,l racemate.
- Data suggest that the d-methylphenidate isomer is the active form.
- **Focalin** (Dexmethylphenidate): d-threo methylphenidate compound
- Form: Focalin (2.5, 5, 10 mg)

long acting Stimulants

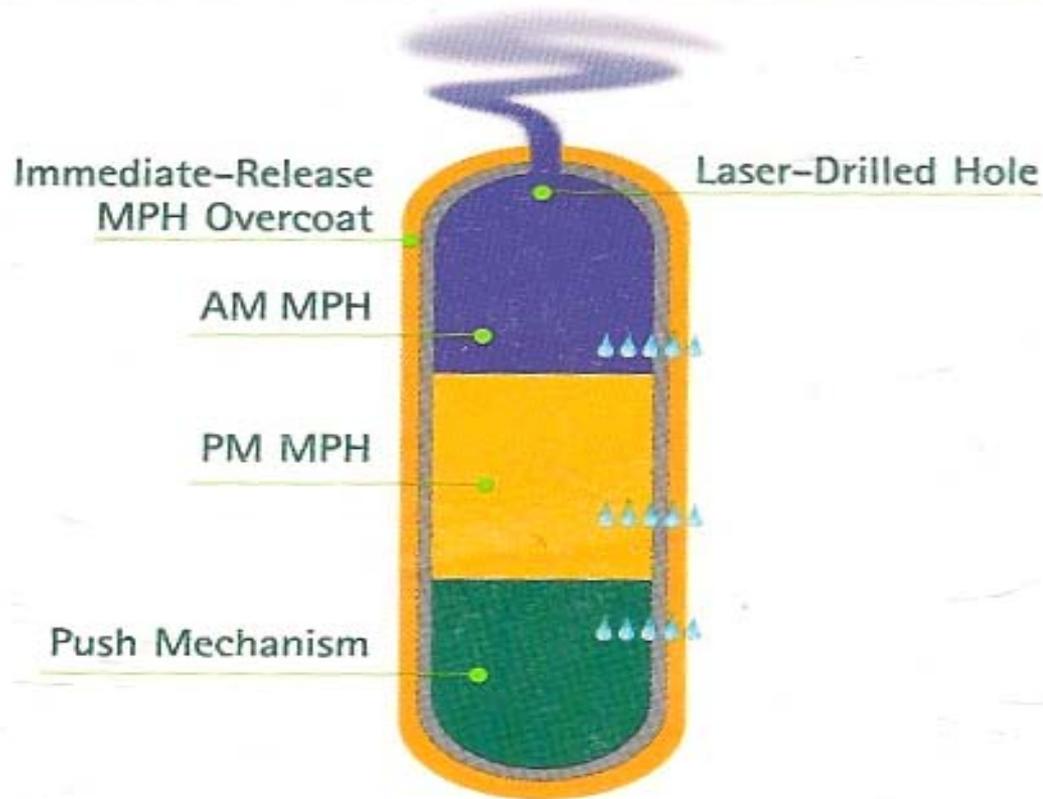
Concerta

- For patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day.
- Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults

Concerta

- Effective for 12 hours
- Well tolerated with mild appetite suppression but no sleep abnormalities
- Form: Capsules(18, 27, 36,54 mg)

The Concerta™ OROS® System



- After the MPH overcoat dissolves, Concerta™ continues to deliver MPH in the morning, followed by a higher concentration in the afternoon to maintain efficacy through 12 hours.^{1,2}
- Smooth delivery minimizes fluctuations in peak-trough plasma concentrations seen with MPH tid.

One morning dose provides smooth delivery throughout the day

Release of Methylphenidate from a Concerta® 18-mg Tablet

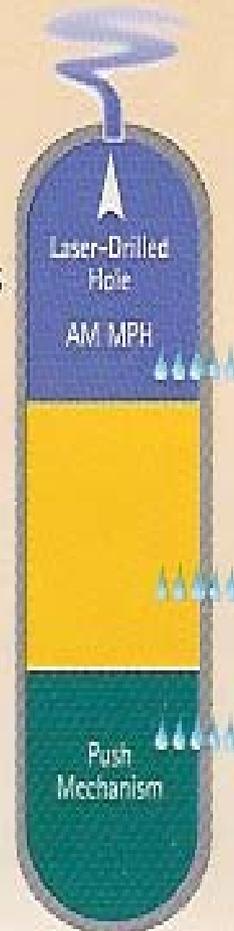
Morning

A MPH overcoat provides an immediate release of 22% of the dose within 1 hour.



1 hour later

The push mechanism absorbs fluid and expands, acting as an osmotic pump to provide smooth delivery of MPH for the rest of the morning.



Afternoon

As the push mechanism continues to expand, a higher concentration of MPH is released during the afternoon.

Delivering an ascending profile results in a smooth effect through 12 hours, with or without food.



Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA

■ Previous Methylphenidate Daily

- 5 mg Methylphenidate three times
- 7/5 mg Methylphenidate three times
- 10 mg Methylphenidate three times daily
- 15 mg Methylphenidate three times daily
- 20 mg Methylphenidate three times daily

■ Dose Recommended CONCERTA® Starting Dose

- daily 18 mg every morning
- daily 27 mg every morning
- 36 mg every morning
- 54 mg every morning
- 72 mg every morning

long acting Stimulants

- **Metadate CD**
- **Form: Capsules(10, 20, 30,40,50,60 mg)**
- **Mixture of immediate and delayed release**
- **30% 70%**
- **Effective for 6-8 hours**

Metadate

- Peak effect is generally around 5 hours and its effect lasts 8 hours
- Metadate CD encapsulates the methylphenidate in two types of beads.
- About 30% of the medication is released immediately.
- The remainder is released over time through beads with a release-control membrane.
- **If the individual cannot swallow the capsule, one can open it and sprinkle it on food**

Ritalin LA

- Provide effective methylphenidate treatment for 8-9 hours
- It uses a bimodal release system
- Consists of a mixture of immediate and delayed release beads in a 50:50 ratio
- Form: Capsules(10, 20, 30,40 mg) to approximate 10,15,and 20 mg bid dosing of MPH-IR
- **May be used as a sprinkle preparation for children unable to swallow pills**

Adderall XR

- Consists of a mixture of immediate and delayed release beads in a 50:50 ratio
- Form: Capsules(5, 10, 15,20 ,25,30 mg)
- Provide effective treatment for 12 hours postdose



Focalin XR

- Consists of a mixture of immediate and delayed release beads in a 50:50 ratio
- Form: Capsules(5, 10, 15,20 ,25,30,35 and 40 mg)
- Provide effective treatment for 10-12 hours
- FDA approved for children , adolescents and adults

Daytrana-a methylphenidate patch

- Methylphenidate transdermal system [MTS]
- The drug does not go through first-pass metabolism in the liver; therefore, more methylphenidate is bioavailable
- Useful for patients who have difficulty swallowing or tolerating oral formulations (e.g., nausea) or patients who need flexible duration of medication effect
- Effective over 12 hours for a wear time of 9 hours

Vyvanse: lisdextroamphetamine dimesylate

- LDX is a novel prodrug in which d-amphetamine is covalently bound to the amino acid l-lysine
- Following oral administration, LDX is converted in the body to the active d- amphetamine after enzymatic hydrolysis in rate-limited manner, at or following absorption
- Saturation of enzymatic hydrolysis at supratherapeutic doses suggests that LDX may be associated with diminished risk for abuse and toxicity
- LDX is available in 20,30,40,50,60, and 70 mg

ADHD

Vyas[®] 30, 50, 70 Lisdexamfetamine dimesylate



- برای اولین بار در ایران
- مصرف یکبار در روز به دلیل نیمه عمر طولانی تر
- یک درمان طولانی اثر، کارآمد و ایمن برای ADHD اطفال و بزرگسالان
- یک درمان طولانی اثر، کارآمد و ایمن برای اختلال پرخوری در بزرگسالان (Binge Eating Disorder)
- احتمال سوء مصرف کمتر در مقایسه با سایر داروهای محرک
- قابلیت باز کردن و حل نمودن محتویات کیسول در آب برای کودکان و مبتلایان به اختلال بلع

ER oral suspension MPH

- Extended-release oral suspension of methyphenidate is supplied as a powder that is reconstituted with water by the pharmacist prior to dispensing
- Suspension has a concentration of 25 mg/5ml (5 mg/ml)
- 20% immediate release IR and 80% ER methyphenidate
- Provide effective treatment for 12 hours postdose

Provigil (modafinil)

- **Provigil** (modafinil): a medication used for Narcolepsy
- studied aggressively for ADHD
- May be used once a day or twice a day
- Does not affect reinforcement pathways; little risk for misuse or diversion
- FDA approval was denied

