Stimulants

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Two major classes of stimulants:

- **Methylphenidate *(MPH)***
- **Amphetamine *(AMP)***
- Stimulant **response rate** in ADHD: **70%**
- **Cumulative** response rate of **2 major classes** of stimulant: **85%**
- Share **similar** risks & benefits

Mechanism of stimulants:

- Increasing the **synaptic availability** of:
- **Dopamine *(DA)***
- **Norepinephrine *(NE)***

- ~ **40%** respond **equally** to AMP & MPH
- → If the initial stimulant **fails** optimal response
- An **alternative** stimulant **class** may be **helpful**
- **<u>In children & adolescents:</u>**
- Tolerability of **AMP < MPH**

Stimulants available in Iran:

- **Methylphenidate** *(short acting)*
- Tab: **10** mg

- **Methylphenidate Sandoz** *(long acting)*
- Tab: **18** mg, **36** mg, **54** mg

- **Lisdexamfetamine** (Vyvance)
- Cap: **30** mg, **50** mg, **70** mg

Methylphenidate (MPH): *(Tab. 10 mg)*

- **Starting** dose**: 2.5-5** mg/day **BD/TDS**
- **Increase** dose**: 5-10** mg/day **Q week**
- **Onset** of action**: 20-60** min
- **Duration** of action: **3-6** h (MPH< AMP)
- **Daily** dose: **2.5 – 20** mg BD, TDS
- ***(Daily dose: 0.5-2** mg /kg/ day)*

The initial dosage:

- May be a **single 2.5-mg** dose in **younger** children
- **Single 5-mg** dose in **older** children.

Dosage may be raised:

- Every **5 to 7** days
- **5** mg bid in **younger** children
- **10** mg bid in **older** children.

Methylphenidate:

- **Preschool** children: **10-40** mg /day
- **School age** children: **10-60** mg /day
- **Adolescents**: **10-90** mg /day

Assess response at:

- Home & school
- **5-7 days** of **observation**
- Is recommended **between dose changes**

- **Delays** in **absorption** with **high-fat** meal
- → May lasts **all day**
- **Potency:** MPH < AMP
- → doses of AMP are ½- **2/3** the dose of MPH
- Both metabolized in **liver**

❑ **Methylphenidate Sandoz *(long acting)*:** *(Tab. 18 – 36 – 54)*

- **Starting** dose**: 18** mg/day
- **Increase** dose: **18** mg/day Q week
- **Onset** of action**: 1/2- 2** h
- **Duration** of action: **12** h
- **Daily** dose**: 18-90** mg / day

- Methylphenidate 10 mg tab: **5** mg **TDS** (**1/2** – ½ - ½)

~ ~ Methylphenidate Sandose **18** mg tab/day

- Methylphenidate 10 mg tab: **10** mg **TDS** (**1** – **1** – **1**)

~ ~ Methylphenidate Sandose **36**mg tab/day

- Methylphenidate 10 mg tab: **15** mg **TDS** (**1** ½ - **1** ½ - **1** ½)

~ ~ Methylphenidate Sandose **54** mg tab/day

- **Lisdexamfetamine** *(Vyvance)*: *(Cap. 30 – 50 – 70)*

- **Starting** dose**: 10** mg
- **Increase** dose: **10-20** mg/day Q week
- **Onset** of action: **2** h
- **Peak** of action: **3-4** h
- **Duration** of action: **12** h
- **Daily** dose: **0.5-1.5** mg /kg /day

Stimulants side effects:

- **Different formulations** of methylphenidate/amphetamine
- **Similar** side-effects
- **Almost similar** in pediatrics/adults
- **Severe side effects** occur in **4–10%** of children

- **More sensitive to adverse effects:**

1. **Preschool** children
2. Those with **developmental delays**
3. The **elderly**

- But still **stimulants** may be the **1st line treatments** in these populations
- Although **50%** response rate

Common side effects:

- Sleep complications (11–30%)
- Anorexia, weight loss (13–20%)
- Headaches (12–15%)
- Abdominal pain (6–12%)
- Emotional lability (2–10%)
- Mild increase in **PR & BP** ***(in normal range)***

Stimulants side effects:

- Most **short-term & acute** side effects
- Likely related to **higher doses**
- **Careful dose titration** mitigates them

- Sleep Disturbances
- Rebound Effect
- Effects on Growth *(uncommon)*
- Emergence of Tics *(uncommon)*
- Cardiovascular effects *(uncommon)*
- Abuse & Dependence *(uncommon)*
- Misuse & Diversion
- Toxic Psychosis *(rare)*
- Absolute Contraindications
- Relative Contraindications
- Uncommon Side Effects

Sleep Disturbances *(1/3)*

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Sleep disturbances *(up to 30%):*

- Many have **sleep difficulties prior** to receiving stimulants
- **Late** afternoon/early **evening** administration
- **Delay** of sleep **onset**
- **Last dose** of methylphenidate should be **lower**
- The **3rd dose** should be **1/2(*or even less*)** of the 1st & 2nd doses
- **Rebound** effects associated with stimulant withdrawal
- ***Clonidine, Risperidone, Melatonine*** as an aid for sleep

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❑ Rebound effect:

- Occur **between doses** or following the **final dose**
- May be due to **environmental effects**
  (late afternoon & evening fatigue, hunger, homework,…)

1. Use of **additional dose** or **long acting** stimulants
2. **Alternative or supplementary** medications

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❑ Effect on Growth *(uncommon)*:

- **Height, Weight, PR, BP** in each visit
- **Monitor growth** in patients taking stimulants.
- **Maximal reduction** occurred in the **1st year**
- **Decreased** in the **2nd year**
- **Normalize** in the **3rd year** of treatment

Effect on Growth *(uncommon)*:

- **Children with ADHD may be:**
- **Shorter** than their age mates **before puberty**
- But "**catch up**" in adolescence.
- **Give stimulants:**
- With **food**
- Or immediately **after meals**.

- **Effect on Growth *(uncommon):***
- **Reductions** are **small**, **attenuate** with time
- & **do not** cause to become **short or thin**
- **Greater** for **children** *(compared with adolescents)*
- **Final** adult **height** is **not affected**

❑ **Effect on Growth *(uncommon):***

- If **weight/height** crossing **2 percentile** on growth curve:
- → **Prompt clinical response**:

1. **Nutritional** supplementation
2. Dose **reduction**
3. Change to **non-stimulant** medication.

- **Effect on Growth *(uncommon):***

- **"Drug holidays" ?**
- **Weighed** against the risk for:
- **Exacerbation** of **symptoms**
- Transient **behavioral deterioration**

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Emergence of tics *(uncommon)*

- For many years, stimulants had been thought to induce/worsen tics
- **Last decade studies:** stimulants do not worsen/reactivate tics
- **MTA of RCTs**: **No causal** association between stimulants & tics
- Even might **improve pre-existing tics** ***(1/3 get better)***

- **Emergence of tics *(uncommon):***

  - In those with **personal/family history** of tics:

  - If tics' exacerbation/de novo tics during stimulant use:

  - Likely to be **coincidental** *(than causative)*

- **In most cases:**

  - → The **benefit** of treating ADHD, **outweighs** the risk of stimulants triggering tics.

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❑ **Cardiovascular effects *(uncommon):***

- **No risk** of cardiovascular **complications**
- **No elevations** in **PR or systolic/diastolic BP**
- **ECG** is **not routinely** indicated in **healthy** youth
- ECG should be at the **physician's judgment**

Cardiovascular effects *(uncommon)*:

- Risk elevated with a **family history** of:
- Early **cardiac death**
- **Arrhythmia**
- Cardiogenic **syncope**

- **Cardiovascular effects *(uncommon)*:**

  - Risk elevated with a **personal history** of:

  - **Structural** cardiac **abnormalities**

  - **Long QT** syndrome

  - **Palpitations**

  - **Shortness** of **breath**

  - **Exercise-induced:** fainting episodes, chest pain

- **In such cases:**

- Consultation with a **pediatric cardiologist** is recommended

- **PR & BP**: greater **significance** in **adults**

- **Stimulants** should **not** be **used** in children with:

  - **Hypertrophic cardiomyopathy**
  - **Coronary artery abnormalities**
  - **Subaortic stenosis**
  - **Tetralogy of Fallot**

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- **Abuse & Dependence *(uncommon)*:**

- **Untreated** cases of **ADHD:**

- Have an increased **risk** of **SUD**

- **MTA:**

- Stimulants **do not** increase risk for **SUD.**

❑ **Abuse & Dependence *(uncommon):***

- **A prospective study**:
- Risk of **SUD increased** with **increased age *(delay in treatment)*** at **initiation** of stimulants
- ➔ **delays** in **treatment** of ADHD
- May be associated with the **development** of **SUD.**

Abuse & Dependence *(uncommon):*

- **No evidence** that youth with ADHD **abuse** prescribed medication

- **Registry study (2012):**

- Medication **reduces** the **risk** of drug abuse **30-40%** in **adult ADHD.**

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Misuse & Diversion:

- Up to **5%** of **16-25 year olds** reported lifetime nonmedical **misuse.**

Diversion:

- Giving away, selling, or otherwise distributing one's own medication

- **1/3** of stimulant prescription holders **diverted** their stimulant

- **Associated factors with diversion:**
- **Immediate-release** formulations
- **Male** gender
- Member of a social **college** organization
- **CD, SUD**
- Using **alcohol/illicit substances**

Misuse & Diversion:

- Obtain **personal/family history** of **SUD**
- **Educate** vulnerable populations

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Toxic Psychosis *(uncommon):*

- Very **rare**
- May occur in **rapid rise** in the dose or **very high** doses
- Resembles a **toxic phenomenon**
  (i.e., visual hallucinosis)
- **Dissimilar** to the **psychotic symptoms** of schizophrenia.

Toxic Psychosis *(uncommon)*:

- Development of **psychotic/manic** symptoms
- → careful evaluation to R/O **preexisting psychotic/bipolar** disorder

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➢ **Absolute Contraindications**

➢ **Relative Contraindications**

- Uncommon Side Effects

Absolute Contraindications:

- Known **severe hypersensitivity** to stimulants
- Current use of **MAOIs**/within **14 days** after MAOIs

Relative Contraindications:

- **Psychotic** disorders
  (potential to worsen/precipitate psychotic symptoms)
- **Severe tic/Tourette** syndrome
- **Severe seizure** disorder
- Unstable **hypertension** *(BP controlled before stimulants)*
- Narrow angle **glaucoma**

Comorbid ADHD & Seizure Disorder:

- **16%** may have **worsening** of seizures while on stimulants.
- **Consultation** with **pediatric neurologist**

Stimulants be used with caution in:

- **Severe** tics
- **Severe** Seizures
- **Histories** of **severe anxiety** symptoms
- **Histories** of **severe mood** symptoms
- **Histories** of **severe psychotic** symptoms.

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Uncommon Side Effects

Uncommon side effects:

- Psychosis, euphoria/mania
- Sadness/isolation, major depressive episodes
- **Over focusing** on details, meticulus behavior, **OCD**
- Cognitive impairment
- Growth retardation

Uncommon side effects:

- **Tic** disorders (i.e., Tourette syndrome)
- Mannerisms, **nervous movement**
- **Skin** picking
- **Clinically** significant **increased PR & BP**
- Dizziness, lethargy, fatigue
- Impaired **liver** functioning *(pemoline only)*

Uncommon side effects:

- Nausea, constipation
- Rash/hives
- Hyperacusis, formication
- Necrotizing angitis brain (IV amphetamine)
- Neuroleptic malignant syndrome?

- **<u>Mechanism of action:</u>**
- Of AMP & MPH
- May be slightly different
- **<u>Methylphenidate promotes:</u>**
- The **release** of **stored** dopamine
- Blocks the **reuptake** of **dopamine**
- At **presynaptic** dopamine **transporter sites**.

Amphetamines

- **Block** dopamine **reuptake** at the transporter
- **Promote** the **release** of newly synthesized dopamine
- Acts more **selectively.**
- These **combined effects**:
- **Enhance** dopamine function in the **striatum**
- & in the **prefrontal cortex** (PFC)

- **Both compounds:**

- **Decrease** the **neuronal firing rate** in the **locus coeruleus (MPH< AMP)**
- Whether the effect on the **NE** system is **facilitatory or inhibitory**
- Is **not clear** at present
- **These combined effects:**
- Are **essential** to the **clinical effects** of the **stimulants**
- → drugs with **more selective action** *(guanfacine or desipramine)*
- Tend to have **smaller clinical effects**.

AMP:

- Have **broader** effects than MPH
- Affect the **availability** of other monoamines *(e.g., serotonin)*

MPH

- Have broader **impacts on** other **transmitter** systems
- At **high & supratherapeutic** doses

Little correlation between:

- **Blood concentration** of AMP
- & **behavioral effect**