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Abuse and Misuse of Stimulants for ADHD

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Abuse and Misuse of Stimulants for Attention Deficit Hyperactivity Disorder

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.
Objectives

1. Compare & contrast the clinical manifestations and criteria for diagnosis of ADHD in adults & children.
2. Review treatment options for adults with ADHD.
3. Differentiate between abuse & misuse of medications.
4. Identify risk factors which may predispose adults to abuse & dependence to stimulant therapy for ADHD.
5. Discuss strategies for preventing misuse & abuse of stimulants.
ADHD Overview

- Most common neurodevelopmental disorder seen in children & adolescents
- Often persists into adulthood (~50%)
  - Among these → 90% are underdiagnosed & undertreated
- Associated with social, academic & economic limitations
- ↑ risk for SUD in adolescents & adults with ADHD
- Estimated worldwide prevalence:

  **Children & adolescents**
  - 5.3-7.1%

  **Adults age 18-44 years**
  - 1.2-7.3%

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ADHD: Attention deficit hyperactivity disorder
SUD: Substance use disorder
Pathophysiology

- Exact pathogenesis unknown
- Complex, multifactorial disorder
- Disrupted DA & NE neurotransmission appears to play an important role

Comorbidities

ADHD

- Behavior problems
- Peer problems
- Anxiety & depression
- Mood disorders
- Learning disorders
- SUD (Substance use disorder)


SUD: Substance use disorder
Clinical Manifestations

Inattention  Impulsiveness  Hyperactivity

More prominent in adults

Differential Diagnoses

Medical Conditions
- Hearing impairment, thyroid disease, lead toxicity, hepatic disease, sleep apnea & drug interactions

Psychiatric Conditions
- Anxiety, depression, mood disorders, obsessive-compulsive, SUD, bipolar disorder, antisocial personality & learning disorders

Medications
- Anticonvulsants, antihistamines, caffeine, nicotine & steroids


SUD: Substance use disorder
Diagnostic Approach

- DSM-5 criteria & rating scales
- Comprehensive clinical interview
- Assess for comorbidities
- Assess risk for SUD
- Physical exam

DSM-5: Diagnostic and Statistical Manual of Mental Disorders. 5th edition
SUD: Substance use disorder

Symptoms divided into 2 domains:
- Inattention
- Hyperactivity/Impulsivity

Diagnosis requires:
- $\geq 6$ symptoms for children ages $\leq 16$ or
- $\geq 5$ symptoms for ages $\geq 17$
- Symptoms present for $\geq 6$ months & inappropriate for developmental level

Additional criteria:
- Several symptoms present before age 12 & in $\geq 2$ settings
- Evidence that symptoms interfere with social, academic or occupational functioning
- Symptoms not caused by other psychiatric disorder
DSM-5: Inattention

- Fail to pay close attention to details
- Have difficulty sustaining attention
- Easily distracted
- Unable to follow instructions
- Do not pay attention when someone is talking
- Have difficulty organizing tasks or activities
- Avoid/dislike tasks that require sustained mental effort
- Lose things necessary for tasks or activities
- Forgetful in daily activities

DSM-5: Hyperactivity/Impulsivity

- Fidget/tap hands or feet, or squirm in seat
- Leave seat inappropriately
- Run about or climb when not appropriate
- “On the go” or act as if “driven by a motor”
- Speak excessively
- Unable to play quietly
- Blurt out answers
- Have trouble waiting his/her turn
- Interrupt or intrude on others

Overall Impact: ADHD

- Poor academic performance
- Problems at work
- ↑ rates of unemployment
- Difficult or failed relationships
- Dangerous driving & motor vehicle accidents
- Delinquent behavior
- Impulsive sexuality
- Self-esteem issues
- ↑ rates of SUD

Daily Challenges: Adult ADHD

Consequences of Untreated ADHD

- Major depression & anxiety
- Bipolar disorder
- SUD
- Conduct disorder
- Oppositional-defiant disorder
- Antisocial personality
- Suicide

Early treatment may ↓ negative outcomes

Treatment Options for Adults with ADHD
Treatment Overview

Assessment & diagnosis

Identify patient & family needs

Establish treatment goals

Initiate treatment

Treatment re-evaluation & monitoring
Non-pharmacologic Treatment

- **Options:**
  - Behavioral therapies (CBT)
  - Psychoeducation
  - Lifestyle & diet

- Helpful as *adjunct* to medication
- Behavioral therapies may be better options for patients with comorbid ADHD & SUD
  - May ↓ risk for misuse, abuse & diversion

- Future studies assessing multimodal treatment strategies are needed

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CBT: Cognitive behavioral therapy
SUD: Substance use disorder
Pharmacotherapy

Treatment Options

Stimulants (1st line)
- Methylphenidate (MPH)
- Amphetamine (AMP)

Non-stimulants
- Atomoxetine (ATX)

Stimulants: MOA

These transporters are the target of the many ADHD therapies. They block the reuptake of norepinephrine and dopamine.

MOA: Mechanism of action
Stimulants: Overview

- Safe & effective when used as prescribed
  - Appropriate use = lower risk for misuse of alcohol & other illicit drugs
- Rapid onset of action (≤ 1 hr)
- Classified as schedule II by the FDA
  - High potential for abuse, which may lead to physiological and/or psychological dependence
- Black Boxed Warning:
  - Abuse & dependence (all stimulants)

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for nontherapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly.

Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.

**Stimulants: Amphetamine**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Form</th>
<th>Duration of Action</th>
</tr>
</thead>
</table>
| **MIXED AMPHETAMINE SALTS (MAS)**  
  [Dextroamphetamine & amphetamine] |                     |                    |
| Adderall®        | Tablet              | 4-6 hrs            |
| Adderall XR®     | Capsule             | 8-12 hrs           |
| Mydayis®         | Capsule             | ≤ 16 hrs           |
| **AMPHETAMINE SULFATE** |                     |                    |
| Evekeo®          | Tablet              | 4-6 hrs            |
| Dyanavel XR®     | Oral suspension     | 8-12 hrs           |
| Adzenys XR®      | ODT                 | 10-12 hrs          |
| Adzenys ER®      | Oral suspension     | 10-12 hrs          |

**LISDEXAMFETAMINE (LDX)**

| Vyvanse®         | Capsule, chewable tablet | 8-14 hrs |

*Pro-stimulant: Prodrug of dextroamphetamine

**Recent meta-analysis concluded AMP moderately more efficacious than MPH in reducing core ADHD symptoms**


ODT: Orally disintegrating tablet
AMP: Amphetamine
MPH: Methylphenidate
# Stimulants: Methylphenidate

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Form</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METHYLPHENIDATE</strong></td>
<td></td>
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<tr>
<td>SHORT-ACTING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritalin®</td>
<td>Tablet</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Methylin®</td>
<td>Oral Solution</td>
<td>3-5 hrs</td>
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<tr>
<td><strong>INTERMEDIATE-ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritalin SR®</td>
<td>ODT</td>
<td>4-8 hrs</td>
</tr>
<tr>
<td>Metadate ER®</td>
<td>Tablet</td>
<td>6-8 hrs</td>
</tr>
<tr>
<td>Methylin ER®</td>
<td>Tablet</td>
<td>6-8 hrs</td>
</tr>
<tr>
<td><strong>LONG-ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotempla XR®</td>
<td>ODT</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>Capsule</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Concerta®</td>
<td>Tablet</td>
<td>8-12 hrs</td>
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<tr>
<td>Aptensio XR®</td>
<td>Capsule</td>
<td>10-12 hrs</td>
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<tr>
<td>Quillivant XR®</td>
<td>Oral suspension</td>
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<tr>
<td>Daytrana®</td>
<td>Transdermal patch</td>
<td>10-12 hrs</td>
</tr>
<tr>
<td>Quillacichew ER®</td>
<td>Chewable tablet</td>
<td>12 hrs</td>
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<td>Jorney PM®</td>
<td>Capsule</td>
<td>12-14 hrs</td>
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<tr>
<td><strong>DEXMETHYLPHENIDATE</strong></td>
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<tr>
<td>SHORT-ACTING</td>
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<tr>
<td>Focalin®</td>
<td>Tablet</td>
<td>3-6 hrs</td>
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<tr>
<td><strong>LONG-ACTING</strong></td>
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<td>Capsule</td>
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</tbody>
</table>

ODT: Orally disintegrating tablet

Stimulants:
Adverse Effects & Monitoring

Common Adverse Effects: (dose-dependent)
- ↓ appetite, weight loss, headache, insomnia, abdominal pain, nausea/vomiting, dizziness, nervousness, emotional lability

Monitoring Parameters:
- Prior to initiation: Assess history and/or risk of abuse, cardiac history, consider obtaining ECG
- After initiation: Signs of misuse and/or abuse, BP, HR, chest pain, unexplained syncope, behavioral changes

Stimulants: Benefits & Downfalls

**Benefits (when used appropriately)**
- Improve *sustained, focused* attention (vigilance)
- May improve executive function
- May improve long-term retention of information
- Facilitate consolidation of information

**Downfalls**
- May worsen *selective* attention & distractibility
- Do not improve (may impair) short-term acquisition of information and/or cognitive flexibility
- *Not shown to improve learning & application of knowledge*

Non-Stimulants: Overview

- Option for individuals who fail stimulant therapy or if stimulants contraindicated
- Recommended for patients with comorbid ADHD & SUD
- Less potential for abuse than stimulants
- Variable onset of action → 2-4 weeks

Non-Stimulants:
Atomoxetine (Strattera®)

- Only FDA-approved non-stimulant for treating adult ADHD
- **MOA:** Selective NE Reuptake Inhibitor (SNRI)
- Little to no abuse potential
- **Duration of action:** 24 hrs
- **Onset of action:** 1-2 weeks

Non-Stimulants: Bupropion (Wellbutrin®)

- Off-label use
- **MOA**: relatively weak inhibitor of NE & DA reuptake
- Option for adults with comorbid ADHD & depression
- **Onset of action**: 1-2 weeks
- **Duration of action**: 12 hrs (SR) to 24 hrs (XL)

Currently no direct comparisons of efficacy between bupropion & stimulants in adult ADHD

Non-Stimulants: Modafinil (Provigil®)

- Off-label use
- **MOA**: Blocks DA transporters, significantly ↑ DA in the brain
  - ↓ affinity for DA receptors compared to AMP
- Classified as **Schedule IV** by FDA
  - Lower potential for abuse than schedule III drugs; abuse may lead to limited physical or psychological dependence relative to schedule III drugs

- Appears to improve reaction time, logical reasoning & problem-solving

Non-Stimulants: Other

**Alpha-2 Agonists**
- Guanfacine (Intuniv®) & Clonidine (Kapvay®)
- FDA approved for treatment of ADHD in children ages 6-17
- *Efficacy, safety & tolerability in adult ADHD not well known*

**Antidepressants**
- Nortriptyline (Pamelor®, Aventyl®)
- Desipramine (Norpramin®)
- Imipramine (Tofranil®)
- Venlafaxine (Effexor® & Effexor XR®)
- *Shown to be less effective & more poorly tolerated than stimulants*
Misuse & Abuse of Prescription Stimulants
Medication Misuse

**Misuse definition:**
- Using a medication with a *therapeutic* intent but taking it inappropriately
  - *Use does not involve seeking psychotropic or euphoric effects*
- **Examples:**
  - Taking Rx medication without a Rx and/or for reasons other than prescribed, taking higher doses than prescribed, accepting or stealing Rx medication from a friend or relative
- Misuse ≈ Non-medical use
- Can *lead to* abuse & dependence

Stimulant Misuse: Overview

- 2nd only to marijuana as most common form of illicit drug use
- Prevalence → 13-23% (17% on average)
  - Greatest risk among individuals 18-25 years of age
- Per SAMHSA → ~ 15.4 million adults reported past-year use of Rx stimulants in 2015
  - ~4.8 million (30.9%) misused Rx stimulants at least once in the past year
- Individuals both with & without ADHD misuse Rx stimulants
- Common sources → friends & relatives

References:
Misuse Comparison

Figure 5. Past year misuse of prescription stimulants among adults aged 18 or older: 2015

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.

Figure 1. Past year misuse of prescription pain relievers among adults aged 18 or older: 2015

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.

Stimulant Misuse: Motives

Figure 6. Main reasons for last episode of prescription stimulant misuse among past year misusers aged 18 or older: 2015

- Help be alert or stay awake: 28.4%
- Help concentrate: 26.2%
- Help study: 22.4%
- Feel good or get high: 9.8%
- Experiment or see what it is like: 5.2%
- Help lose weight: 4.3%
- Increase or decrease effects of other drugs: 1.5%
- "Hooked" and have to have it: 0.1%
- Other: 2.1%

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.

Stimulant Misuse: College Students

- Exact prevalence of ADHD among college students **unknown**
- Rates of misuse ➔ 8-34%
  - Estimated lifetime prevalence ➔ 5.3-55%
- ↑ rates of misuse among college students diagnosed *with* ADHD (43%) or those with Rx for stimulants (45.2%)
  - Highest rates among fraternity members (55%)
- **Risk factors:**
  - Male, Caucasian, member of fraternity/sorority, low GPA, illicit drug use
- Found to be *negatively* associated with academic performance (i.e. poorer study skills, skipping class, procrastination, lower GPA)

Stimulant Misuse: Graduate Health Care Students

- **Lifetime prevalence of misuse:**
  - Pharmacy students → 7%
  - Graduate health care students → 11%
  - Dental & dental hygiene students → 12.4%

- **Medical students are a high risk population**
  - Lifetime prevalence → 20%
  - Prevalence of use during medical school → 15%
  - Common motives → cognitive enhancement & staying awake

High prevalence among medical students may influence future prescribing patterns & physician attitudes towards patients seeking Rx stimulants

Stimulant Misuse: Adults Outside University Setting

- Few studies have addressed the prevalence of Rx stimulant misuse among adults outside the university setting.
- Reported lifetime prevalence → 7.1-29%.
- ↑ rates reported among adults with Rx for stimulants.
- 2006 - 2011:
  - Misuse of Rx stimulants by adults in general population ↑ by ~67%.
  - ER visits ↑ by ~156%.
  - Rx stimulants involved in ER visit:
    - **MAS** → 21%.
    - **MPH** → 18.2%.


ER: Emergency room
MAS: Mixed amphetamine salts
MPH: Methylphenidate
Diversion of Stimulants

**Diversion definition:**
- The act of buying, receiving for free, trading or stealing a medication from an individual for whom it was prescribed.
- May begin in childhood, adolescence or young adulthood
- Reported lifetime diversion rates → **16-29%** of students with Rx for stimulants
- One study reported diversion in **23.3%** of middle/high school students & **54%** of college students

Medication Abuse

Abuse definition:

- Taking a medication for *non-therapeutic* purposes to obtain psychotropic or euphoric effects; often leads to addiction & dependence
  - **Addiction**: compulsive substance use despite personal harm or negative consequences
  - **Dependence**: associated with cravings, withdrawal symptoms and/or development of tolerance

Examples:

- Using medication to ‘get high’, exceeding recommended dose, continuing to take a medication after no longer needed (medically), compulsive use, not able to carry out normal daily activities

Stimulant Abuse

- Approximately **80%** of Rx stimulant abusers → ages 12-25 years

- **Theory behind abuse:**
  - Stimulants ↑ DA concentrations in the brain
    - DA is involved in reinforcement of rewarding behaviors
    - Presumed to mediate abuse potential

- **Influencing factors:**
  - Dose, PK properties, route of administration, individual personality traits, context of use, concomitant psychiatric medications, co-morbid psychiatric disorders or concurrent illicit drug use

Risk Factors for SUD in ADHD

- Starting Rx stimulants later in course of ADHD
- Severe ADHD
- Antisocial personality disorders
- Bipolar disorder
- Eating disorders
- Dropping out of school


SUD: Substance use disorder
Does Stimulant Use Lead to SUD?

- Research shows that people of any age receiving Rx stimulants for ADHD are **not** at ↑ risk for SUD compared to the general population.

- Rx stimulant use (specifically MPH) during childhood for ADHD does not appear to affect the risk of SUD in adulthood.

One review showed ↓ risk of SUD by ~27%
Consequences of Stimulant Misuse & Abuse

Adverse events:
- Heart failure
- Myocardial infarction
- Stroke
- Arrhythmias
- Cardiomyopathy
- Hypertension
- Seizures
- Paranoia
- Psychosis
- Sudden death

Risk even higher when combined with other drugs or alcohol

Stimulant Overdose

- **Signs & symptoms:**
  - Hyperthermia, agitation, tachycardia, hyperhidrosis, tachypnea, ↑ BP, palpitations, chest pain, mydriasis, restlessness, convulsions, seizures, psychosis, nausea, vomiting, abdominal pain

- **Complications:**
  - Rhabdomyolysis, liver/kidney damage, cognitive deficit, death (rare)

- **Inpatient Management:**
  - Mainly supportive care measures
  - Activated charcoal or gastric lavage
  - Benzodiazepines → for sedation or persistent seizures
  - Antipsychotics → for agitation & psychosis
  - Temperature control → within 15-20 minutes

Preventing Misuse & Abuse: Role of Prescribers

- Prescribing physicians (major source for misuse & abuse)
  - Estimated 20% of individuals misusing Rx stimulants obtain them by fraudulently misrepresenting symptoms of ADHD to physicians

- Proper diagnosis & treatment of ADHD
  - Consider comorbidities & baseline risk for SUD

- Prescribe medications with ↓ potential for misuse & abuse
  - Pro-stimulant, LA Rx stimulant formulations, non-stimulants
  - Avoid IR & SA formulations in patients at ↑ risk for SUD


SUD: Substance use disorder
Preventing Misuse & Abuse: Role of Prescribers (cont.)

- Educate patients on addictive nature of Rx stimulants
- Re-evaluate patients periodically for need to continue Rx stimulant treatment
  - Consider drug-free periods
- Regularly monitor adult use of Rx stimulants for ADHD
  - Check PDMP

**Interventions to minimize drug misuse based on patient risk stratification**

**If at low risk for misuse**
- Education, including:
  - Abuse potential
  - Consequences of sharing or selling
  - Interactions with illicit substances
  - Safe storage
- Check a prescription monitoring program, if available

**If at high risk for misuse**
- Education
- Check prescription monitoring program
- Use delayed-release preparations
- Prescribe small quantities at a time

**If showing red-flag behavior**
- Education
- Check prescription monitoring program
- Pill counts at each visit
- Urine drug screens

*Red-flag behavior: missed appointments, early refill requests, appearing intoxicated at visit, requesting dose increase.*

PDMPs

- State-run programs designed to encourage safer prescribing & prevent abuse of controlled substances
- Electronic monitoring of the prescribing and dispensing of controlled substances
- **E-FORCSE** = PDMP in Florida
- **House Bill 21**
  - Requires consultation of PDMP *prior to* prescribing or dispensing a controlled substance to a patient ≥ 16 years of age
  - Dispensing must be reported to database no later than close of next business day
Preventing Misuse & Abuse: Role of Pharmacists

- **Counsel patients on:**
  - Using Rx stimulants only as prescribed
  - Health & legal risks associated with misuse & diversion of Rx stimulants (provide medication guides)
  - Importance of safe storage of medication
  - Dangers of co-ingestion of Rx stimulants with alcohol and/or other illicit substances

- Frequent monitoring to ensure appropriate use
  - Check PDMP

- Watch for ADHD medication shopping (i.e. overlapping prescriptions by ≥ 2 prescribers & filled at ≥ 3 pharmacies)

Summary

- Failure to diagnose and treat ADHD in adults is linked to negative outcomes & ↑ risk for SUD
- Pro-stimulant (LDX) & LA Rx stimulant formulations less prone to misuse, abuse & diversion
- Non-stimulants are preferred options for ADHD patients at ↑ risk for SUD
- Future studies needed to assess prevalence & factors associated with adult Rx stimulant misuse outside the university setting
- Prevention strategies are key!

SUD: Substance use disorder
LDX: Lisdexamfetamine
True or False?

1. Clinical manifestations of ADHD are the same in both adults & children. **F**

2. Behavioral therapies, such as CBT, may be effective in preventing misuse & abuse of Rx stimulant medications in patients at ↑ risk for SUD. **T**

3. Rx stimulant medications ↑ the activity of certain neurotransmitters, such as DA & NE. **T**
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