Looking Beyond the Opioid Epidemic —
Minimize Risk of Abuse Across Multiple Categories

Alexander Kraus, PhD, Grünenthal USA, Inc. – Morristown, New Jersey
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Overview

- What is the role of prescription stimulants in ADHD treatment and why are they being abused
- Abuse patterns for prescription stimulants
- Abuse-deterrent properties for prescription stimulants
- Summary and Conclusions
What is the role of prescription stimulants in ADHD treatment and why are they being abused
Relevance of Rx stimulant treatment for ADHD patients

- A stimulant is almost always the first-line choice for treatment of ADHD, excluding patients with certain comorbidities.
- Physicians believe that stimulants offer superior efficacy and good safety\(^1\).

**ADHD Treatment Algorithm\(^1\)**

![Diagram showing treatment algorithm with stimulant and non-stimulant options.]

**Source:** 1. Commissioned market research report 2015 (data on file)
Relevance of Rx stimulant treatment for ADHD patients

- In patients affected with ADHD, the condition is often associated with widespread effects on social functioning and academic outcomes.
- In many cases, ADHD persists from childhood into adulthood, impacting on the entire lifespan.

### Common ADHD Stimulant Medications

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>Amphetamine (extended release)</td>
</tr>
<tr>
<td>Concerta</td>
<td>Methylphenidate (long action)</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>Dextroamphetamine</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>Dextmethylphenidate (extended release)</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Methylphenidate (extended release)</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Prodrug Lisdexamfetamine Dimesylate (dextroamphetamine)</td>
</tr>
</tbody>
</table>

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Concerta® is a trademark owned by Janssen Pharmaceuticals.
Dexedrine® is a trademark owned by Amedra Pharmaceuticals.
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Why non-oral abuse of Rx stimulants is attractive for abusers

- Prescription stimulants are classified as Schedule II drugs under the Controlled Substances Act because they have a high potential for abuse and addiction.
- ADHD medications affect catecholamine levels, particularly dopamine, and are known to be associated with high risk for abuse potential.

Source: Presentation by Dr. Nora Volkow at Nat Rx Drug Abuse Summit 2013, Orlando/FL.
Abuse patterns for prescription stimulants
Prescription stimulant abuse is one of the nation's fastest growing areas of substance abuse

- In 2015, 5.3 million people aged 12 or older (2% of population) misused prescription stimulants in the past year, of which 1.3 million were recent initiates (i.e. misused for the first time) for stimulant misuse¹

- Approximately 900,000 Americans abuse prescription stimulants every month²

- Lifetime rates of diversion ranged from 16% to 29% of students with stimulant prescriptions asked to give, sell, or trade their medications³

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Study Overview

Population:
- Adults assessed for substance abuse problems for purposes of treatment planning
  Data Source = NAVIPPRO® Addiction Severity Index – Multimedia Version (ASI-MV®)

Study Period: January 1, 2013 through September 30, 2015

Study Sample:
- Total Sample (N=174,640)
  - Prescription Stimulant Abusers (n=3,413)
- 698 assessment sites
- 43 states

Design: Cross-sectional surveillance study
Amphetamine versus Methylphenidate Abuse Prevalence
Adults assessed for substance abuse problems for purposes of treatment planning (ASI-MV, Jan 2013 – Sept 2015)

- Availability is a main driver for stimulant abuse.
- Both amphetamines and methylphenidates are abused depending on availability.
- Abuse of IR stimulants is higher than for ER/XR products.

*Methylphenidate includes only oral formulations and excludes patch products
Data Source = ASI-MV® (N=174,640)
Data on file
Methylphenidate Abuse - Route of Administration
(Adults assessed for substance abuse problems for purposes of treatment planning, ASI MV, Jan 2013 – Sept 2015)

Note: Individuals report multiple routes of administration. Therefore, ROA categories are not mutually exclusive and will not sum to 100%. Analyses for ROA are presented as percentages of individual ROA categories among only those who reported abuse of that compound.

*Methylphenidate includes only oral formulations and excludes patch products
Data Source = ASI-MV® (N=174,640)
Data on file

Alternate = all routes of administration excluding oral - swallowed whole
Amphetamine Abuse - Route of Administration
(Adults assessed for substance abuse problems for purposes of treatment planning, ASI MV, Jan 2013 – Sept 2015)

Note: Individuals report multiple routes of administration. Therefore, ROA categories are not mutually exclusive and will not sum to 100%. Analyses for ROA are presented as percentages of individual ROA categories among only those who reported abuse of that compound.

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Data on file
Nonmedical use of Rx Stimulants – Increasing awareness and concerns

Source: [http://abusedeterrent.org](http://abusedeterrent.org) (accessed 2/23/2017; courtesy of Abuse Deterrent Coalition)
Nonmedical use of Rx Stimulants – An increasing problem from the Federal Health Agency's view

"[…] Taking high doses of a stimulant may result in dangerously high body temperature and an irregular heartbeat. There is also the potential for cardiovascular failure or seizures."


Abuse-deterrent properties for prescription stimulants
FDA generally acknowledges the relevance of abuse-deterrence for prescription stimulants

Source: regulations.gov - FDA-2006-P-0453
Possible AD testing approach for Rx stimulant product

- Assume that AD Guidance for Opioids will provide a framework for development, testing, and labeling for ADF Rx stimulant product:
  1. In-vitro testing for manipulation, extraction, injectability, ability to smoke, insufflate
  2. PK profile after manipulation
  3. Human abuse potential study (HAP - IN, IV?)
  4. Post-marketing surveillance/epi

![Diagram showing the relationship between evidence strength and labeling tier]

- Category 1, 2, and 3 data is generally required for any ADF label claim
Technical approaches possible to create abuse-deterrence

- AD Guidance for Opioids

1. Physical/Chemical barriers (crush-resistance, gelling, specific excipients)
2. Agonist/Antagonist combinations (naloxone, naltrexone)
3. Aversion (SLS, capsaicin, niacin)
4. Delivery systems (depots, injectables, implants)
5. New molecular entities and pro-drugs (esters, PEGs, bioactivated cleavage)
6. Combination approaches (two or more of the above approaches)
7. Novel mechanisms (not yet known)

Except for the Agonist/Antagonist combination all common approaches to introduce abuse-deterrent properties should be applicable to prescription stimulants already today.
Currently there is no prescription stimulant product with abuse-deterrent labeling on the market in the US.

Lisdexamfetamine (Vyvanse® / Shire) is a pro-drug of D-amphetamine and has been designed to reduce the ability for abuse.

At the time of initial review and approval, it was believed that the compound will mainly be metabolized in the GI tract or by first-pass metabolism, and that this would protect it from non-oral routes of abuse, but ...

![Chemical structure of Lisdexamfetamine dimesylate](image)
Section 12 – Pharmacokinetics (April 2015)

Metabolism and Excretion

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine is converted to dextroamphetamine and L-lysine primarily in blood due to the hydrolytic activity of red blood cells. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). Lisdexamfetamine is not metabolized by cytochrome P450 enzymes. Following the oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers.

- Lisdexamfetamine is rapidly cleaved in blood which may make it vulnerable to intravenous abuse.
Besides oral route stimulants are preferrably abused by snorting and injection.

Among other stimulants intravenous abuse of lisdexamfetamine is the highest according to this survey study.
Technical approaches under development for stimulants
(not necessarily all inclusive)

- **Physicochemical approach**
  - Egalet/Guardian – undisclosed stimulant
  - Collegium/DeterX – Methylphenidate
  - DURECT/OraDur – Methylphenidate
  - Alcobra/Capsugel – Dexamphetamine
  - Grünenthal/INTAC – Methylphenidate, Amphetamine

- **Pro-drugs**
  - KemPharm/LAT – Methylphenidate
  - Ensysce/Bio-MD – Dexamphetamine
Approved prescription stimulants have specific properties

- Once-a-day administration is a standard option in ADHD treatment
- Based on clinical and medical needs, most prescription stimulant products show a distinct modified release profile
- IR and ER components are often combined at various ratios to support benefit and improve compliance of treatment

Combination of INTAC® IR and ER process to yield abuse-deterrent modified release (MR) forms

**INTAC® IR**
- Micro Pelletization
- TRF IR Pellets
- Hot-Melt-Extrusion
- Cooling & Cutting
- TRF ER Extrudates

**Core HME process**

**INTAC® ER**

**INTAC® IR + INTAC® DR coated pellets**

**INTAC® IR pellets + INTAC® ER**

**Immediate release (IR)**
- Cumulative release
  - Drug release (mg)
  - Time (min)

**Extended release (ER)**
- Cumulative release
  - Drug release (mg)
  - Time (min)

DR = Delayed Release
Summary and Conclusions
Summary and Conclusion

- Prescription stimulants are a class of CSA-II products which offer a standard of care for pharmacological treatment of ADHD.

- As disease understanding and diagnosis criteria improve, the number of prescriptions for prescription stimulant products increase over time.

- Indicators for misuse and abuse of prescription stimulants show alarming increases of abuse rates specifically in vulnerable populations.

- Although, as with opioids, oral abuse of prescription stimulants dominates the abuse, manipulation of the products is common and increases the potential harm from abuse and the risk for addiction.

- Abuse-deterrent forms of prescription stimulants might offer benefit to reduce abuse rates and prevent abusers from progressing into severe forms of abuse and addiction.
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