Understanding and Addressing Abuse of ADHD Stimulants

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ABUSE DETERRENT FORMULATIONS SUMMIT
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Disclosures

- I am a full-time employee of Alcobra Inc.
- Alcobra is a public, CNS specialty pharmaceutical company (NASDAQ: ADHD)
- Alcobra is developing an Abuse-Deterrent formulation of Amphetamine Immediate Release (ADAIR)
Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 and other Federal securities laws. Because such statements deal with future events and are based on Alcobra's current expectations, they are subject to various risks and uncertainties and actual results, performance or achievements of Alcobra could differ materially from those described in or implied by the statements in this press release. For example, forward-looking statements include statements regarding the timing of filing an NDA for ADAIR, if filed at all, the proposed development path to approve ADAIR, the sufficiency of Alcobra’s financial resources for its future plans and the potential benefits of ADAIR. In addition, historic results of scientific research do not guarantee that the conclusions of future research would suggest similar conclusions or that historic results referred to in this press release would be interpreted similarly in light of additional research or otherwise. The forward-looking statements contained or implied in this presentation are subject to other risks and uncertainties, including those discussed under the heading "Risk Factors" in Alcobra's Annual Report on Form 20-F for the fiscal year ended December 31, 2015, filed with the Securities and Exchange Commission (SEC) and in subsequent filings with the SEC. Except as otherwise required by law, Alcobra disclaims any intention or obligation to update or revise any forward-looking statements, which speak only as of the date they were made, whether as a result of new information, future events or circumstances or otherwise.
Outline

- The ADHD Market
- ADHD Stimulant Misuse & Abuse
  - Diversion
  - Routes of Abuse
  - Consequences
- Alcobra’s ADAIR Program
Total ADHD Market TRxs (US):

67M TRxs in 2015 with a 4-year CAGR of 5.4%

2015 Total ADHD Sales in US = $9.6 billion

Source: IMS, NPA, TRxs
IR Amphetamines are the Fastest Growing Segment of US ADHD Market

ADHD Market Growth by Class
2011-2015 CAGR

- Short Acting AMPH: 12.3%
- Long Acting AMPH: 5.5%
- Short Acting MPH: 3.5%
- Long Acting MPH: 0.1%
- Non-Stimulants: 3.9%

Overall Market CAGR: 5.4%

24M IR Stimulants TRx in 2015 in the US

Source: IMS, NPA
IR Amphetamine Leads the ADHD Market in Share & Growth

**TRx Monthly Share for Key Products**

- **Adderall + Generic AMPH Salts**, 25.2%
- **Adderall XR + Generic AMPH Salts XR**, 18.6%
- **Vyvanse**, 16.7%
- **Concerta + MPH LA**, 13.1%
- **Ritalin + MPH**, 8.0%
- **Intuniv + Generics**, 4.0%
- **Strattera**, 3.7%

Source: IMS, NPA, TRxs
Stimulants are Extensively Diverted

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>% Approached to Divert</th>
<th>% Actual Diversion of Prescribed Stimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping Medication (n=108)</td>
<td>13</td>
<td>Rabiner et al., 2009 (n=115), previous 6 months</td>
</tr>
<tr>
<td>Anti-anxiety Medication (n=104)</td>
<td>12</td>
<td>Sepulveda et al., 2011 (n=50), previous 12 months</td>
</tr>
<tr>
<td>Stimulant Medication (n=141)</td>
<td>24</td>
<td>Garnier et al., 2010 (n=81), in a lifetime</td>
</tr>
<tr>
<td>Opioid Medication (n=704)</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Source: McCabe et al. Drug Alc Depend 2011

1 Drug diversion = Transfer of legally prescribed controlled substance to another person by selling, trading, or giving away
ADHD Stimulant Misuses & Abuse is Common

- Over **5 million** adolescents & adults (2% of the population) misuse prescription stimulants annually
  - 1.3 MM first time misusers/abusers of Rx stimulants in 2015
  - 90% of those who misuse/abuse stimulants do so with Rx amphetamines

<table>
<thead>
<tr>
<th>Stimulant Subtype</th>
<th>(Misuse (000)</th>
<th>(%) Misuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Rx Stimulant</td>
<td>5,251</td>
<td>2.0%</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>4,778</td>
<td>1.8%</td>
</tr>
<tr>
<td>Methyphenidates</td>
<td>979</td>
<td>0.4%</td>
</tr>
<tr>
<td>Anorectics</td>
<td>121</td>
<td>0.0%</td>
</tr>
<tr>
<td>Provigil</td>
<td>103</td>
<td>0.0%</td>
</tr>
<tr>
<td>Any Other Rx Stimulant</td>
<td>96</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

- Misuse/Abuse appears to peak at age 21 (10% vs 2% across all ages)

Source: NSDUH, 2015, Table B.6 – Any Use & Misuse of Stimulants in the Past Year among Individuals Aged 12 or Older
ADHD Stimulant Misuses & Abuse is Common

- Stimulant misuse/abuse occurs in both ADHD and normative populations:
  - 14% of adolescents & adults in an ADHD treatment clinic endorsed misusing/abusing their Rx (Bright, 2008) (n=545)
  - 16% of college students reported misusing/abusing stimulants (White, 2006) (n=1,025)
  - 10% of high school seniors reported misusing/abusing Rx stimulants (McCabe, 2013) (n=4,572)
  - 8% of general adult population 18-49 reported misusing/abusing Rx stimulants (Cassidy, 2015) (n=10,000)
Associated Medical Complications of Chronic Stimulant Abuse/ Dependence/Overdose*/Withdrawal

- **Psychological/Behavioral**
  (depression, suicidal thoughts, impaired judgment, violence)
- **Neurological complications**
  (seizures, strokes, hemorrhages, cerebral atrophy and brain lesions, neurological deficiencies, cognitive deficits)
- **Cardiovascular system effects**
  (cardiovascular damage, every form of heart disease, fatal reactions)
- **Respiratory/pulmonary effects**
  (respiratory depression, hemorrhage, death from respiratory failure)
- **Muscular and renal toxicity**
  (skeletal muscle destruction that may cause kidney failure)
- **Gastrointestinal complaints**
  (weight loss and anorexia, severe bowel infarction)
- **Reproductive function and fetal/neonatal effects**
  (low birth weight , spontaneous abortion, impotence, infertility)

*The amount needed to produce a toxic dose varies widely and is not related to body weight

**Source:** Treatment for Stimulant Use Disorders, Guide For Clinicians, The Substance Abuse and Mental Health Services Administration (SAMHSA), the U.S. Department of Health and Human Services, Published in 1999
IR Stimulants are Abused More Frequently

Illicit Use Survey in ADHD Clinic (n= 545)

- Short acting: 80%
- Long acting: 17%
- Both: 3%

Internet Survey of 10,000 Adults 18-49 years old (% of respondents)

- Bright, G. Medscape Jrl. of Medicine 2008; 10 (5): 111
- Cassidy, et al, Jrl. Attention Disorders, 2015 19 (7) 630-640
Rapidity of Brain Dopamine Surge Drives Reinforcing Effects of Stimulants

- CNS stimulants inhibit the dopamine transporter, leading to elevated synaptic dopamine levels.

- Rapid increases in brain dopamine levels are associated with the reinforcing or euphoric effects of stimulants (Swanson 2003, Volkow 2003, Volkow 2002, Volkow 2000).

- OROS methylphenidate, with its slow ascending plasma concentration profile, shows lower reinforcing responses during early hours as compared with an IR formulation (Parasrampuria 2007; Spencer 2006).

- Intranasal d-amphetamine has greater reinforcing effects than oral amphetamine (Lile 2011).
Snorting is a Frequent Route of Abuse

Method of Stimulant Abuse by College Students (n=1,025)

- Swallow: 55%
- Snort: 40%
- Other: 4%

Method of Stimulant Abuse by Adults Admitted to Abuse Treatment Centers (n=1,905)

- Swallow: 74%
- Snort: 38%
- Inject: 10%
- Smoke: 3%

White et al, Stimulant Medication Use, Misuse, and Abuse in an Undergraduate and Graduate Student Sample, JRN of Am College Health, 2006; Random sample: anonymous surveys at the University of New Hampshire administered via email and paper, 1,025 received out of 5,000 distributed, 6.6% diagnosed with ADHD, over 16% of students abuse stimulants

Snorting or injecting stimulants is especially concerning due to higher risk of serious events

Quick entry into the bloodstream increases risk

- Chest pain and rapid, irregular heart beat
- Heart attack
- Seizures
- Hallucinations
- Hostile/aggressive behavior
- Suicidal thoughts and behaviors
- Stroke

While the fatal dose for adults is generally around 20-25mg/kg, as little as 1.5mg/kg of Adderall has been known to cause death.

Excerpts from: http://prescription-drug.addictionblog.org/snorting-adderall/
UM football student manager dies from an overdose at 22

Published September 16, 2014

On the morning of July 20, Levine was found unconscious on a sidewalk in the neighborhood of Wicker Park, in Chicago. He spent the previous Saturday night pushing his body to limits through binge drinking and snorting crushed Adderall. This was enough to stop his heart. He was taken to the hospital where he was put on life support in intensive care. The ventilator was turned off the next day.
Drug Severity is Greater Among IV/IN Abusers Compared to Oral Misusers

Source: Navippro, ASI-MV, Data on File
Stimulants are Scheduled, Controlled Substances with High Potential for Abuse and Addiction

According to FDA and DEA:

AMPHEMATINES 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 NON-THERAPEUTIC 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.

Source: Prescribing information, Adderall
“The Agency agrees that the abuse and misuse of controlled substances, including CNS stimulant drugs, present a serious public health concern, and we support efforts by drug manufacturers to modify formulations to reduce the risk of abuse.”

Janet Woodcock, MD, Director
Center for Drug Evaluation & Research, FDA
Alcobra’s Abuse Deterrent Amphetamine Immediate Release (ADAIR)
Alcobra’s ADAIR: Designed to Deter Intranasal & IV Abuse

- An oral, semi-solid, gelatin capsule
- Developed under a services agreement with Capsugel®
- Patent-pending, potentially first in class product
- Formulation resists manipulation/preparation for insufflation (“snorting”)
- Meaningful barriers for abuse via injection
ADAIR Resists Preparations for Insufflation

Multiple Manipulation Methods Were Investigated:

- Cutting
- Grinding
- Freezing
- Heating
- Mixing with Talc & other flow enhancers
- Longer durations

<1% of ADAIR mass is under 500µm in size (vs. 42-47% of reference drug)
Includes Meaningful Barriers When Manipulated for Injection Purposes

**ADAIR**

*Multiple Manipulation Methods Investigated:*
- Range of volumes
- Range of needles
- Range of preparation techniques

**Viscosity Comparison of Water, d-AMPH and ADAIR utilizing Texture analysis**

**ADAIR is difficult to expel from a syringe:**
Texture analysis profiles of water (blue), filtered manipulated d-AMPH (red) and ADAIR (green) for depressing a plunger of a Leur-Lok 5 mL syringe by 9 mm, whilst expelling the material under test through a 26 G needle (Internal Data).
Recent FDA meeting charts a rapid and cost efficient development path for ADAIR

- A 505(b)(2) pathway (<2 years development timeline)
- 2 PK studies in small (n=24) groups of healthy volunteers (BE, Food Effect)
  - Studies are expected later this year under IND
- Alcobra to potentially conduct 1-2 additional studies for support of commercialization efforts
  - Intranasal abuse potential (if feasible)
  - Single adult ADHD P3 efficacy study (for label expansion)
- Abbreviated non-clinical work (bridging animal study to IR d-Amph) and standard 1-year stability before NDA filing

Current plan targets NDA filing in 2H 2018
Summary

- ADHD stimulants are abused a lot too; it’s not just opioids
- Stimulant abuse is mostly with amphetamines
- The big issue with stimulant abuse is with IR not ER meds
- There is a lot of abuse by snorting (and IV); it’s not all kids taking it orally to study for exams
- Alcobra has an advanced technology to address a large part of the problem with plans to file an NDA by late 2018
Thank You!

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Appendix B: Drug Severity Score

The drug severity score is a calculated score provided by the ASI-MV for each individual based on responses to certain questions within the ASI-MV assessment. As such, the calculated severity ratings are estimates of problem status, derived at a single point in time and subject to change with alterations in the immediate context of the patient's life (McLellan et al., 1992).

The drug severity rating is based on a number of items measured during the interview assessment including drug use (including both illegal and prescription drugs) in the past 30 days as well as the duration of use (i.e., number of years) for these substances, and the current level of drug problem and need for treatment. Severity ratings from the ASI-MV been shown to be reliable and valid (Butler et al., 1998).

ASI-MV severity score category definitions include 0-1: No real problem, treatment not indicated; 2-3: Slight problem, treatment probably not indicated; 4-5: Moderate problem, some treatment indicated; 6-7: Considerable problem, treatment necessary; 8-9: Extreme problem, treatment absolutely necessary. Drug severity rankings are calculated estimates of problem status based on several items measured from the ASI-MV interview regarding drug use, duration of use, and current need for treatment.
Misuse of Stimulants Peaks at 10% of Population at Age 21

Misuse in Past Year of Prescription Stimulants

Average across all ages: 2.0%

Source: SAMHSA, Center for Behavioral Health Statistics & Quality, National Survey on Drug Use and Health, 2015
Emergency Department visits due to non-medical use of stimulants more than quadrupled (2004-11)

ED visits due to non-medical use of Amphetamines and Methylphenidate from 2004-2011

4.7x increase

Drug Abuse Warning Network Report, 2011, pg 21, table 5.2, Central Nervous System Stimulants, amphetamine/dextro-amphetamine and methylphenidate only (excluded caffeine)