Amphetamines
A Brief Review

Southern Medical Association’s  The 3 “Rs” of Prescribing Controlled Substances: Rules, Regulations, and Risks
Hattiesburg, Mississippi
Mark S. Williams, MD, MBA, JD

Topics

• Basic chemistry
• Evolution of ‘Drug Control’
• Current drug classification
• History of amphetamine and its uses
• Current indications
• Amphetamine withdrawal
• Amphetamines and Cognitive Enhancement
Amphetamine - Chemistry

- Potent CNS Stimulant
- Smooth Muscle Relaxant
- Many others

Amphetamines - Mechanism of Action

- Effects stem largely from influences on neurotransmitters
- Predominantly work via increasing levels of dopamine and norepinephrine
- Explains many of their therapeutic benefits
The Commission recommended decriminalization of simple possession, finding:

["T"]he criminal law is too harsh a tool to apply to personal possession even in the effort to discourage use. It implies an overwhelming indictment of the behavior which we believe is not appropriate. The actual and potential harm of use of the drug is not great enough to justify intrusion by the criminal law into private behavior, a step which our society takes only 'with the greatest reluctance'
Schedule I Drugs

- Drug or other substances have a high potential for abuse
- Drug or other substances have no currently accepted medical use in treatment in the U.S.
- Lack of accepted safety for use

- Heroin
- Psilocybin Mushrooms
- Cannabis
- LSD
- Peyote

Schedule II Drugs

- Drug or other substances have a high potential for abuse
- Drug of other substances have currently accepted medical use in treatment in the U.S.
- Abuse of the drug or other substances may lead to severe psychological or physical dependence

- Cocaine
- Adderall
- Methadone
- Oxycodone
- Fentanyl
- Ritalin
- Methylene
- Amphetamine
### Alternatives to Scheduling

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Harm</strong></td>
<td>Acute</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td>Parenteral</td>
</tr>
<tr>
<td><strong>Dependence</strong></td>
<td>Intensity of pleasure</td>
</tr>
<tr>
<td></td>
<td>Psychological dependence</td>
</tr>
<tr>
<td></td>
<td>Physical dependence</td>
</tr>
<tr>
<td><strong>Social Harms</strong></td>
<td>Intoxication</td>
</tr>
<tr>
<td></td>
<td>Other social harms</td>
</tr>
<tr>
<td></td>
<td>Healthcare costs</td>
</tr>
</tbody>
</table>

*Drug Classification: making a hash of it?, UK Science and Technology Select Committee, 2006*

### Government Policy in Conflict with Scientific Evidence?

**Drug harms in the UK: a multi-criteria decision analysis**
David J Nutt, Lancet 2010
Amphetamines - Brief History

- Adrenaline, 1901 at Johns Hopkins
- Amphetamine synthesized by George Alles, 1928, approached Smith, Kline and French (SKF)
- SKF introduced Benzedrine inhaler, 1932
- SKF introduced Benzedrine sulfate tabs in 1936 - offered free to any physician, no clinical trials

'Initially, a drug looking for a disease'
On June 3, 1929, a doctor injected 50 mg of amphetamine into Alles’ body . . .

7 minutes later, his nose was dry and clear, at 17 minutes he had palpitations but also a feeling of ‘well being’ . . . he grew chatty at a dinner later that evening and found himself to be unusually witty . . . during the night, his mind “seemed to run from one subject to another”

A 1932 patent declared him the inventor of amphetamine sulfate and amphetamine hydrochloride - substances lacking any obvious medical application at that time

Amphetamines - Role in the Military

- Heavy pharmaceutical and physician promotion during 30s and 40s
- Germans, then British and then Americans embraced use of amphetamines
- Britain purchased 72 million Benzedrine tablets from SKF, America purchased 250 million
For the ‘Patient with Mild Depression’
JAMA, 1937

Symptoms included:
apathy,
discouragement,
difficulty in thinking,
subjective feelings of
weakness.
.hypochondria’
Not the only example . . . .

1960s - Diet Doctors and Weight Loss Clinics

Subsidiaries of off-brand diet pill manufacturers

Cost Selling Price

<table>
<thead>
<tr>
<th>Cost</th>
<th>Selling Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0</td>
<td>$3,000</td>
</tr>
<tr>
<td></td>
<td>$6,000</td>
</tr>
<tr>
<td></td>
<td>$9,000</td>
</tr>
<tr>
<td>$12,000</td>
<td></td>
</tr>
</tbody>
</table>

100,000 off-brand tablets

1970 Comprehensive Drug Abuse Prevention and Control Act (precursor of modern 'schedules')

Schedule II All Amphetamine Products

Bureau of Narcotics and Dangerous Drugs (forerunner to DEA)
Amphetamines - Current Indications

• Narcolepsy
• Attention Deficit Hyperactivity Disorder (ADHD)
• Other ‘off-label’ uses
  • Use as anorectics
  • Atypical depression and dysthymic disorder
ADHD

• Described in 1901

• One of most common childhood disorders (psychiatric behavioral)

• Three types
  • Hyperactive-Impulsive (HI)
  • Predominantly Inattentive (IN)
  • Combined (CB) - most common

---

New York Times
March 31, 2013

National Survey of Children’s Health, Department of Health and Human Services, 2013
“It is highly implausible that there has been a 50% increase in ADHD in the last decade . . . trend is being driven by Big Pharma, pressure from overwhelmed teachers . . . and now by parents and students who are seeking ‘performance enhancement’ . . . perhaps it is time for elite high schools and colleges to ‘drug test’ for Adderall and Ritalin so that students who are not taking performance enhancing medications aren’t left by the wayside”

Ethics of Mental Enhancement
J Thomas, Modern Healthcare, July 2013

Some believe that children who are more high spirited or high-strung are being mistakenly diagnosed with ADHD (see www.adhdfraud.org)

Congressional testimony has included statements describing the excessive use of psychostimulants for ADHD (Breggin 2000)

‘Most experts are in agreement that ADHD is a psychiatric condition that responds well to psychostimulant medication . . . environmental studies help to explain the increasing number of children affected by ADHD’
‘When a drug is treated not only as a legal medicine but as a virtually harmless one, it is difficult to make a convincing case that the same drug is terribly harmless if used non-medically’

America’s First Amphetamine Epidemic 1929-1971, N Rasmussen, RedOrbit, June 2008

‘Epidemics’ of Amphetamine Abuse

- Introduction of ‘medical use’ to a large segment of population
- Widespread dissemination of the amphetamine ‘experience’
- Development of a core of amphetamine users
- Initial oversupply of amphetamine
- Development of clandestine labs and distribution channels
Amphetamines - Issues of Abuse and Dependency

‘Potential for amphetamine abuse has curtailed many legitimate uses and contributed to success of illegal drug trade’

E Moore, The Amphetamine Debate, 2011

‘Abuse’ ‘Dependency’ ‘Addiction’

Why are we here discussing these issues?

What about the medical profession... us?

Deaths from Opioid Pain Relievers Exceed Those from All Illegal Drugs

Amphetamines - Toxicity and Deaths

- Hypertensive cerebral hemorrhage
- Cardiovascular collapse secondary to ventricular fibrillation (usually <30 years of age)
- Hyperpyrexia
- Miscellaneous - septicemia from bacterial endocarditis, etc

Amphetamines - Tolerance

- Tolerance = reduction in effects with same dose of drug
- Side effects of amphetamines typically diminish over 6 - 8 weeks of use
- Effects subject to tolerance include the hyperthermic, appetite suppressant, mood elevating and cardiovascular effects
- Beneficial effects on behavior may persist for years
Amphetamines - Chronic Use and Abuse

- Many individuals take amphetamines for long periods of time without any obvious effects or need to increase dose
- Certain individuals begin using larger doses to intensify the pharmacological euphoria
- Repeated and higher doses are needed to achieve the intense euphoric sensations
- Numerous factors are believed to influence specific cases of dependence

Amphetamines - Withdrawal

- Effects of withdrawal often do not occur before several days
- Include dysphoria, fatigue, depression, vivid dreams, agitation and sleep disturbances
- May crave excessive amounts of food and develop affective disorders
- Withdrawal from high doses may evoke more intense symptoms including drug craving and depression
Amphetamines - Treatment of Dependence

- No one treatment effective for withdrawal or dependence
- During withdrawal, symptoms are managed with appropriate measures
- Treatment similar to that for cocaine dependence
- Therapies include tricyclic antidepressants and behavioral therapies (Matrix Model)

Methamphetamine

- Desoxyephedrine (Desoxyn)
- Used in treatment of ADHD
- Widely known for clandestine manufacture
- ‘Matchbook + iodine + ephedrine = ‘Meth’
- More potent CNS activity, less potent cardiovascular effects (adds to abuse potential)
Methamphetamine Abuse

- America’s first epidemic - Haight-Ashbury, 70s
- ‘Speed freak’ versus the ‘love drug’
- Studies suggest that 4.3% of population has used methamphetamine at least once
- 50% of users smoke the drug
- Can devastate small communities

How methamphetamine works in the body

- Methamphetamine works by stimulating the release of dopamine in the brain, altering behavior and mood.
- Users experience feelings of euphoria, increased energy, and reduced appetite.
- Prolonged use can lead to addiction, mental health issues, and physical harm.

- Significant restrictions on chemical ingredients in U.S.
- Most ‘meth’ is of poor quality and is produced in Mexico
- ‘Meth’ users have depleted stores of dopamine and significant loss of transporters
- Areas of brain associated with emotions and memory may reveal severe changes
- Imaging studies in certain regions of brain suggest that recovery may be very prolonged or unlikely
Methamphetamine - Consequences of Abuse

- Malnutrition, severe dental problems
- Anorexia, anemia, hypertension, cardiac irregularities
- Ischemic bowel disease, nasal septal defects, COPD, impotence
- Psychosis, paranoia, memory loss
- Use may contribute to spread of HIV, other

Jean-Paul Sartre

Amphetamines - Claims as to Improvements in Cognitive and Performance Enhancement

W H Auden

- Improved academic performance, recall
- Increased creativity
  - Writing
  - Mathematics
  - Painting
  - Musicians
- Increased endurance

Graham Greene
“Safe and effective cognitive enhancers will benefit both the individual and society”

From Commentary in the Journal *Nature*
H. Greely, Dec 2008

‘Ethics of Mental Enhancement’
Modern Healthcare, July 2013

‘Do I have a right to know if someone I am competing against in the workforce is mentally enhanced in any way?’

‘I can definitely see a time in the near future when, just like in professional sports, doctors, lawyers, accountants and hospital CEOs are going to demand to know if their colleagues have an “edge.”’
I have not argued that direct brain enhancements are good, let alone that they should be added to the water supply. I have argued that they are not necessarily bad. There appropriate use will depend on their safety and effectiveness, along with how we choose to use them and what steps we take to mitigate the challenges to fairness they may pose or the invasions on individual autonomy they may provoke . . .

I am confident, though, that a knee-jerk rejection of all direct brain enhancements will be at least a missed opportunity and at worst an opening for a damaging underground and uncontrolled world of enhancements . . .

Henry T. Greely, JD
Professor of Law and Genetics, Stanford University
Director, Stanford Center for Law and Biosciences
“Amphetamine is like a Christmas package with a time bomb inside” (1969)

“We’ve decided as a society that it’s too expensive to modify the kid's environment,” he explains. “So we have to modify the kid.”

The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex

- Procognitive actions associated only with low doses
- Involve preferential elevation of catecholamines in PFC
- Moderately elevated doses appear to improve certain cognitive processes at the expense of others
- Differential modulation of these processes appears to be associated with differential involvement of noradrenergic alpha-2 versus alpha-1 receptors
Amphetamine’s persistence - both as a recreational and a medical treatment - suggests a nearly irresolvable dilemma

• It blurs the line between treatment and enhancement
• Prompts the question “how important is a subjective feeling of well being?”
• When does a lack of such feeling become a medical problem?
• How should it be treated?
• How should society regard those who “abuse” such a drug?
Thanks

Questions?

Mark S. Williams, MD, MBA, JD