AMPHETAMINE RELATED "IMPAIRMENT" AND "REVERSE IMPAIRMENT"

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Pharmacology - Amphetamines

CNS - Sympathomimetic promotes synthesis and release of:

* Norepinephrine
  - alerting, anorectic, locomotor effects

* Dopamine
  - Euphoria
  - locomotor stimulating effects
  - psychosis, disturbances in perception

* 5-HT
  - delusions, psychosis
Amphetamine Effects

Low Dose (NE)

Central: Increased alertness; relief from fatigue; insomnia; motor restlessness; appetite suppression; mood changes.

Peripheral: Dilated pupils, increased pulse and blood pressure.
Amphetamine – Military use

Performance and Alertness Effects of …
Amphetamine… on …Sleep Deprivation

• Compared effects of caffeine, modafinil, and amphetamine on alertness and executive function.
• 20mg d-amphetamine after 64 hours without sleep improved psychomotor vigilance and alertness.
• Performance in tests of executive function mixed.
Amphetamine – Military use

Psychostimulants and Military Operations


- Modafanil and amphetamines both improve wakefulness-induced impairment.

- Both drugs useful in managing operational fatigue, wakefulness, but not necessarily executive function.

- Modafinil has fewer side effects than dextroamphetamine.

- Typical amphetamine doses of up to 30mg (3x10mg)
Amphetamine Effects

High Dose Acute (NE, DA, 5HT)

Central: Euphoria; elation; excitability; agitation; hyperreflexia; hypervigilance; logorrhea; sexual arousal; motor agitation; dizziness; inability to sleep.

Peripheral: Greatly dilated pupils, dry mouth; increased pulse and blood pressure.

High Dose Chronic (NE, DA, 5HT)

Central: Delusions, paranoia, pseudohallucinations, psychosis, dissociation
Amphetamine Effects

High Dose Withdrawal (NE, DA, 5HT deficit)

Central: Dysphoria; extreme sleepiness; fatigue; agitation; irritability; depression; insomnia.

Peripheral: Constricted pupils; decreased pulse and blood pressure.
Effects of d-Amphetamine on Risk Taking

Hurst, Psychopharmacologia 5;3(2), 1962

• Found evidence that a 10mg oral dose increased risk taking.

• Decisions to accept risk, and self-appraisal of performance increased – actual performance declined.

• Study design involved gambling however, rather than driving.
Psychoactive Drugs and Traffic Accidents

*Smart et al, J Safety Res 1(2) pp 67 – 73 (1969)*

- Amphetamine-using subjects displayed significantly (3X) more accidents per mile traveled than subjects using other drugs or no drugs at all.
Stimulants in Drivers

Abnormally High Concentrations of Amphetamine in Blood of Impaired Drivers
Jones and Holmgren, JFS 50(5), 1-5 (2005)

• 46 cases, amphetamine >5mg/L
• Median 6.6mg/L (5-17mg/L)
• Common symptoms:
  • bloodshot and glazed (watery) eyes,
  • Slurred speech
  • sweeping arm movements and restlessness
  • Often unsteady gait.
  • Pupil size, inconsistent
In 644 cases, amphetamine and methamphetamine were present in blood samples at mean (median) concentrations of 0.85 mg/L (0.60 mg/L) and 0.34 mg/L (0.20 mg/L), respectively.

Amphetamine/methamphetamine ratio indicates abuse primarily of amphetamine.

Methamphetamine Drivers

Methamphetamine Concentrations in Impaired Drivers
Logan (unpublished, 2006)

- n = 1159
- Mean = 0.31mg/L
- Median = 0.21mg/L
- Mode = 0.10
- Lo = 0.05*
- Hi = 9.46
- >2mg/L = 47
Amphetamines in Drivers

First nationwide study on driving under the influence of drugs in Switzerland.


<table>
<thead>
<tr>
<th>DRUG (ng/mL)</th>
<th>N</th>
<th>P5</th>
<th>P25</th>
<th>Median</th>
<th>P95</th>
<th>Mean</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>170</td>
<td>13</td>
<td>27</td>
<td>59</td>
<td>557</td>
<td>145</td>
<td>10 - 3500</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>41</td>
<td>22</td>
<td>63</td>
<td>93</td>
<td>565</td>
<td>184</td>
<td>18 - 1372</td>
</tr>
<tr>
<td>MDMA</td>
<td>223</td>
<td>24</td>
<td>95</td>
<td>206</td>
<td>690</td>
<td>279</td>
<td>11 - 2600</td>
</tr>
<tr>
<td>MDEA</td>
<td>32</td>
<td>10</td>
<td>14</td>
<td>19</td>
<td>131</td>
<td>63</td>
<td>10 - 969</td>
</tr>
<tr>
<td>MDA</td>
<td>77</td>
<td>11</td>
<td>15</td>
<td>21</td>
<td>147</td>
<td>33</td>
<td>10 - 176</td>
</tr>
</tbody>
</table>

- 4,794 DUID cases, men (89%) women (11%).
- Drivers arrested for suspected drug only DUI.
Methamphetamine and Driving

Lemos NP, Science and Justice, (2009); 49: 247-249

Case 1.

- Motorcycle, tailgating, rapid lane changes, no signaling, reckless driving.
- Eyes bloodshot, eyelids droopy, rapid, mumbling fragmented speech.
- HGN – Lack of smooth pursuit, incomplete
- Pupils normal, pulse 120bpm
- Poor performance on SFSTs
- Blood, 1hr 40 mins after driving
  - Methamphetamine 0.66mg/L
  - Amphetamine 0.17mg/L
Methamphetamine in Drivers

Methamphetamine and Driving
Lemos NP, Science and Justice, (2009);49:247-249

Case 2

• Police pursuit, driver jumps from moving vehicle, fights with police, tasered, highly combative.
  • Dilated pupils, eyes watery and red
  • Rapid mumbling speech, agitated, fidgeting.
• Blood, 1hr 30 mins after driving
  • Methamphetamine 0.51mg/L
  • Amphetamine 0.10mg/L
Drugs in Oral Fluid

Relationship between oral fluid and blood concentrations of drugs of abuse in drivers suspected of driving under the influence of drugs.


<table>
<thead>
<tr>
<th>DRUG</th>
<th>OF/B</th>
<th>MEDIAN</th>
<th>OF/B</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>13</td>
<td>0.5</td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>MDMA</td>
<td>6</td>
<td>0.9</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>5</td>
<td>2</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>22</td>
<td>4</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>2</td>
<td>0.8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>10</td>
<td>0.8</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.02</td>
<td>0.01</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>0.04</td>
<td>0.01</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>15</td>
<td>0.01</td>
<td>569</td>
<td></td>
</tr>
</tbody>
</table>
Impairment related to blood amphetamine and/or methamphetamine concentrations in suspected drugged drivers.


• 878 suspected impaired drivers
• 79% amphetamine positive
• 18% methamphetamine positive
• 3% positive for both
• Median concentration: 0.52mg/L
• Range 0.04 – 3.74mg/L
• 643/878 (73.2%) were judged impaired
Stimulants and Drivers

Stimulants and Drivers

• Demonstrated a modest but significant relationship between impairment and blood amphetamine concentration.
• OR for being judged impaired was elevated above 0.27mg/L
• Caveats:
  • Selection bias – all were arrested
  • Lack of clinical indicators at high concentrations.
Amphetamines and Impairment

The Effects of Dexamphetamine on Simulated Driving Performance.

- Acute, oral, 0.42mg/Kg amphetamine
- Small decline in daytime driving perf.
- Blood concentrations 0.08 – 0.09mg/L
- Most frequent behaviors:
  - Incorrect signaling, failing to stop at red lights, slow reaction times
Laboratory Assessments

An Evaluation of … Standardised Field Sobriety Tests to Detect.. Amphetamine.


• Acute, oral, 0.42mg/Kg methamphetamine
• Corresponding concs. ~0.07 mg/L
• HGN, WAT, OLS
• No significant impairment in performance
• Detected impairment in 0% of cases
Stimulants in Drivers

Methamphetamine and Driving Impairment

Logan, JFS 41(3) 457-464 (1996)

• Typical driving behaviors included:
  • Drive-off-the-road type behaviors 46%
  • Speeding 25%

• Impairment attributed to:
  • Distraction/Disorientation
  • Drug withdrawal/fatigue/hypersomnolence
  • Motor excitation
  • General cognitive impairment
  • Hyperactive reflexes
Methamphetamine Hysteresis

Symptomatology

- improved reaction time
- relief from fatigue
- euphoria
- light sensitivity
- nervousness
- headache
- motor restlessness
- tremor

Blood methamphetamine concentration (mg/L)

- fatigue
- exhaustion
- confusion
- extreme fatigue
- drug craving
- depression
- hypersomnia
- uncontrolled sleepiness
- suicidal behavior
- agitation
- hyperactive reflexes
- apprehensiveness
- confusion
- suspiciousness
- paranoia
- hypervigilence
- delusions
- hallucinations
- irrational behavior
- violence
- severe hypertension/chest pains
- seizures
- coma
- death
## Stimulants and the DRE Matrix

<table>
<thead>
<tr>
<th></th>
<th>CNS Depressant</th>
<th>Inhalants</th>
<th>Dissociative Drugs</th>
<th>CNS Stimulants</th>
<th>Hallucinogens</th>
<th>Narcotic analgesics</th>
<th>Cannabis</th>
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</thead>
<tbody>
<tr>
<td>Horizontal nystagmus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vertical Nystagmus</td>
<td>Present *</td>
<td>Present*</td>
<td>Present</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lack of Convergence</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>Pupil Size</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Dilated</td>
<td>Dilated</td>
<td>Constricted</td>
<td>Dilated*</td>
</tr>
<tr>
<td>Reaction to Light</td>
<td>Slow</td>
<td>Slow</td>
<td>Normal</td>
<td>Slow</td>
<td>Normal</td>
<td>Little to none</td>
<td>Normal</td>
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<tr>
<td>Pulse Rate</td>
<td>Down</td>
<td>Up</td>
<td>Up</td>
<td>Up</td>
<td>Up</td>
<td>Down</td>
<td>Up</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Down</td>
<td>Up/Down</td>
<td>Up</td>
<td>Up</td>
<td>Up</td>
<td>Down</td>
<td>Up</td>
</tr>
<tr>
<td>Body Temperature</td>
<td>Normal</td>
<td>Up/Down/Normal</td>
<td>up</td>
<td>Up</td>
<td>Up</td>
<td>Down</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Methamphetamine Hysteresis

Symptomatology

- improved reaction time
- relief from fatigue
- euphoria
- fatigue
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- confusion
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- irrational behavior
- violence
- severe hypertension/chest pains
- seizures
- coma
- death

Blood methamphetamine concentration (mg/L)
A laboratory driving simulation for assessment of driving behavior in adults with ADHD: a controlled study.

- Driving simulator assessment of ADHD subjects (20) against controls, all unmedicated.
- One hour driving course with high stimulus segment and low stimulus segment with two distinct monotonous periods.
Reverse Impairment


• ADHD subjects were more likely than controls to crash into an object suddenly appearing.
• Deficits on directed attention may underlie driving impairments in this population.
Reverse Impairment

What we know about ADHD and Driving Risk: A literature Review, Meta Analysis, and Critique

- There is an association between individuals with ADHD and increased driving risk.
- Indicators include increased self reports of being rear ended and involved in highway accidents; higher proportion of MVC’s in ADHD cohort studies; higher proportion of injury related MVC’s in participants with high attentional deficiencies.
Reverse Impairment


Figure 1. Meta Analysis on ADHD Status and Proportion of Self-Reported MVCs

- ADHD and Driving (1)
- Comparison: 01 Proportion of Motor Vehicle Collisions
- Outcome: 01 Self Report MVCs

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>ADHD n/N</th>
<th>nonADHD n/N</th>
<th>RR (fixed)</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkley et al (1993)</td>
<td>20/35</td>
<td>14/36</td>
<td>30.46</td>
<td>1.47</td>
<td>[0.89, 2.42]</td>
</tr>
<tr>
<td>Barkley et al (1996)</td>
<td>20/25</td>
<td>12/23</td>
<td>27.59</td>
<td>1.53</td>
<td>[0.99, 2.38]</td>
</tr>
<tr>
<td>Nada-Raja (1997)</td>
<td>8/73</td>
<td>30/523</td>
<td>16.22</td>
<td>1.91</td>
<td>[0.91, 4.01]</td>
</tr>
<tr>
<td>Woodward (2000)</td>
<td>6/46</td>
<td>43/895</td>
<td>9.20</td>
<td>2.71</td>
<td>[1.22, 6.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>284</td>
<td>1541</td>
<td></td>
<td>100.00</td>
<td>1.88 [1.42, 2.50]</td>
</tr>
</tbody>
</table>

Total events: 81 (ADHD), 105 (nonADHD)
Test for heterogeneity: $\chi^2 = 3.38$, df = 4 ($P = 0.49$), $I^2 = 0$
Test for overall effect: $Z = 4.40$ ($P < 0.0001$)
Reverse Impairment


Figure 2. Meta Analysis on ADHD Status and Proportion of Official Reports of Citations

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>ADHD n/N</th>
<th>nonADHD n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barklay et al (1996)</td>
<td>19/25</td>
<td>12/23</td>
<td>6.00 1.46 [0.93, 2.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nada-Raja (1997)</td>
<td>12/73</td>
<td>29/523</td>
<td>3.41 2.96 [1.58, 5.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barklay et al (2002)</td>
<td>94/105</td>
<td>38/64</td>
<td>22.67 1.35 [1.08, 1.69]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fischer (In press)</td>
<td>110/148</td>
<td>45/73</td>
<td>28.93 1.21 [0.98, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>464</td>
<td>1018</td>
<td></td>
<td>100.00</td>
<td>1.35 [1.20, 1.50]</td>
</tr>
</tbody>
</table>

Total events: 296 (ADHD), 285 (nonADHD)
Test for heterogeneity: Chi² = 7.55, df = 4 (P = 0.11), I² = 47.0%
Test for overall effect: Z = 5.23 (P < 0.00001)
Reverse Impairment


- Adverse effects are attributed various causes:
  - Risky driving behaviors/impulsiveness
  - Increased driving errors, lapses and violations
  - Distractability
  - Vehicle control
  - Cognitive abilities
  - Driving knowledge and decision making
  - Driving anger
Reverse Impairment

*Jerome L et al, J Can Acad Child Adolesc Psych 15:3, 2006*

- There is an association between individuals with ADHD and increased driving risk.
- Indicators include increased self-reports of being rear ended and involved in highway accidents; higher proportion of MVC’s in ADHD cohort studies; higher proportion of injury related MVC’s in participants with high attentional deficiencies.
Reverse Impairment


- Positive effects of stimulant medications.
  - Methylphenidate and Dexamphetamine
- Improved self report and actual performance in ADHD subjects but not non-ADHD controls with 10mg methylphenidate.
- Reduced inattention-related errors.
- Better scores on inappropriate braking, missed stop signs, collisions and erratic speed control.
Reverse Impairment


- 12 month outcomes study showed improvements in ADHD symptoms, and driving profile from self report and collateral assessment.
- Drivers were less prone to speeding, reduced distractability, less irritable with other road users.
- In head to head studies methylphenidate performs better than dexamphetamine.