Cocaine: Effects on Human Performance and Behavior

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Detroit, MI
Physiological Effects - NE

- Fight or Flight
- Increased blood pressure
- Increased heart rate
- Increased respiration
- Pupil dilatation
- Sweating
- Tremors
Desirable Behavioral Effects - DA

- Euphoria ("Rush")
- Elevation of "mood"
  (self confidence)
- Increased energy
- Alertness
- Sexual excitement
- Decreased need for food or sleep
Undesirable Behavioral Effects - DA

- Dysphoria ("Crash")
- Paranoia
- Irritability
- Assaultive behavior
- Craving
- Excited Delirium
Characterization of Excited Delirium

- Bizzare, violent behavior
- Unexpected strength
- Hyperthermia
- Sudden death
Died in Custody
Dade County, FL 1979-1990

Excited Delirium
38%

Other Cocaine Deaths
2%
Pharmacokinetics

and Pharmacodynamics
## Administration of Cocaine

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability (mean %)</th>
<th>Onset of Effects</th>
<th>Duration of Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked</td>
<td>57-70%</td>
<td>5-10 sec.</td>
<td>15 min.</td>
</tr>
<tr>
<td>Intravenous</td>
<td>100 %</td>
<td>30-60 sec.</td>
<td>30 min.</td>
</tr>
<tr>
<td>Intranasal</td>
<td>25-94%</td>
<td>15-30 min.</td>
<td>60 min.</td>
</tr>
<tr>
<td>Oral</td>
<td>20-50%</td>
<td>~60 min.</td>
<td>hours</td>
</tr>
</tbody>
</table>
Hysteresis of Cocaine in Plasma Versus Physiologic Effects

A) Pupils
- IV, 25 mg, N = 5
- SM, 42 mg, N = 5

B) Diastolic BP

A) Pulse

A) Systolic BP

(Cone, JAT, 1995)
Hysteresis of Cocaine in Plasma Versus Behavioral Effects

A) VAS
- IV, 25 mg, N = 5
- SM, 42 mg, N = 5

B) Subject Liking

C) MBG
(Cone, JAT, 1995)

D) LSD

Score vs. Cocaine, ng/mL
injected & snorted cocaine

rest of body

smoked cocaine
- Physiological effects SM = IV
- Behavioral effects SM > IV
- Suggests SM COC has greater abuse liability and potential to cause addiction
1. Plasma PChE
   Liver benzoylesterase
2. Chemical hydrolysis
   Liver methylesterase
3. Liver methylesterase
   Ethyl alcohol

ECGONINE METHYL ESTER → BENZOYLECGONINE → ETHYLCOCAINE

3.5 x faster than 2
Mean Plasma Concentration

Cone, 1995
Cocaine: Half-Life

- IV 37-87 min (8 studies); mean = 65 min
- SM 38-88 min (4 studies); mean = 55 min
- IN 42-90 min (7 studies); mean = 75 min
# Single-Dose Studies: IV & SM

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Mean Peak Conc. (mg/L, range or +/- SD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.09-0.31</td>
<td>Javaid et al., 1978</td>
</tr>
<tr>
<td>23</td>
<td>0.180 (+/- 0.056)</td>
<td>Jeffcoat et al., 1989</td>
</tr>
<tr>
<td>25</td>
<td>0.230 (0.098-0.349)</td>
<td>Cone, 1995</td>
</tr>
<tr>
<td>32</td>
<td>0.23 (0.13-0.34)</td>
<td>Isenschmid et al., 1992</td>
</tr>
<tr>
<td>64</td>
<td>0.47 (0.29-0.74)</td>
<td>Isenschmid et al., 1992</td>
</tr>
<tr>
<td><strong>SM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>0.227 (0.154-0.345)</td>
<td>Cone, 1995</td>
</tr>
<tr>
<td>50</td>
<td>0.21 (0.08-0.36)</td>
<td>Isenschmid et al., 1992</td>
</tr>
<tr>
<td>50</td>
<td>0.203 (+/- 0.088)</td>
<td>Jeffcoat et al., 1989</td>
</tr>
<tr>
<td>100</td>
<td>0.38 (0.20-0.60)</td>
<td>Isenschmid et al., 1992</td>
</tr>
</tbody>
</table>
### Single Dose Studies: IN

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Mean Peak Conc. (mg/L, range or +/- SD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>0.063 (0.040-0.088)</td>
<td>Cone, 1995</td>
</tr>
<tr>
<td>64</td>
<td>0.115</td>
<td>Javaid et al., 1978</td>
</tr>
<tr>
<td>64</td>
<td>0.067 (+/- 0.016)</td>
<td>Javaid et al, 1983</td>
</tr>
<tr>
<td>96</td>
<td>0.134 (+/- 0.021)</td>
<td>Javaid et al., 1983</td>
</tr>
<tr>
<td>106</td>
<td>0.220 (+/- 0.039)</td>
<td>Jeffcoat et al., 1989</td>
</tr>
<tr>
<td>0.38*</td>
<td>0.045 (+/- 0.007)</td>
<td>Wilkinson et al., 1980</td>
</tr>
<tr>
<td>1.5*</td>
<td>0.308 (0.120-0.474)</td>
<td>Van Dyke et al., 1976</td>
</tr>
<tr>
<td>2*</td>
<td>0.37 (0.13-1.0)</td>
<td>Brogan et al., 1992</td>
</tr>
</tbody>
</table>

*mg/kg

Less consistency between dose & plasma concentrations
## Metabolite Concentrations

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>BE</th>
<th>EME (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>SM</td>
<td>0.20</td>
<td>0.020 Isenschmid, et al., 1992</td>
</tr>
<tr>
<td>100</td>
<td>SM</td>
<td>0.35</td>
<td>0.020 Isenschmid, et al., 1992</td>
</tr>
<tr>
<td>42</td>
<td>SM</td>
<td>0.085</td>
<td>0.00 Cone, 1995</td>
</tr>
<tr>
<td>32</td>
<td>IN</td>
<td>0.12</td>
<td>&lt;0.01 Cone, 1995</td>
</tr>
<tr>
<td>25</td>
<td>IV</td>
<td>0.11</td>
<td>&lt;0.01 Cone, 1995</td>
</tr>
<tr>
<td>32</td>
<td>IV</td>
<td>0.24</td>
<td>&lt;0.01 Isenschmid, et al., 1992</td>
</tr>
<tr>
<td>64</td>
<td>IV</td>
<td>0.40</td>
<td>0.04 Isenschmid, et al., 1992</td>
</tr>
</tbody>
</table>
Stability in Blood at 25 °C
Unpreserved, Physiological pH

COC → EME
Stability in Blood at 4 °C
Unpreserved, Physiological pH

COC → EME
Stability in Buffers, 25 °C

COC, pH 10
COC, pH 7.4
COC, pH 5
BE, pH 10
BE, pH 7.4
BE, pH 5

mg/L

time (days)

COC → BE
Stability in Blood at 4 °C
2% NaF, Physiological pH

COC ➔ BE
Stability in Blood at 4 °C
2% NaF, pH 5

COC "Stable"
Pharmacokinetics: BE

- Rate of BE elimination slower than the rate of formation allowing BE to accumulate
- Peak BE conc. were observed at 1-4 h
- Mean $t_{1/2}$ of formation and elimination:

<table>
<thead>
<tr>
<th>Route</th>
<th>Formation</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>0.56 h</td>
<td>5.79 h</td>
</tr>
<tr>
<td>SM</td>
<td>0.49 h</td>
<td>5.40 h</td>
</tr>
<tr>
<td>IN</td>
<td>1.86 h</td>
<td>3.55 h</td>
</tr>
</tbody>
</table>

- from Cone, 1995
## Multiple Doses: IV and SM

Mean Peak Concentrations (mg/L, N=2)

<table>
<thead>
<tr>
<th>Dose (5-7x in 90 min)</th>
<th>COC</th>
<th>BE</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 x 50 mg SM; 1 x 32 mg IV</td>
<td>0.85</td>
<td>1.0</td>
<td>0.07</td>
</tr>
<tr>
<td>6 x 50 mg SM; 1 x 16 mg IV</td>
<td>0.99</td>
<td>0.84</td>
<td>0.07</td>
</tr>
<tr>
<td>6 x 50 mg SM</td>
<td>0.86</td>
<td>0.66</td>
<td>0.03</td>
</tr>
<tr>
<td>5 x 32 mg IV</td>
<td>0.83</td>
<td>0.68</td>
<td>0.03</td>
</tr>
<tr>
<td>5 x 16 mg IV (N=3)</td>
<td>0.45</td>
<td>0.37</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Peak [COC] overlaps “toxic” and “lethal” concentrations

No evidence of toxicity in these subjects

Isenschmid et al., JAT, 1992
## Multiple Doses: Oral

Examples of Data from Jufer et al., 1997

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose</th>
<th>COC</th>
<th>BE</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg q hr</td>
<td>max</td>
<td>max</td>
<td>max</td>
</tr>
<tr>
<td>A</td>
<td>5 x 400</td>
<td>1.26</td>
<td>5.39</td>
<td>3.07</td>
</tr>
<tr>
<td>B</td>
<td>5 x 300</td>
<td>0.73</td>
<td>3.83</td>
<td>2.65</td>
</tr>
<tr>
<td>C</td>
<td>5 x 125</td>
<td>0.27</td>
<td>2.24</td>
<td>0.38</td>
</tr>
<tr>
<td>D</td>
<td>5 x 400</td>
<td>1.26</td>
<td>4.42</td>
<td>2.27</td>
</tr>
<tr>
<td>E</td>
<td>5 x 300</td>
<td>0.65</td>
<td>3.70</td>
<td>1.77</td>
</tr>
<tr>
<td>F</td>
<td>5 x 350</td>
<td>1.90</td>
<td>4.23</td>
<td>2.72</td>
</tr>
</tbody>
</table>
Pharmacokinetics: EME
After Repeated PO Administration

- EME more prominent after PO dosing

- May be due to…
  - metabolic changes with chronic COC use
  - first pass metabolism
  - EME may be produced pre-hepatically in gut

- EME may also be observed in naïve COC users
Specimens from patients with history of COC toxicity
- Mean [COC] overlaps “therapeutic” concentration
- Median concentrations – BE and ECG greatest
- EME - May be naïve users - abusers don’t go to ED

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Range (mg/L)</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC</td>
<td>102</td>
<td>0.00-3.92</td>
<td>0.34</td>
<td>0.07</td>
</tr>
<tr>
<td>ECOC</td>
<td>33</td>
<td>tr - 0.34</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>BE</td>
<td>130</td>
<td>tr - 6.96</td>
<td>1.57</td>
<td>1.06</td>
</tr>
<tr>
<td>EME</td>
<td>97</td>
<td>0.00-2.72</td>
<td>0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>ECG</td>
<td>126</td>
<td>0.00-2.94</td>
<td>0.45</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Interpretation - Based on Pharmacokinetic Studies

- Typical single doses: peak plasma conc. 0.2-0.4 mg/L
- Concentrations of >0.75 mg/L (even up to 3.8 mg/L) reported without adverse effects
- Therapeutic and toxic cocaine concentrations overlap
- When [COC] > [BE] = recent COC use
- A high BZE / COC ratio (particularly when accompanied by a significant COC concentration) MAY BE indicative of recent binge COC use.
PO COC: Multiple Doses – “Binge Type”
100 mg PO (q hr to 4 h ) [ng/mL]

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>COC</th>
<th>BE</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.50</td>
<td>6.15</td>
<td>86.26</td>
<td>80.53</td>
</tr>
<tr>
<td>1.00</td>
<td>74.00</td>
<td>560.54</td>
<td>171.86</td>
</tr>
<tr>
<td>2.00</td>
<td>86.86</td>
<td>923.87</td>
<td>270.16</td>
</tr>
<tr>
<td>3.00</td>
<td>67.66</td>
<td>1203.66</td>
<td>457.91</td>
</tr>
<tr>
<td>4.00</td>
<td>100.01</td>
<td>1532.42</td>
<td>540.75</td>
</tr>
<tr>
<td>5.00</td>
<td>138.22</td>
<td>1882.58</td>
<td>696.80</td>
</tr>
<tr>
<td>6.00</td>
<td>59.36</td>
<td>1626.72</td>
<td>528.76</td>
</tr>
<tr>
<td>8.00</td>
<td>24.54</td>
<td>1229.79</td>
<td>334.73</td>
</tr>
<tr>
<td>12.00</td>
<td>7.72</td>
<td>707.73</td>
<td>152.52</td>
</tr>
<tr>
<td>24.00</td>
<td>2.70</td>
<td>160.23</td>
<td>9.51</td>
</tr>
</tbody>
</table>

High BE / COC ratio may be indicative of binge cocaine use
Effects of Cocaine on Performance
Attentional Abilities

■ Digit Symbol Substitution Test
  – subject draws symbol or types pattern associated with numerals
  – COC (48 & 96 mg, IN) - Higgins et al., 1990, 1993
    » improved performance above pre-drug
    » improved after repeated testing without drug
  – one study reported decreased response after 96 mg (IN) but has not been replicated
    - Fischman, 1984
Attentional Abilities (2)
Fischman and Schuster, 1980

- COC restores impairment in reaction times induced by sleep deprivation
  - N=8; tested at 0, 24, 48 h; placebo & COC
- Without sleep deprivation, COC tended to enhance reaction time above baseline but not statistically significant
Cognitive Abilities

- Up to 30 min disruption in accuracy of learning response sequences after 32 mg IV - Fischman, 1984
- Brief disruption in accuracy of learning word lists after 32 mg IV - Foltin et al., 1993
- After 96 mg IN
  - decreased response rate for acquisition
  - increased accuracy for performance - Higgins et al, 1992
Motor Abilities
Heishman and Crouch, SOFT, 1997

- 18 Volunteers
- COC: 4, 48, 96 mg / 70 kg IN
- Effects:
  - increased rating of drug strength
  - FST: one leg stand, finger to nose
    - improved performance vs. to THC
DRE Observations – Low Dose

Subjects given IN cocaine alone or in combination with other drugs or a different drug

<table>
<thead>
<tr>
<th>Observation (N=18)</th>
<th>PL</th>
<th>48mg</th>
<th>96 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not impaired</td>
<td>11</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Dosed with stimulant</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dosed with other</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

(Heishman and Crouch, JAT, 1996)
150 Reckless Drivers
Brookoff et al., NEJM, 1994

- It can be tough for the DRE!
- 150 reckless drivers not impaired by alcohol
  - 13% positive for prior cocaine use
  - 12% positive for cannabinoids + cocaine
- 50% performed normally on FST’s
- Large variability in behavior of cocaine users
  - 21% sleepy or slow
  - 39% happy
  - 39% combative, argumentative, paranoid
Abilities with Ethanol - Low Dose

- COC reversed or left unchanged EtOH-induced learning and performance decrements (5 studies)
- NO instance of > impairment than by EtOH alone
- Effects of NOT predictable based on performance with either drug alone
- Attenuation of effects may be bi-directional
- Subjects less sleepy not less drunk
- Caveat: low doses by IN route
  - 48 to 100 mg IN COC after 0.5-1.0 g/kg EtOH PO
Lab Studies - Summary

- Learning, memory - not significant
- Behavioral and cortical arousal - increased
- Attentional abilities - enhanced
- Improvements greatest in behaviorally impaired subjects (e.g. EtOH, sleep deprived) and least in well-rested subjects
Limitations to Laboratory Studies

- More deleterious effects are expected after higher doses, chronic ingestion and during withdrawal.
- Stimulants may enhance performance of simple tasks but not complex tasks (e.g. driving).
Factors Affecting Driving

- Coordination Skills
- Reaction Time
- Risk Taking
- Emotional State
  - anger, fear, stress, hostility
- Personality Style
  - relaxed, tense, aggressive
- Fatigue
- Mental health
- Hunger
- Distraction
  - radio, cell phones, smoking, thoughts, conversation
- Other Drugs
  - synergism, antagonism
Wayne County, MI 1996-98
Cocaine-Related Driving Fatalities

- 253 Drivers - Motor Vehicle Fatalities (2 years)
- 25 (10%) positive for COC/CE and/or BE (blood)
- Other studies – 6-23% where cocaine use is endemic - many published citations

- Québec Study – Dussault et al., 2001
  - Controls - Random drivers (collected 24hr/day)
  - Cocaine / Mbs 1.1% urine (n=8,177)
  - Cocaine / Mbs 1.0% saliva (n=5,931)
Wayne County, MI 1996-98
Cocaine-Related Driving Fatalities

- 56% Cocaine (COC)
- 44% Cocaine and Methylbenzylethylamine (COC&MBS)
- 14 (71%) Cocaine or CE

10 (71%) Cocaine or CE
Wayne County, MI 1996-98
Cocaine-Related Driving Fatalities

- COC + EtOH – ALL 14 cases involved loss of vehicle control; many at high speed

- 3 cases involved police chases
  - Also observed by others
  - Wetli and Fishbain, J. For. Sci., 1985
Literature Reports

- 62% of smokers self-report suspiciousness, distrust, paranoia
  - Siegel, J Psychoact. Drugs, 1982

- Cocaine associated with road rage
  - Fong et al., Soc Psychiatry Psychiatr Epidemiol, 2001

- Suspiciousness correlated to cocaine dose, not plasma concentration
  - Sherer et al., Arch Gen Psych, 1988
**COC/BE/CE + EtOH (blood)**

**Police Chases**

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE (g %)</th>
<th>CE</th>
<th>EtOH</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>1200</td>
<td>49</td>
<td>0.05</td>
<td>police chase, struck by police car, hit tree</td>
</tr>
<tr>
<td>13</td>
<td>260</td>
<td>12</td>
<td>0.12</td>
<td>police chase, ran stop sign, struck car</td>
</tr>
<tr>
<td>nd</td>
<td>100</td>
<td>nd</td>
<td>0.19</td>
<td>police chase, high speed, lost control, hit hydrant &amp; bldg., ejected</td>
</tr>
</tbody>
</table>
COC/BE/CE + EtOH (blood)
Parent Cocaine Detected
Order of Decreasing Cocaine Concentration

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE</th>
<th>CE</th>
<th>EtOH (g %)</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100</td>
<td>1800</td>
<td>170</td>
<td>0.07</td>
<td>collided head-on with truck</td>
</tr>
<tr>
<td>530</td>
<td>510</td>
<td>34</td>
<td>0.04</td>
<td>high speed, lost control, hit hydrant, rolled into sign and caught fire</td>
</tr>
<tr>
<td>320</td>
<td>660</td>
<td>110</td>
<td>0.08</td>
<td>lost control, went through 4 front yards, hit tree</td>
</tr>
</tbody>
</table>
### COC/BE/CE + EtOH (blood)

Parent Cocaine Detected

Order of Decreasing Cocaine Concentration

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE (g %)</th>
<th>CE (ng/mL)</th>
<th>EtOH (g %)</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>270</td>
<td>5500</td>
<td>160</td>
<td>0.08</td>
<td>stole truck, high speed, lost control, hit wall, ejected</td>
</tr>
<tr>
<td>60</td>
<td>140</td>
<td>55</td>
<td>0.22</td>
<td>high speed, jumped curb, rolled</td>
</tr>
<tr>
<td>49</td>
<td>2100</td>
<td>nd</td>
<td>0.09</td>
<td>up embankment, rolled, ejected</td>
</tr>
<tr>
<td>36</td>
<td>170</td>
<td>46</td>
<td>0.21</td>
<td>high speed, crossed median, hit overpass</td>
</tr>
</tbody>
</table>
**COC/BEC/EC + EtOH (blood)**

**Metabolites Only Detected**

<table>
<thead>
<tr>
<th>COC</th>
<th>BE</th>
<th>CE</th>
<th>EtOH (g %)</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>nd</td>
<td>450</td>
<td>nd</td>
<td>0.09</td>
<td>high speed, lost control, hit lamp post</td>
</tr>
<tr>
<td>nd</td>
<td>230</td>
<td>27</td>
<td>0.33</td>
<td>struck parked car, rolled, ejected</td>
</tr>
<tr>
<td>nd</td>
<td>110</td>
<td>nd</td>
<td>0.16</td>
<td>high speed, lost control, hit lamp post</td>
</tr>
<tr>
<td>nd</td>
<td>&lt;50</td>
<td>nd</td>
<td>0.21</td>
<td>rear-ended stopped semi</td>
</tr>
</tbody>
</table>
Ethanol + Cocaine - Lab Data

- Higher doses - reflect “real” use
- Cocaine - 1mg/kg IN q 30 min for 2h
- Ethanol – BAC maintained at 0.10%
- Peak plasma [COC] higher when combined with EtOH, than for same dose of COC alone
  - pH shift … less hydrolysis to BE
- Peak plasma [EtOH] lower and later with COC, than for EtOH alone
  - Competition … EtOH used to make ECOC
Ethanol + Cocaine - Lab Data

- ECOC - Longer $t_{1/2}$ than COC - inc. toxicity?
  - Methylesterase converts COC to ECOC 3.5x faster than it hydrolyzes COC to BE

- COC + EtOH > euphoria than COC alone
  (McCance et al. Biol Pharmacol, 1998)

- May result in feelings of increased mental and physical abilities
  - disinhibition (EtOH) + stimulant (COC)

- Increased risk-taking in drivers

- May play a role when interpreting impairment

((McCance et al. Biol Pharmacol, 1998))
Wayne County, MI 1996-98
Cocaine-Related Driving Fatalities

- COC &/or mbs. – no EtOH (11 / 25)
- Fault or 50% fault, N = 7
  - Lost vehicle control, N = 4
  - Accident due to illegal maneuvers, N = 2
  - Drivers at 50% fault, N = 1
- Drivers NOT at fault, N = 4
COC/BE/CE + no EtOH (blood) Lost Vehicle Control

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE</th>
<th>CE</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>nd</td>
<td>2100</td>
<td>nd</td>
<td>crossed-over median and stuck mini-van</td>
</tr>
<tr>
<td>nd</td>
<td>690</td>
<td>nd</td>
<td>crossed center-line and stuck car head-on</td>
</tr>
<tr>
<td>310</td>
<td>2000</td>
<td>nd</td>
<td>crossed center-line and struck tree head-on</td>
</tr>
<tr>
<td>94</td>
<td>580</td>
<td>40</td>
<td>police chase, hit while making turn</td>
</tr>
</tbody>
</table>
Crossing the Center-Line

- Self-reported effects on vision - mydriasis
  - Increased sensitivity to light
  - Halos around bright objects
  - Difficulty focusing
  - Blurred vision
  - Glare recovery problems

- Hallucinations
  - “Snow Lights” most commonly reported

- Or fatigue? Only BE detected in 2 cases

Siegel – Alcohol, Drugs & Driving, 1987
**COC/BE/CE + no EtOH (blood)**

**Illegal Maneuvers**

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE</th>
<th>CE</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>nd</td>
<td>260</td>
<td>nd</td>
<td>pulled to side, <strong>made U-turn</strong> and got hit by a bus</td>
</tr>
<tr>
<td>110</td>
<td>540</td>
<td>nd</td>
<td><strong>made U-turn in front of another car</strong> and got hit</td>
</tr>
<tr>
<td>nd</td>
<td>&lt;50</td>
<td>nd</td>
<td><strong>ignored red light while making left</strong>, hit by oncoming car which also ignored red light</td>
</tr>
</tbody>
</table>
COC/BE/CE + no EtOH (blood)  
Drivers not at fault

<table>
<thead>
<tr>
<th>COC (ng/mL)</th>
<th>BE</th>
<th>CE</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>1100</td>
<td>nd</td>
<td>hit by van after inching forward to check traffic</td>
</tr>
<tr>
<td>28</td>
<td>29</td>
<td>28</td>
<td>struck by another vehicle while turning into driveway, pushed into utility pole</td>
</tr>
<tr>
<td>nd</td>
<td>2100</td>
<td>nd</td>
<td>lost control during seizure, crossed median, hit lamp</td>
</tr>
<tr>
<td>nd</td>
<td>&lt;50</td>
<td>nd</td>
<td>hit by car which ran stop sign</td>
</tr>
</tbody>
</table>
High risk driving is associated with cocaine use with or without EtOH.

However, EtOH may play a larger role in accident occurrence than cocaine.

Fault more likely when EtOH present.

These findings are consistent with other studies examining crash responsibility.

Stimulant vs Depressant?
## Fatal Crashes - Responsibility

<table>
<thead>
<tr>
<th></th>
<th>Wayne County</th>
<th>Québec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (blood)</td>
<td>25 / 253</td>
<td>14 / 233</td>
</tr>
<tr>
<td>COC/BE</td>
<td>7/11 (64%)</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>COC/BE/EtOH</td>
<td>14/14 (100%)</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>EtOH Only</td>
<td>not performed</td>
<td>14/14 (100%)*</td>
</tr>
<tr>
<td>Drug-Free</td>
<td>not performed</td>
<td>26/39 (67%)*</td>
</tr>
</tbody>
</table>

*males 16-45
Fatal Crashes - Responsibility

- **Timby et al., 1998 (Sweden)**
  - Alcohol positive (96% responsible)
  - Drug free (70%)
  - Drug positive - not significantly more responsible than drug negative

- **Williams et al., 1985 (California)**
  - Alcohol associated with increased responsibility; other drugs uncertain
Wayne County, MI 1996-98
Summary - Cocaine-Related Driving Fatalities

- No evidence that COC and Mtb. concentrations were related to accident occurrence
  - Consistent with a consensus study; JAMA, 1995

- Single Vehicle Crashes – more frequent with EtOH

<table>
<thead>
<tr>
<th></th>
<th>Wayne County</th>
<th>Québec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coc/BE</td>
<td>1/11 (9.1%)</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>Coc/BE/EtOH</td>
<td>9/14 (64%)</td>
<td>5/6 (83%)</td>
</tr>
</tbody>
</table>
Wayne County Study - Caveats

- No testing for cannabinoids in this study.
- Only cocaine positive cases were studied. The role of fatigue or “cocaine crash” not evaluated.
- Fatally injured drivers tend to have high crash responsibility rates and may not represent general responsibility rates.
- The prevalence of cocaine in postmortem studies is not related to the prevalence in random drivers.
- This study does not take into account other driving factors – distractions, driver personalities.
168 Fatally Injured Truck Drivers

- NTSB, 1988; Crouch et al., J For Sci, 1993
- 14 (8.3%) positive for COC and/or BE
- Drug impairment sole cause 4 / 14
  - All 4 also positive for either delta-9-THC, EtOH (>legal limit) or PCP
- Cocaine and/or BE in absence of other drugs - only 2 / 14 cases
  - Fatigue considered contributing factor in both
  - Cocaine “crash”? - Hard to study
Problems Performing “Crash-Phase” Studies

- Cannot administer COC to non-users
  - Effects of “crash”, if any, in infrequent users is not known
- Difficult to evaluate accident data in these cases – blood negative
  - Urine suggests only past use
  - NOT related to impairment or withdrawal
- Difficult to distinguish lost vehicle control due to fatigue vs aggressive driving
- Abstinence studies have limitations
Limitations to Abstinence Studies

- Studies may begin too late after COC use to study “crash” symptoms
- Amount of COC use and timing of that use prior to the studies not controlled
- Subjects’ sensitivity to COC-related cues often not assessed
- Subjects seeking treatment are not typical COC users
Interpretive Issues

- Stability (prior to and during analysis)
- Interindividul variation - kinetics and dynamics
- Pathological conditions - diseases may affect metabolism
- Pharmacological agents - synergism + antagonism
Interpretive Issues

- Tolerance and sensitization
- Arteriolar vs. venous blood
  - $[\text{COC}] >$ in arteriolar blood for up to 30 min.
- Single use versus “binge” use – altered kinetics
- Delayed toxicity possible (little or no “parent” drug)
- Postmortem – stability (PMI), hydrolysis and release, pathology, delayed death, specimen collection sites, preservation
Conclusions

The presence of cocaine at a given concentration in the blood cannot usually be associated with the degree of impairment or with a specific effect for a given individual without additional information.
Investigation Triad

INVESTIGATION

WITNESS (DRE)          TOXICOLOGY