19th Annual Mastering Scientific Evidence in DUI/DWI Cases
March 22-24, 2012
The Royal Sonesta Hotel
New Orleans, Louisiana

Topic:
Clinical Pharmacologic Factors that Determine if CNS Depressants or Opiates will Cause Impairment in Automobile Drivers

Speaker: Fran M. Gengo Pharm D.
Dent Neurologic Institute
Buffalo, New York
Clinical Pharmacologic Factors that Determine if CNS Depressants or Opiates will Cause Impairment in Automobile Drivers

Fran M. Gengo Pharm D.
Dent Neurologic Institute
Buffalo NY

Why CNS Depressants and Opiates are different than Alcohol

- Medical Indication for the CNS Depressant or the Opiate
- Duration of Treatment
- Time After last Dose
- Drug Associated Sleep related Behaviours
Pharmacologic Classification as per NHTSA

- Cannabis
- Inhalants
- Narcotics
- Dissociative Anesthetics
- Hallucinogens
- CNS Stimulants
- CNS Depressants

“CNS Depressants” as per DRE protocol

- Antihistamines
  - Agonist at histamine 1 receptors & anticholinergic receptors
- Barbiturates and Benzodiazepines and ‘Z’ drugs
  - Act to facilitate GABA receptors
- Antipsychotic
  - Antagonist at dopamine and serotonin receptors
- Skeletal Muscle Relaxants and Anti-depressants
  - Inhibit reuptake of norepinephrine
- Newer Antidepressants
  - Inhibit reuptake of serotonin

DRE just throws them all into the same drug class
As though they all produce the same effects
Percent Correct Drug Identification by DRE Officer

<table>
<thead>
<tr>
<th>Drug Given</th>
<th>Officers' Decision</th>
<th>Officers' Decision</th>
<th>Officers' Decision</th>
<th>Officers' Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>30</td>
<td>16</td>
<td>20</td>
<td>8.2</td>
</tr>
<tr>
<td>Depressant</td>
<td>8.2</td>
<td>43</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Narcotic</td>
<td>39</td>
<td>12.2</td>
<td>36.7</td>
<td>2</td>
</tr>
<tr>
<td>Stimulant</td>
<td>7.8</td>
<td>3.9</td>
<td>8.8</td>
<td>41.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>20</td>
<td>14.7</td>
<td>2</td>
</tr>
</tbody>
</table>

The Prosecutors Argument

- The Officer reports staggering gait, slurred speech, failed SFSTs or DRE exam and no ethanol
- The Toxicologist reports measured benzodiazepines in blood
- Ergo Driving while ability impaired drug
Pharmacologic Factors Relevant to Interpretation of Benzodiazepine concentrations

- Medical History / Indication for Benzodiazepine or opiate
- Tolerance
- Time after last dose
- Specific Benzodiazepine
- Age

Spasticity associated with Multiple Sclerosis or Stroke
- Dystaxic gait, nystagmus, speech apraxia
- Performance can improve if spasticity is relieved

Generalized Anxiety Disorder, PTSD
- Apparent Confusion, word finding difficulties, near syncope
- Performance can improve with reduced anxiety

Seizures
- Post ictal confusion, nystagmus

Migraine
- Visual field cuts, focal weakness, photophobia,

Insomnia
- Excessive day time somnolence, blepharospasm
- Performance can improve if sleep deprivation is reduced

Chronic Pain
- Dystaxic gait, depressed affect, poor balance
- Performance can improve if chronic pain is lessened

Conditions where symptoms can mimic intoxication and benzodiazepine of opiate can improve performance.

Is the Officer seeing Drug Impairment or Disease related symptoms?

Do Anxiolytics Improve or Impair Performance?

Performance

Anxiety
The Drug Evaluation and Classification procedure is a systematic and standardized method of examining a person to determine:
• Whether the person is impaired, and if so;
• Not supported by data
• Whether the impairment relates to drugs or a medical condition, and if drugs;
  • Validation studies performed in healthy individuals
• The category or combination of categories of drugs that are the likely cause of the impairment
  • Not supported by data

Pharmacologic Factors Relevant to Interpretation of Benzodiazepine or Opiate concentrations

• Tolerance
  – Episodic Recreational Use
  – Short Term Medical Use
  – Chronic Medical Use

Table 3. Risk (odds ratio (confidence limits)) of hospitalization for accident injury after BZD use

<table>
<thead>
<tr>
<th>Potential risk factor</th>
<th>Within 4 wk of index prescription (n = 89)</th>
<th>Within 2 wk of index prescription (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZD hypnotics</td>
<td>3.9* (1.9–8.3)</td>
<td>6.5* (1.9–22.4)</td>
</tr>
<tr>
<td>BZD anxiolytic</td>
<td>2.9* (1.3–5.2)</td>
<td>5.6* (1.7–18.4)</td>
</tr>
</tbody>
</table>
Pharmacologic Factors Relevant to Interpretation of Benzodiazepine concentrations : Tolerance

Testing after first dose

<table>
<thead>
<tr>
<th>TABLE 2: Memory functioning after acute administration of diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam dosage (mg)</td>
</tr>
<tr>
<td>% of tests showing impairment</td>
</tr>
<tr>
<td>Total number of tests</td>
</tr>
</tbody>
</table>

Testing after 24 days of treatment

<table>
<thead>
<tr>
<th>TABLE 3: Psychomotor performance after repeated administration of diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam dosage (mg)</td>
</tr>
<tr>
<td>% of tests showing impairment</td>
</tr>
<tr>
<td>Total number of tests</td>
</tr>
</tbody>
</table>

Alprazolam Tolerance after 5 days of Treatment

Tolerance to Alprazolam 0.5 mg/day but not Lorazepam 2mg /day

Alprazolam Concentrations on Day 10 would have been higher then on Day 1.

Euro J Clin Pharmacol 1986 29 709-712
**Pharmacologic Factors Relevant to Interpretation of Benzodiazepine concentrations**

- Medical History / Indication for Benzodiazepine
- Tolerance
- Specific Benzodiazepine
- Time after last dose
- Age
Pharmacologic Factors Relevant to Interpretation of Benzodiazepine concentrations: Time after last dose

Concentration at which effect = placebo

Effects of age on Culpability Ratio in Fatal Crashes involving Drugs

Drummer et al

BENZODIAZEPINE METABOLISM
Some Benzodiazepine Metabolites are also Marketed Products

Benzodiazepine Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset of Action</th>
<th>Half-Life (hr)</th>
<th>Duration</th>
<th>Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam 2 mg</td>
<td>1 hour</td>
<td>10–24</td>
<td>6–8 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam 30 mg</td>
<td>15–20 minutes</td>
<td>47–100</td>
<td>8–10 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonazepam 0.5 mg</td>
<td>30–60 minutes</td>
<td>39–73</td>
<td>&lt;12–14 hours</td>
<td>No</td>
</tr>
<tr>
<td>Temazepam 15 mg</td>
<td>1–2 hours</td>
<td>9.5–12.4</td>
<td>6–8 hours</td>
<td>No</td>
</tr>
<tr>
<td>Triazolam 0.25 mg</td>
<td>15–20 minutes</td>
<td>1.5–5.5</td>
<td>3–4 hours</td>
<td>No</td>
</tr>
<tr>
<td>Alprazolam 0.5 mg</td>
<td>1 hour</td>
<td>6–12</td>
<td>5 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam 5 mg</td>
<td>10–20 minutes</td>
<td>50–100</td>
<td>8–10 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>30–60 minutes</td>
<td>12–15</td>
<td>&lt;12–14 hours</td>
<td>No</td>
</tr>
<tr>
<td>Zolpidem 10 mg</td>
<td>15–30 minutes</td>
<td>1.4–3.8</td>
<td>4–6 hours</td>
<td>No</td>
</tr>
<tr>
<td>Zopiclone 7.5 mg</td>
<td>15–30 minutes</td>
<td>5</td>
<td>6–8 hours</td>
<td>No</td>
</tr>
<tr>
<td>Zaleplon 10 mg</td>
<td>15–30 minutes</td>
<td>1.0–1.5</td>
<td>2–3 hours</td>
<td>No</td>
</tr>
</tbody>
</table>

Pharmacologic Factors Relevant to Interpretation of Benzodiazepine concentrations: Age

- "effects of concentrations produced by benzodiazepines depend on duration of treatment, time after dose, and age of driver"
- "Old age produces pharmacokinetic and pharmacodynamic changes to benzodiazepines, that is for any given concentration, behavioral effects will be greater in the elderly"
Lack of impairment during morphine 30 – 120 mg in chronic pain patients. 
Response was not related to dose (conc).

Lack of deterioration of performance or electrophysiologic measures of alertness before and during morphine infusion in patients with chronic pain objective endpoints.

While measures of pain indicated effective analgesia, objective, behavioral, and physiologic indicators of vigilance or cognitive function yielded lack of sedation or even improved alertness during morphine. 

My own experience in patients indicates the presence or absence of myosis is unrelated to drug associated impairment in patients taking opiates.
Driving records of 104 methadone maintenance patients reviewed for motor vehicle accidents during the 1st year of treatment

- 15/104 had driving accidents
- Not different than the expected frequency, based on all Texas licensed drivers estimated to be 10/104
- No relationship between dose of methadone (concentration) and accidents
- Similar to reports conducted in New York State
- Authors conclude “on the basis of these data we recommend no restrictions for driving privileges of persons maintained on methadone”

Am J Drug Alcohol Abuse 4(1) 91-100 1977

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline (M, SE)</th>
<th>Two months (M, SE)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 1-5 (words recalled)</td>
<td>40.3 (2.73)</td>
<td>47.4 (2.56)*</td>
<td>11.20</td>
<td>.004</td>
</tr>
<tr>
<td>Complex Figure Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy condition</td>
<td>46.3 (1.39)</td>
<td>47.3 (1.48)</td>
<td>0.42</td>
<td>.59</td>
</tr>
<tr>
<td>Immediate condition</td>
<td>14.4 (1.31)</td>
<td>15.4 (1.48)</td>
<td>0.84</td>
<td>.39</td>
</tr>
<tr>
<td>Delay condition</td>
<td>15.8 (1.41)</td>
<td>14.03 (1.46)*</td>
<td>5.50</td>
<td>.03</td>
</tr>
<tr>
<td>Digit Symbol Test</td>
<td>42.3 (4.35)</td>
<td>45.2 (4.32)*</td>
<td>2.00</td>
<td>.15</td>
</tr>
</tbody>
</table>

Methadone Maintenance Improves Objective Measures of Cognitive Performance
Experimental and Clinical Pharmacology
2006-14 157-162

Clinical Pharmacologic Factors in Interpretation of Serum Benzodiazepine or Opiate Concentrations in Automobile Drivers

Whether or not specific concentrations of an opiate or benzodiazepine in a specific driver will likely produce impairment requires knowledge of:

- medical condition being treated (if any)
- the dose of the drug taken,
- the duration of treatment with that drug,
- the time since the last dose of that drug.
A case-control study on 3398 fatally-injured drivers

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>%</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug and alcohol free</td>
<td>1704</td>
<td>(50.1%)</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>All psychoactive drugs</td>
<td>484</td>
<td>(14.2%)</td>
<td>1.80</td>
<td>1.3–2.4</td>
</tr>
<tr>
<td>Drugs Plus Ethanol</td>
<td>285</td>
<td>(8.4%)</td>
<td>1.70</td>
<td>1.3–2.3</td>
</tr>
<tr>
<td>Stimulants (all drivers)</td>
<td>53</td>
<td>(1.9%)</td>
<td>2.27</td>
<td>0.9–5.6</td>
</tr>
<tr>
<td>Stimulants (truckers)</td>
<td>22</td>
<td>(15.8%)</td>
<td>8.83</td>
<td>1.00–78</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>34</td>
<td>(1.0%)</td>
<td>1.27</td>
<td>0.5–3.3</td>
</tr>
<tr>
<td>Opiates</td>
<td>59</td>
<td>(1.7%)</td>
<td>1.41</td>
<td>0.7–2.9</td>
</tr>
<tr>
<td>Other psychoactive drugs</td>
<td>51</td>
<td>(1.5%)</td>
<td>3.78</td>
<td>1.3–11</td>
</tr>
<tr>
<td>Miscellaneous drugs</td>
<td>95</td>
<td>(2.8%)</td>
<td>1.47</td>
<td>0.8–2.7</td>
</tr>
</tbody>
</table>

Drummer et al

The Prosecutors Argument
- The Officer reports staggering gait, slurred speech, failed SFSTs or DRE exam and no ethanol
- The Toxicologist reports measured benzodiazepines in blood
- Ergo Driving while ability impaired drug

Elements of the States Case “Impairment”
- Arresting Officer
  - SFST are validated to detect impairment from ethanol ONLY
- DRE Officer
  - DRE reports many drug effects that are unrelated to impairment (ie pupil size, muscle tone, blood pressure etc)
  - DRE reports symptoms that are often due to the disorder being treated by the opiate or benzodiazepine
  - Often guesses correctly about which drug your client is being treated with because your client honestly answered the Officers questions
  - The DRE protocol is not Scientifically Valid
- States “Toxicologist”
Sensitivity → 0.76
Specificity → 0.63
#57 % false positive
The likelihood ratio for identifying impairment caused by alprazolam is 2.03

Ability to Identify the Specific Drug Category with the DRE Process:

<table>
<thead>
<tr>
<th>DRE Prediction</th>
<th>Actual Condition</th>
<th>Alcohol</th>
<th>Impaired</th>
<th>Not Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Alcohol</td>
<td>26</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Impaired</td>
<td>Impaired</td>
<td>11</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Not Impaired</td>
<td>Not Impaired</td>
<td>35</td>
<td>19</td>
<td>32</td>
</tr>
</tbody>
</table>

The chance of a subject being impaired by alcohol was 2.03 times greater than the chance of a subject being not impaired by alcohol.

Elements of the States Case
“The States expert”

- Chemist
- Chemist with the title “toxicologist”
- Analytical Toxicologist (MSc or PhD)
- Toxicologist with clinical training and experience (MD or Pharm D, DDS etc)
Even with Clinical Training there is Critical Information not known to the States expert

- What medical problems does the patient have and how they could influence the DRE evaluation
- What medical problem is the drug being prescribed to treat and how it would influence drug effect
- How other medications might influence drug effect
- How long has the drug been prescribed
- How long after the last dose was the DRE performed and sample taken
- What are expected concentrations drug effects and concentrations at steady state

Elements of the States Case
“ The States expert”

- The states expert’s opinion about the possible effects of a drug without knowing the dose your client took, the duration of your client’s treatment, the time between last dose and collection of your clients blood and the medical condition of your client is mere speculation and should not be allowed
- The states experts testimony should be limited to “we did this in the lab and the results were ….”

Drug Associated Sleep Related Behaviors
Pharmacology and the Law

Fran M Gengo Pharm.D. FCP
Allen Trapp JD
Sleep Stages

REM = rapid eye movement.


EEG Recordings

Typical Nighttime Sleep Pattern in Young Adult

Letter sent to all Health care providers March 2007 regarding Complex Sleep Behaviors following Zolpidem
Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with Ambien alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien appears to increase the risk of such behaviors. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events.

CONCLUSIONS
We describe the clinical presentation and review the relevant literature on zolpidem and sleep-driving. In 2005, more than 23 million prescriptions were issued for zolpidem. Physicians should be aware of the risk of both parasomnia and driving impairment. A history of parasomnia without precedent sedative-hypnotic use may predispose people to further episodes on such medication. Caution is warranted when prescribing zolpidem and other sedative-hypnotics. We conclude that zolpidem can cause sleep-driving.

John A. Doane, MD, FACP
Anthony S. Dalpiaz, PharmD

Drug associated Sleep Related Behavior

- Patients do not make normal memory until they are fully awakened, usually greater than 4 hours after a 5 mg dose
- More likely to occur in:
  - Patients in whom it has already occurred
  - Patients with a history of somnambulism
  - Patients with specific other medical disorders
  - Patients with environmental risk factors

Drug associated Sleep Related Behavior

Why are these more likely with the Z drugs compared to benzodiazepine

- Z drugs act preferentially at only 1 subunit of the benzodiazepine receptors
- Benzodiazepines act at all subunits and likely produce more generalized CNS depressant effect
- Z drug preferentially increase delta sleep, delta sleep is increased in non-medicated sleepwalkers
SUMMARY

Sleep driving is not often classified as a variant of drowsy driving, but should be distinguished from impaired driving due to misuse or abuse of sedative/hypnotic drugs. X-drugs, zolpidem and eszopiclone in particular, have been associated with the majority of reported cases of impaired driving. Numerous studies have found X-drugs to increase the risk of adverse events. Impaired driving is reported to be (1) a clinical feature of certain psychiatric conditions, (2) a result of insufficient sleep, and (3) a result of co-administration of drugs with other CNS depressants. The clinical features of CNS depression include the use of traditional hypnotics.

Drug associated Sleep Related Behavior

- Medical Disorders that increase risk
  - Restless leg syndrome
  - Obstructive Sleep apnea (or bed partner with OSA)
  - Benign prostatic hypertrophy
  - Severe chronic pain syndromes

- Environmental Risk Factors
  - Living near an airport, train tracks fire/police station
  - Living in a loud apartment building
  - A newborn child in the house

Pharmacology Principles in the Courtroom “CNS Depressants”

- Drug associated Sleep Related Behavior
  - Engaging in behaviors while not fully awake after ingestion of a drug
- Reported after benzodiazepines and the “Z” drugs
  - Associated with drugs that increase delta sleep
- Tsai et al report an incidence of 5.1 % of patients using zolpidem to experience “unusual behavior” of parasomniac activities
- Report authored by FDA “Sleep driving events are not predictable or under the control of the patient”
Drug associated Sleep Related Behavior

- An unpredictable Adverse Effect
- Not Dose related
- Not duration of treatment related
- Not influenced by tolerance or lack of tolerance

High Alcohol Concentrations can cause amnestic episodes

- With ethanol a client can reasonably expect that high doses of ethanol will cause amnestic episodes
- With the Z drugs a client could not have reasonably expected that their usual dose would produce this adverse drug effect