CNS Depressants

Human Performance & Driving

WA State Toxicology Laboratory

- 10,000 cases per year
- 5,000 driving cases
- 5,000 death investigation cases
- Unique perspective in that we can assess the differences in these 2 populations

2004 – Drugs Detected

TopTwenty Reported Drugs (excluding ethanol) 2004

Top Ten DUI Drugs - 2005
Top Twenty DUI Drugs - 2005

THC/carboxy-THC (23%)
methamphetamine/amphetamine (12%)
cocaine/met.(7%)
diazepam/nordiazepam (5.1%)
methadone (4.3%)
morphine (3.9%)
carisoprodol/meprobamate (3.4%)
hydrocodone (3%)
alprazolam (2.9%)
oxycodone (2.4%)
lorazepam (1.9%)
citalopram (1.7%)
diphenhydramine (1.6%)
zolpidem (1.6%)
venlafaxine (1.5%)
temazepam (1.2%)
trazodone (1.2%)
7-aminoclonazepam (1.1%)
codeine (1.1%)
fluoxetine (1.1%)

Anti-Depressants vs CNS Depressants

- Anti-depressants commonly seen
- Typically we do not see driving cases with anti-depressants alone
  - When we do, the evidence for impairment is poor

SSRIs (SNRIs) Bupropion

- Side effect profile does not typically include impairment
- In impaired drivers – other drugs present alone could account for impairment
- Effects on Driving
  - Data does not support driving impairment
- AND –
  - Is the treated depressed patient a better driver than a non-treated depressed patient

Assessing role of drug in driving impairment

- Most are poly-pharmacy cases
- Look for those cases with the drug of interest alone
- Assess the driving behaviors to look for patterns
- Anti-depressants – No patterns
What is the common thread?

- Co-ingestion with CNS depressants

Outline

CNS Depressants – GHB (Not recently)
- Carisoprodol (Soma®)/Zolpidem (Ambien®)
- Diphenhydramine (Benadryl®, etc)
- Benzodiazepines
- Anti-epileptics drugs

- Pharmacology / Pharmacokinetics
- Effects and Side Effects
- Effects on Driving
  - Laboratory studies/Driving studies
  - DUI / DRE observations & Case Reports

CNS Depressants

General Effects

- CNS depressants slow down operations of the brain
- Initially affect brain areas controlling conscious and voluntary actions
- As dosage increases, depressants affect brain areas controlling unconscious and automatic processes
- Emotional effects range from euphoria to depression
- Reduced social inhibitions, slow reflexes
- Slurred, mumbled or incoherent speech
- Impaired judgment, concentration, vision & coordination

Carisoprodol
(Soma®)

Meprobamate
(Miltown®, Equanil®)
Carisoprodol
- Skeletal muscle relaxant
- Indicated for acute muscle pain
- Centrally acting, CNS depressant
- 350 mg tablets (or 200 mg combined with aspirin/codeine)
- 1-2 tablets every 6 hr (800 - 1400 mg)
- Peak concentration in ~1 hr
- Onset of effects within 30 mins; duration 4-6 hr
- Metabolized via P450 2C19
- t½ is 99 +/- 45 mins

Meprobamate
- Anxiolytic
- CNS depressant
- 400 mg, 4 tabs per day
- Equipotent to parent drug
- Peak concentration in ~4 hr
- Longer duration of action compared to parent drug
- t½ is 6-17 hr
- Accumulation may occur with chronic therapy

Soma®
- Single dose of SOMA
  - 350 mg Carisoprod ~ 2.1 mg/L Meprobamate ~ 2.0 mg/L
  - 700 mg ~ 3.5 mg/L ~ 4.0 mg/L
  - 700 mg ~ 3.1 mg/L ~ 4.8 mg/L

- Chronic dosing with SOMA
  - Carisoprodol = 3-15 mg/L Meprobamate = 5-30 mg/L

Effects
- Clinical and Adverse Effects
  - Dizziness, drowsiness, sedation, confusion
  - Slowed thinking, disorientation, drunken behavior
  - Nystagmus, slurred speech
  - Loss of balance & coordination, sluggish
  - Headache, nausea, weakness
  - Ataxia, tremor, agitation, irritability

- Toxicity
  - Extreme sedation, shallow breathing, clammy skin
  - Respiratory depression, hypotension, shock
  - Coma, possible death
Drug Interactions

Alcohol
- increases impairment of physical abilities
- increased sedation, extreme weakness, dizziness, agitation, euphoria & confusion
- inhibits metabolism of meprobamate

Drugs
- opiates, benzodiazepines, barbiturates and other muscle relaxants likely to contribute to impairment

Effects

Tolerance & Dependence
- cross-tolerance with barbiturates
- development of abuse with chronic use
- moderate physical & psychological dependence develops
- abrupt discontinuation of long-term use can lead to mild withdrawal symptoms

Withdrawal
- anxiety, confusion, insomnia, ataxia, muscle twitching
- abdominal cramps, headache, nausea, vomiting
- occasional chills, convulsions, hallucinations

Soma® - Driving Studies

Waterloo et al. 1997
- 10 males (19-23 y.o.) 1 x 700 mg
- Tested several times within 3 h post dose
- Psychomotor/cognitive tests
  - No significant effect observed on any test

Compared to meprobamate......
- single doses capable of causing significant performance impairment
  - (e.g. divided attention, vigilance, reaction time)

Note: Impairment most likely a product of both parent & metabolite

Soma® - Epidemiology

Logan et al. 2000

- 104 Soma® cases in total (16 months)

- 83 poly-drug case
  - benzodiazepines N = 45
  - narcotic analgesics N = 43
  - cannabinoids N = 13
  - barbiturates N = 12
  - ethanol N = 9 (mean BAC 0.05 g/dL)
Soma® - Epidemiology

21 of the 104 cases were Soma® only

- Carisop. blood = 4.6 mg/L (0 - 15)
- Meprob. blood = 14.5 mg/L (1.0 - 36)

Combined blood = 19 mg/L (1 - 42)

- Soma® contributes to driving impairment, particularly if combined drug conc. > 10 mg/L

Logan et al 2000

Soma® - Epidemiology

Driving behavior
Extreme lane travel, weaving, striking other vehicles and fixed objects, slow speed, hit and run accidents, driving in the wrong direction on freeway

Psychophysical symptoms
Poor balance and coordination, gaze nystagmus, unsteadiness, blurred speech, slow responses to questions, slow movements, difficulty standing & walking, difficulty exiting their vehicles, and disorientation

Logan et al 2000

Soma® only DRE cases (N=7)

Gender: 4 female, 3 male
Age: median 42 y (31 - 49 y)

Blood Concentrations

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>med</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>carisoprodol</td>
<td>6.2 mg/L</td>
<td>5.6 mg/L</td>
<td>(0 - 9.4)</td>
</tr>
<tr>
<td>meprobamate</td>
<td>17 mg/L</td>
<td>20 mg/L</td>
<td>(2.2 - 25)</td>
</tr>
<tr>
<td>combined</td>
<td>21 mg/L</td>
<td>24 mg/L</td>
<td>(2.2 - 35)</td>
</tr>
</tbody>
</table>

Data: Seattle, WA

Soma® only DRE cases (N=7)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>‘Normal’</th>
<th>DRE</th>
<th>SOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGN</td>
<td>No</td>
<td>Yes</td>
<td>Yes ✓</td>
</tr>
<tr>
<td>VGN</td>
<td>No</td>
<td>Yes/No</td>
<td>No ✓</td>
</tr>
<tr>
<td>Lack of converg.</td>
<td>No</td>
<td>Yes</td>
<td>Yes ✓</td>
</tr>
<tr>
<td>Pupil size</td>
<td>Normal</td>
<td>Norm-Dilated</td>
<td>Dilated ✓</td>
</tr>
<tr>
<td>React. to light</td>
<td>Normal</td>
<td>Slow</td>
<td>Slow ✓</td>
</tr>
<tr>
<td>SFST’s</td>
<td>Normal</td>
<td>Poor</td>
<td>Poor ✓</td>
</tr>
</tbody>
</table>
**Soma® only DRE cases (N=7)**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>‘Normal’</th>
<th>DRE</th>
<th>SOMA cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>60 - 90</td>
<td>Down</td>
<td>89 (58-126) x</td>
</tr>
<tr>
<td>B.P.</td>
<td>sys 120-140/ dias 70-90</td>
<td>Down</td>
<td>124 (100-150) x 82 (70-90) x</td>
</tr>
<tr>
<td>Body Temp</td>
<td>98.6 ±1° F</td>
<td>Normal</td>
<td>97.9 (97.1-99.2) ✓</td>
</tr>
</tbody>
</table>

**SOMA**
- 58 y.o. male
- Driving 10 mph on a major urban freeway ~ 10 am
- Very poor lane travel
- Subject took several minutes to stop (continued to weave, ignored flashing lights, siren)
- Subject took ~6 min to retrieve his wallet from pocket
- Thick, slurred and incoherent speech
- Could not stand or walk unassisted
- Carisoprodol 9.5 mg/L Meprobamate 32.9 mg/L

**Soma + Diazepam**
- Crosses center line 3 times; 10 mph in 35 mph zone
- Nearly struck southbound vehicle after officer activated emergency equipment
- Vehicle made U-turn before coming to a stop
- Small child in car
- Appeared confused, slurred speech, unsteady on feet
- Could not perform finger dexterity test
- Stumbled, almost fell to ground, no other tests performed
- Meprobamate 43 mg/L, Carisoprodol 6 mg/L
- Diazepam 0.3 mg/L, Nordiazepam 0.6 mg/L

**Soma® - Summary**
- Key parameters:
  - Erratic driving, collisions
  - Poor balance & coordination, slow/slurred speech
  - Poor performance on SFST’s
  - HGN, lack of convergence, slow reaction to light
- Blood concentrations observed in DUI’s often represent high doses or chronic administration
- Frequently found in combination with other drugs
- Soma® is a significant CNS depressant which can impair driving
Diphenhydramine

e.g. Benadryl®, Dramamine®
Dytuss®, Unisom SoftGels®
& Tylenol® preps

Diphenhydramine (DPH)

- Antihistamine (first generation)
- Indicated for temporary relief of allergy symptoms
- Antiemetic, sedative/sleep aid, motion sickness, antitussive
- Tablets, capsules and liquid form
- Adult dose – antihistamine:
  25-50 mg, every 6-8 hr (max. 50-100 mg, every 4-6 hr)
- Adult dose – sleep aid:
  50 mg at bedtime
- Often in combination with pseudoephedrine, acetaminophen

DPH - Pharmacology

- $H_1$ receptor antagonist
- Blocks effects of histamine
  - Inhibits smooth muscle effects
  - Inhibits vasoconstrictor effects
- Peak plasma concentration: 2-3 hr
- Duration of effects: 4-6 hr
- Plasma $t_{\frac{1}{2}}$: 8.5 hr ($\pm$ 3 hr)
- Some tolerance to sedative effects with repeated daily dosing

DPH – Side Effects

- Diminished alertness
- Confusion, dizziness, fatigue
- Significant sedation / drowsiness
- Disturbed coordination, slowed reaction time
- Impaired cognitive and psychomotor performance
- Blurred vision, altered mood, depression
- Agitation, restlessness, nervousness
- Inability to sleep
- Anticholinergic effects (e.g. dry mouth)
DPH – Drug Interactions

Effects of diphenhydramine are increased by:
- alcohol, diazepam, hypnotics, sedatives
- tranquilizers, other CNS depressants

e.g. Alcohol
- enhances drowsiness and sedation
- decreases motor skills (esp. in elderly)
Increasing incidence in combination with opiates (drug:drug interaction effect?)

DPH - blood concentrations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 50 mg</td>
<td>0.08 mg/L</td>
<td>3 hr</td>
</tr>
<tr>
<td>1 x 100 mg</td>
<td>0.11 mg/L</td>
<td>2 hr</td>
</tr>
</tbody>
</table>

- 0.03-0.04 mg/L drowsiness observed
- > 0.06 mg/L mental impairment observed

DPH & Human Performance

- Iowa Driving Simulator  Weiler et al, 2000
- 40 subjects, aged 25-44 yr
- Diphenhydramine 50 mg, alcohol 0.10%, placebo
- Single dose, double blind, crossover study
- DPH signif less coherence and impaired lane travel
- DPH had greater impact on driving than alcohol (0.10%)
- Self-reported drowsiness was not a good predictor of impairment

Verster & Volkerts, 2004

- Review of 16 studies
- 1st, 2nd and 3rd generation antihistamines
- On-the-road driving tests
- Double blind, placebo controlled, positive controls
- DPH signif impaired driving performance after both one-time and repeated (daily) administration
- Decreased alertness, reaction time and learning ability
- Impaired concentration, time estimation, tracking, attention and memory
  *Ann Allergy Asthma Immunol 2004;92(3):294-303*
Zolpidem (Ambien®)
Zaleplon, Zopiclone (Sonata®, Imovane®)
- Significant sedative & hypnotic properties
- Indicated for short-term treatment of insomnia
- Shortens sleep latency & prolongs sleep time in insomniacs
- Zolpidem Dose 10 mg immediately before bedtime (elderly 5 mg)
- Often concurrent meds (antidepressants, narcotic analgesics, muscle relaxants)

Pharmacology
- Non-benzodiazepine agonists of GABA$_A$ receptor with different affinity than benzodiazepines

Zolpidem
- Rapid absorption Cmax 1.5-2.5 hr
- Short half-life t½ ~ 2.4 hr

Zaleplon
Shorter t½: 0.9-1.2 hr

Zopiclone
Longer t½: 3.5-6.5 hr

Pharmacodynamics
- All 3 exhibit less rebound insomnia than benzodiazepines
  - More natural sleep patterns
- Antegrade amnesia (less so than benzodiazepines)
- Less tolerance to the effects of these drugs as compared to benzodiazepines
- Only Zaleplon should be used for night-time waking

Zolpidem Effects
- Sleep induction with altered consciousness (somnolence to light coma)
- Memory impairment, confusion, concentration difficulties
- Nausea, ataxia, slow & slurred speech
- Slow reflexes, coordination difficulties
- Sleep walking
  - Duration of effects 4-5 hr (10-20 mg)
  - Sedation may last 8-16 hr following intoxication
Sleep walking has been a noted side effect
- Sleep driving
- Sleep Eating
- Abuse of Zolpidem
  - Take the drug and forced staying awake
  - Visual disturbances
  - Erowid advises against mixing with alcohol
  - Some proponents suggest use with cannabis

Zolpidem: Side - Effects & Abuse Potential

Zolpidem - blood concentrations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax</th>
<th>Range</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 5 mg</td>
<td>0.06 mg/L</td>
<td>(0.03 – 0.11)</td>
<td>1.6 hr</td>
</tr>
<tr>
<td>1 x 10 mg</td>
<td>0.12 mg/L</td>
<td>(0.06 – 0.27)</td>
<td>1.6 hr</td>
</tr>
<tr>
<td>1 x 10 mg</td>
<td>0.13 mg/L</td>
<td>1.7 hr</td>
<td></td>
</tr>
<tr>
<td>1 x 15 mg</td>
<td>0.20 mg/L</td>
<td>1.5 hr</td>
<td></td>
</tr>
<tr>
<td>1 x 20 mg</td>
<td>0.23 mg/L</td>
<td>2.1 hr</td>
<td></td>
</tr>
<tr>
<td>1 x 20 mg</td>
<td>-</td>
<td>(0.19 – 0.32)</td>
<td>2.6 hr</td>
</tr>
</tbody>
</table>

Zolpidem - Human Performance & Driving Summary of Vermeeren studies

- Zolpidem
  - Significant effects when driving within 6 hr of use (10 mg dose)
  - No significant risk of severe impairment at 8 hr (10 mg dose)

- Zaleplon
  - Significant impairment within 1 - 3 hr of use (10 mg dose)
  - No significant impairment after 5 hr (20 mg dose)

- Zopiclone
  - Severe impairment 1-5 hr (7.5 mg dose)
  - Residual / hangover effects up to 10-11 hr (7.5 mg dose)

Other studies

- Patat et al, 2001
  - Zaleplon 10 mg produced little or no impairment of psychomotor or memory skills, or driving, when given as little as 1 hr prior to testing
  - Zaleplon 20 mg produced significant impairment 1 hr post dose but no impairment of driving ability at 4 hr

- Zolpidem 10 mg impairs up to 5 hr
- Zopiclone 7.5 mg impairs up to 10 hr
Zolpidem DUI cases
- 29 DUI cases positive for zolpidem
- Concentrations:
  - mean: 0.29 mg/L
  - median: 0.19 mg/L
  - range: 0.05 - 1.4 mg/L
- 24 cases positive for other drugs
- (antidepressants, alcohol, narcotic analgesics, muscle relaxants)
- 5 cases zolpidem only

Logan & Couper 2001, JFS

Zolpidem only cases (N=5)
- Concentrations:
  - mean: 0.65 mg/L
  - median: 0.47 mg/L
  - range: 0.08 - 1.4 mg/L
- Driving circumstances
  - Slow & slurred speech, slow reflexes
  - Disorientation, confusion, loss of balance & coordination
  - Loss of short-term memory, blacking out, somnolence

Logan & Couper 2001, JFS

Zolpidem
- 17 y.o male
- Stopped for weaving / lane travel
- Dilated pupils, double vision
- Lack of balance & coordination
- Poor performance on SFST's
- Admitted taking “2 white pills” 30 min before stop
- Blood zolpidem conc. = 0.08 mg/L

Zolpidem
- 59 y.o. male
- Causing driver of a 2-car collision
- Unable to stand or walk unassisted
- Dazed, lethargic, disoriented
- Poor attention
- Admitted taking “2 Ambien®” 30 min before collision
- Blood zolpidem conc. = 0.43 mg/L
<table>
<thead>
<tr>
<th>Wisconsin: Repeat Customer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Driving</strong></td>
</tr>
<tr>
<td>- Witness: Incorrect stop position at 1st stop light</td>
</tr>
<tr>
<td>- Didn’t proceed when light turned green</td>
</tr>
<tr>
<td>- Weaving</td>
</tr>
<tr>
<td>- Crashed into truck stopped at next red light</td>
</tr>
<tr>
<td>- Driver said brakes needed fixing.</td>
</tr>
<tr>
<td>- Officer tested brakes, found no problems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wisconsin: Repeat Customer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior/Physical Abilities</strong></td>
</tr>
<tr>
<td>- Confused</td>
</tr>
<tr>
<td>- Disoriented</td>
</tr>
<tr>
<td>- Eyes barely open – drowsy</td>
</tr>
<tr>
<td>- Extremely slow slurred speech</td>
</tr>
<tr>
<td>- Poor balance</td>
</tr>
<tr>
<td>- Drugs Detected:</td>
</tr>
<tr>
<td>- Zolpidem – 1,000 ng/mL</td>
</tr>
<tr>
<td>- Sertraline/Norsertraline - Present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wisconsin: Repeat Customer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Further Investigation (Per Daughter)</strong></td>
</tr>
<tr>
<td>- Prescribed Ambien in 1997</td>
</tr>
<tr>
<td>- Subject increased doses after 6 years</td>
</tr>
<tr>
<td>- Subject no longer has prescription</td>
</tr>
<tr>
<td>- Obtains zolpidem on-line</td>
</tr>
<tr>
<td>- Medbizsupply.com</td>
</tr>
<tr>
<td>- Previous arrest 1.5 months before in neighboring jurisdiction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wisconsin: Repeat Customer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Driving</strong></td>
</tr>
<tr>
<td>- Driving to mall</td>
</tr>
<tr>
<td>- Attempted to turn around - struck several mailboxes</td>
</tr>
<tr>
<td>- Drove on rim after getting flat tire Citizen Police</td>
</tr>
<tr>
<td><strong>Behavior/Physical Abilities</strong></td>
</tr>
<tr>
<td>- Very confused</td>
</tr>
<tr>
<td>- Speech extremely slurred</td>
</tr>
<tr>
<td>- Could not maintain eye contact w/officer</td>
</tr>
<tr>
<td>- Poor balance while standing</td>
</tr>
<tr>
<td><strong>Drugs Detected:</strong></td>
</tr>
<tr>
<td>- Zolpidem – 4,400 ng/mL</td>
</tr>
</tbody>
</table>
**SFST - HGN**

<table>
<thead>
<tr>
<th>HGN Clues</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5a</th>
<th>5b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack smooth pursuit</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>HGN at max. dev.</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Onset prior to 45º</td>
<td>No</td>
<td>No</td>
<td></td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Instructed many times</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Didn’t Finish/Perform</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Pupil description</td>
<td>Dilated</td>
<td>Dilated</td>
<td>Dilated</td>
<td>Dilated</td>
<td>Normal</td>
<td>-</td>
</tr>
</tbody>
</table>

**SFST – Walk and Turn**

<table>
<thead>
<tr>
<th>WAT Issues</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5a</th>
<th>5b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didn’t hold instruct. pos.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Balance Probs/BODY sway</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Did not Count Out Loud</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Did not walk heel to toe</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stepped off the line</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Did not take 9 steps</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Incorrect or no turn</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was reminded to continue</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Unable to Complete/Perform</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
</tr>
</tbody>
</table>

**SFST – One Leg Stand**

<table>
<thead>
<tr>
<th>OLS Issues</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5a</th>
<th>5b</th>
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<td>Body Sway noted</td>
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<td>-</td>
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<td>Almost Fell Over</td>
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<td>-</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Many attempts</td>
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<td>-</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Unable to Complete/Perform</td>
<td>Yes</td>
<td>Didn’t Try</td>
<td>Yes</td>
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</table>

**2005 – WA State DUI cases**

23 DUI cases with zolpidem as the only identified impairing substance

Blood concentration
- mean = 0.23 mg/L
- median = 0.11 mg/L
- range = 0.05 – 1.31 mg/L

57% female; avg. 46 yrs (med 47) range: 16 - 62
Zolpidem Cases: A Common Theme

- Extreme driving impairment
- Wide lane deviations & many near collisions
- Bizarre driving maneuvers
- Mode of driver detection – citizen cell phone
- Profound loss of balance
- Incomplete SFST’s – stopped for safety
- Confused & Disoriented
- No recognition of poor driving
- Greatly reduced comprehension
  - Unusual, exaggerated delays in responses
  - Unable to follow directions
  - Do not remember recent events

Zolpidem - summary

- Zolpidem is an effective sleep inducer
- Frequently taken with other CNS drugs
- At clinically effective doses, zolpidem is capable of impairing driving within 5-6 hr of use
- No residual (next-day) impairing effects
- Therapeutic Dose for Driving? 0 mg/L

CNS Depressants

Benzodiazepines

- Most common classes of drugs prescribed
- Anxiolytic, sedative, amnestic, hypnotic, anticonvulsant and relaxant properties
- More than 50 worldwide
  - Short (Triazolam, Alprazolam, Midazolam)
  - Intermediate (Clonazepam, Lorazepam)
  - Long acting (Diazepam, chlordiazepoxide)
Pharmacology

- GABA_A Agonists with different affinities for different subtypes
  - Vary from complete agonists to partial agonists
- Used to treat anxiety disorders, sleep disorders, as an anesthetic adjunct, alcohol withdrawal and seizure disorders
- Side effects:
  - Sedation, lethargy, mental confusion, motor and cognitive impairment, disorientation, slurred speech, amnesia and induction or extension of dementia
- Synergistic effects when combined with alcohol

Tolerance

- Tolerance develops with regular use
- Important to know history and pattern of use
  - How long has subject used drug?
  - Has there been a recent dose increase?
  - How does subject use drug?
- Some cross tolerance with each other and alcohol
- Tolerance may take weeks to months to develop

Interpretation of Results

- Numbers mean very little
  - Use therapeutic ranges with caution
- For some benzos, parent:metabolite ratios can assist in interpretation of results
  - Diazepam:Nordiazepam (post-accident administration?)
  - Chlordiazepoxide:nordiazepam
- Look at “totality” of circumstances
  - Driving pattern/circ. of accident
  - FST performance
  - Observations (officers, medical personnel, others)
  - Tox Report History, if known

Side Effects (Symptoms of Impairment)

- Typical CNS depressant
- Sedation – lethargy
- Confusion
- Slow slurred speech
- HGN (VGN)
- Amnesia
Driving

- Lateral travel
- Increased crash incidence
- Polypharmacy is common

Lorazepam & Driving

- 23 Lorazepam only DRE/DUI cases
  - 13/23 involved in a crash
  - 20/23 traffic infractions (lane travel, speeding, failure to stop at traffic stop)
  - 1/23 Unknown
  - Concentration = mean 0.05 mg/L (<0.01 – 0.38)
- DRE cases (n=10):
  - All exhibited slow, thick and/or slurred speech
  - Poor coordination 9/10
  - Poor performance on Romberg, modified finger to nose, WAT & OLS
  - HGN (10/10), VGN (5/10)

Lorazepam Case Study

- 17 yo male
- Stopped for speed & lane travel
- Driving on rims (evidence of recent accident
- Upon contact, subject confused & unaware and mumbling
- Droopy eyes, swaying and stumbling, unable to stand still
- 6/6 HGN, VGN
- Admitted to fluoxetine
- Toxicology - 0.03 mg/L lorazepam

CNS Depressants

Antiepileptic Drugs
Not Just for Seizure Control

- Chronic Pain
- Bi-polar Disorders
- Other Psychiatric Disorders

Newer Anti-epileptics - VPA

- Valproic Acid - 1978 (ten more since 1990)
- ½ life – 6 – 12 hours
- Used widely with children
- Augments the post-synaptic action of GABA
- Useful for bi-polar disorder (GABAergic function), pathologic aggression and schizophrenia
- SE profile: nausea, sedation, weakness
- Stupor results in some patients when added to other AED regimens

Newer Anti-epileptics - Gabapentin

- Gabapentin - Structural analog of GABA
- Promotes release of GABA from presynaptic nerve terminals
- Typically used as an adjunct treatment with other AEDs
- 1995 – reported to be effective in treating phobias and pain and has seen wide use for bi-polar disorder, dementia induced aggression, and treatment of chronic pain
- Increasingly being used as an alternative to lithium for bi-polar disorder
- SE profile: ataxia, fatigue and nystagmus
- High therapeutic index

Newer Anti-epileptics - Lamotrigine

- Introduced in 1995
- ½ life 12-62 hours
- Inhibits presynaptic release of neurotransmitters, particularly glutamate
- Used mostly as adjunct therapy, shown to improve mood and social interactions of epileptics
- Increasingly used as an antidepressant and antimaniac and for bi-polar disorders
- SE profile: headache, dizziness, somnolence, ataxia, blurred vision, nausea
Newer Anti-epileptics – Levitiracetam

- ~ 2000 (US)
- Adjunct therapy more recently being used as monotherapy
- SE profile: Psychiatric symptoms (depression, irritability, hallucinations, psychosis)
- No pharmacokinetic interactions with older AEDs
- SE: Behavioral effects, agitation, hostility, anxiety, apathy, emotional lability, depersonalization and depression and rarely suicidal ideation
- Metabolism - Renal excretion and hydrolysis

Antiepileptic Drugs – Topiramate

- Many uses in addition to seizure disorders
- Chronic pain
- Psychiatric disorders

- Multiple mechanisms of action
  - Potentiates GABA inhibitory transmission
  - Blocks excitatory neurotransmission by non-NMDA receptors
  - Modulates voltage gated Ca+ channels to inhibit brain carbonic anhydrase

Off-Label Uses

- Tx of Alcohol and Drug Dependency
- Migraine, cluster and childhood headaches
- Psychiatric Disorders
  - Schizophrenia, Bi-polar disorder, kleptomania
- Eating Disorders
  - Bulimia, binge eating, obesity, anorexia nervosa
- Adjunct to tx weight gain with anti-psychotic drugs
- Neuropathic pain
- Tx for refractive scars and psoriasis

Washington State Toxicology Laboratory

- First case 1998
**WSTL Cases**
- 132 Cases
  - 63 Death Investigation Cases
  - 68 Impaired Driving Cases
  - 1 Sexual Assault
- 69% female
- Mean age – 42 (median 41.5)
- Topiramate Drug Concentration
  - Mean: 8.4 mg/L (Range 1-180 mg/L)
  - Median: 6.4 mg/L
  - SD: 6.4

**Reported Topiramate Concentrations**
- Patients stabilized on 800 mg/day
  - Plasma concentration – 5.5 mg/L
- Blood:Plasma ratios
  - Inversely proportional
    - 7.1 at 3 mg/L
    - 1.3 at 15 mg/L

**Topiramate Concentrations**
- Mean 10.5 ± 18.3 mg/L
  - Median 6.2
- Mean 7.8 ± 5.5 mg/L
  - Median 6.5

**WA: Topiramate Positive Drivers**
- Higher incidence of females (78%)
- Mean topiramate concentration 7.0 mg/L (median 5.9 mg/L; range 1-20.4 mg/L)
- 7.4% topiramate alone
- 16% also had illicit drugs present
Topiramate & Impairment

- All AEDs have cognitive impairment
- Degree of impairment varies
- There is evidence that it is not subject to tolerance
- Potentiation occurs with polypharmacy treatment, particularly with other AEDs
- Cognitive impairment examined - quality of life issue for epilepsy patients

Impairment Studies – Epilepsy Patients

- Bootsma & Aldenkamp et al:
  - Retention rate (measure of drug efficacy & safety)
    - 1 yr = 53%
    - 2 yr = 45%
    - 3 yr = 38%
    - 4 yr = 30%
- 65% discontinuations were due to adverse effects
  - Mental slowing (28%)
  - Dysphasia (16%)
  - Mood problems (12%)

Study – Healthy Volunteers

- Martin et al:
  - 6 subjects
  - 200 mg/day titrated to 400 mg/day
  - Low dose:
    - Impaired: Verbal function, Sustained attention
  - High dose:
    - Impaired: Verbal memory, Mental Speed

Case Study #1:

- 31 y.o. female
- Car into center median of a State Highway
- Observations:
  - Slow, thick, slurred speech
  - Heavy eyelids, dilated pupils, 4/6 clues HGN
  - No other FSTs performed, (back and neck injury)
- Toxicology:
  - Topiramate = 8.5 mg/L
  - Lorazepam = 0.01 mg/L


Gordon, Logan 2006
Case Study #2:
- 50 y.o. male, bus driver
- Hx: seizure disorder & corrective surgery
- Struck & killed colleague in bus yard
- DRE examination – 2/6 HGN
- Poor FSTs, balance and coordination difficulty
- Difficulty following instructions
- Speech – slow with delayed responses
- Rx drugs: topiramate, lamotrigene

Findings:
- Topiramate 3.71 mg/L
- Lamotrigene 6.61 mg/L
- Despite his complaints to his physician regarding his problems with topiramate, MD wrote a letter to re-instate driving responsibilities

Subject – weaning from topiramate
- Slowed his thought processing & delayed response times
- Made it difficult to multi-task
- Made him walk slow
- Expressed that meds made it difficult to follow instructions and perform FSTs
- Put his jacket on “upside down”

Case Study #3:
- 50 y.o. female
- Non-injury no-damage collision
- Left the scene, severe lane drift, repeatedly hitting curb, nearly hit children on sidewalk
- Called in as “DUI”
Case Study #3

- HGN – 6/6
- Balance so poor – could not perform SFSTs
- Officers did note that her clothes were on ‘inside out’
- Findings: Topiramate – 14.2 mg/L

Conclusions

- Clear evidence for topiramate induced cognitive impairment
- AEDs are often used in conjunction with other potentially impairing drugs
- From the epilepsy patient studies, impairment may be potentiated when used in combination with other AEDs
- Expanded use of topiramate for non-epilepsy patients may present new challenges for human performance toxicologists

CNS Depressants

Commonly seen in DUI cases with Anti-depressants
- General effects are sedation, disorientation, lack of balance & coordination & concentration, inebriation
- Similar effects to those seen with alcohol intoxication

Empirical data, laboratory studies and actual driving cases all indicate that:
- CNS depressants are capable of impairing human performance and behavior
- No simple relationship between blood concentration and specific degree of impairment

Overall Summary

CNS Depressants