Motor vehicle crashes and psychotropics (and other medications) in older adults

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Disclosures

- Grant funding
  - Canadian Institute for Health Research
  - Canadian Consortium on Neurodegeneration and Aging
- No personal financial disclosures
Learning Outcomes

- To understand the application of observational study designs to research pertaining to risks of motor vehicle collisions associated with psychotropics and other drugs in later life.

- To discuss approaches to translating this knowledge into practice.
Assessing the literature

- Neuropsychiatric Illness
- Antidepressants
- Age
- Benzodiazepines
- Sex/Gender
Research reasons for heterogeneous response
Benzodiazepines and Z-Drugs
Benzodiazepines

- **Pharmacology**
  - known as “sedative hypnotics”!
  - Agonists of GABA-A receptor complex
  - sedative, anxiolytic, anticonvulsant and relaxant effects
  - Disinhibition, Impulsivity
Cognitive Effects of Benzodiazepine

- **Acute Use**: Sedation, Slowing, Drowsiness, Anterograde Amnesia.

- **Sedation vs Amnesia??**

- **Chronic Use** Barker et al (04).
  - Meta-Analysis - 13 studies.
  - Mean N = 33.5 (SD28.9), Mean 9.9 yrs (range 1-34).
  - Moderate-to-large effect sizes for all cognitive domains (Mean –0.74, SD 0.25).
  - (NB, Heterogeneous Dx!)
Cognitive Effects: Reversible?

- Barker et al (04).
  - Second meta-analysis
  - Yes, but:
  - Not to level of non-benzo controls.
Some Sleeping Pill Users Range Far Beyond Bed

By STEPHANIE SAUL

Published: March 8, 2006

With a tendency to stare zombie-like and run into stationary objects, a new species of impaired motorist is hitting the roads: the Ambien driver.
Crashes – Clinical Scenario. 
Mr. B.

- 80s man
- Volunteer, active lifestyle.
- 60 years of driving experience
- Mild Hearing Impairment, Decreased vision left eye.
- Past history of Panic Attacks (remotely on Fluoxetine).
- PMHx COPD, AAA, MI 5 yrs earlier, HTN, DM, HH, Hypercholesterolemia.
- Mar 15/05: ER visit – for COPD.
- Mar 17/05: ER visit – feeling unwell.
  - Mar 17/05: Fam Doc Visit: Clonazepam Prescription.
- Mar 17/05: Pharmacy – picked up Clonazepam prescription.
- No recollection until police came to his home later that evening.
Mr. B.

Mar 17: Police report: 5pm:

- Driving recklessly
- Speeding on shoulder of HWY 401
- Hit two cars.
- Left scene.
- Drove home.
Benzodiazepines

- **36 Simulator Studies with Placebo Control**
  - No Experimental studies of driving in older adults (highest age of 65)!!
  - Mostly double-blind cross-over studies in healthy populations.
  - Many studies showing increased collisions, speed variability, delayed brake reaction time, and reduced tracking control
  - Even with some studies of Zopiclone & Zoldipem.
  - Many studies showing potentiation of BZD effect w ETOH.
  - **BUT variability**
    - Specific Benzodiazepine, Dose, Age, Time of testing
    - Meta-analysis pending.

Rapoport et al, CNS Drugs, 2005
Benzodiazepine On-Road Studies
Standard Deviation of Lateral Position

Verster, 05
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Design</th>
<th>Time</th>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 HV,m</td>
<td>C, Pc</td>
<td>1h, e</td>
<td>diazepam 5 mg, diazepam 10 mg</td>
<td>NS</td>
<td>------</td>
</tr>
<tr>
<td>16 HV,b</td>
<td>C, Pc</td>
<td>1-2h,e</td>
<td>diazepam 5 mg, tid, oxazepam 1 mg, tid</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>18 HV,b</td>
<td>C, Pc</td>
<td>2-3h,a</td>
<td>suriclone 0.2 mg, tid, ondansetron 1 mg, gid</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>19 AO,b</td>
<td>B, Pg</td>
<td>3-4h,m</td>
<td>alpidem 50 mg, tid</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>18 AO,b</td>
<td>B, Pg</td>
<td>3-4h,m</td>
<td>lorazepam 2 mg, tid</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>12 AO,b</td>
<td>B, Pb</td>
<td>1-2h,e</td>
<td>diazepam 5 mg, tid, oxazepam 5 mg, tid</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>18 HV,m</td>
<td>C, Pc</td>
<td>3h,a</td>
<td>lorazepam 1.5 mg, tid, ritanserin 5 mg, tid</td>
<td>-----</td>
<td>*</td>
</tr>
<tr>
<td>20 HV,b</td>
<td>C, Pc</td>
<td>1h</td>
<td>alprazolam 1 mg</td>
<td>*</td>
<td>-----</td>
</tr>
<tr>
<td>18 HV,m</td>
<td>C, Pc</td>
<td>10h²</td>
<td>oxazepam 50 mg</td>
<td>*</td>
<td>-----</td>
</tr>
<tr>
<td>17 HV,w</td>
<td>C, Pc</td>
<td>10h²</td>
<td>zolpidem 10 mg</td>
<td>NS</td>
<td>-----</td>
</tr>
<tr>
<td>30 HV,b</td>
<td>C, Pc</td>
<td>4h⁶</td>
<td>zolpidem 10 mg, zolpidem 20 mg</td>
<td>*</td>
<td>-----</td>
</tr>
</tbody>
</table>
Meta-Analysis

**Background:**

- 1.2 million people world-wide are killed in MVCs annually.
- Five benzodiazepines were listed among the top 50 drugs prescribed in the US in 2005.
- Benzodiazepines are prescribed for > 1/5 older adults in Ontario, Canada.

**Purpose:** To examine the role of benzodiazepines in motor vehicle collisions (MVCs).

**Two complementary study approaches:**

- Epidemiological studies
- Experimental studies

Methods

Search strategy

- Medline, PsychINFO, Cochrane, Embase
- key terms: “benzodiazepines or exp benzodiazepines and automobile driving; Accidents, traffic”; “Driving; Or driver$”
- from 1996 - Aug 1, 2005, w/ Auto-Updates to Nov 30, 2007

Inclusion criteria

- English-language studies
- real-world collisions in case-control or cohort studies
- studies using driving simulators or on-road tests

Exclusion criteria

- did not examine benzodiazepines
- combination with other drugs
- no control group
- newer non-benzo, sedative-hypnotics
- no driving simulator or road test
- unique driving outcome measure
404 studies obtained

376 studies excluded
- Did not match search criteria (98)
- No benzodiazepine-only group (43)
- Reviews or editorials (62)
- No control group (75)
- Non-driving psychomotor tests (57)
- Duplicate publication or population (5)
- Unique outcomes or measures (36)

28 studies included
- 11 epidemiological studies
- 6 case-control studies
- 3 cohort studies
- 2 case-control culpability studies
- 17 experimental studies
- 9 computer-simulated driving tests
- 8 on road driving tests

Among the experimental driving studies, only 10 of 97 outcome variables were comparable.
<table>
<thead>
<tr>
<th>Study design/Cases</th>
<th>Outcome variable</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 DB X-over/9 healthy</td>
<td>Tracking errors and severity</td>
<td>Diazepam 10mg hs; Testing 1.5 and 3 hrs post-dose</td>
</tr>
<tr>
<td>11 DB X-over/12 healthy</td>
<td>Tracking errors and severity</td>
<td>Diazepam 15mg; Testing 1 and 3.5 hrs post-dose</td>
</tr>
<tr>
<td>12 DB parallel/54 healthy, 6 per group</td>
<td>BRT (brake reaction time) Abs speed deviation</td>
<td>Diazepam 5, 10, 20mg; Chlorazepate 10, 20, 40mg</td>
</tr>
<tr>
<td>13 DB Parallel/60 healthy male</td>
<td>BRT</td>
<td>Diazepam avg 7 or 14mg (1 dose) Testing shortly post-dose</td>
</tr>
<tr>
<td>14 DB X-over/18 healthy</td>
<td>BRT</td>
<td>Lormetazepam 1mg, Oxazepam 50mg 2 consec nights, testing 7 &amp; 16hrs post-dose</td>
</tr>
<tr>
<td>15 DB parallel/70 drivers</td>
<td># of collisions</td>
<td>Diazepam 25mg; Testing 30mins post-dose</td>
</tr>
<tr>
<td>16 DB X-over/19 women with insomnia</td>
<td>Deviation from instructed speed</td>
<td>Temazepam 20mg/Placebo (1 dose) Testing 5.5 hrs post-dose</td>
</tr>
<tr>
<td>17 DB X-over/23 patients with insomnia</td>
<td>Speed deviation, # of collisions</td>
<td>Lormetazepam 1mg/plcb; 1 &amp; rpt’d doses Testing 9-11 hrs post-dose</td>
</tr>
<tr>
<td>18 DB X-over/12 anxious male patients</td>
<td>BRT</td>
<td>Chlorazepate 20mg hs x7d Testing on days 3, 10, 17; 8 hrs post-dose</td>
</tr>
</tbody>
</table>
Simulator Studies: Tracking Error Severity Index for Diazepam

Other Variables:
- BRT (4 studies) – homogeneous stratified for dose – no differences.
- Deviation Instructed Speed (2 studies) – homogeneous – no differences.
- # of Collisions (2 studies), Absolute Speed deviation (2 studies) - heterogeneous
<table>
<thead>
<tr>
<th>Study design/Cases</th>
<th>Outcome variable</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 DB X-over/20 healthy</td>
<td>SDLP (Std Dvtn Ltr Pstn) Speed Deviation</td>
<td>Alprazolam 1mg; 1 dose Testing 1 hr post-dose</td>
</tr>
<tr>
<td>20 DB X-over/18 healthy</td>
<td>SDLP</td>
<td>Lormetazepam 1mg; Oxazepam 50mg 2 nights, testing 7 &amp; 16 hrs post-dose</td>
</tr>
<tr>
<td>21 DB X-over/16 healthy</td>
<td>SDLP</td>
<td>Diazepam 5mg TID x8d (Lorazepam 0.5mg TID separate n=19)</td>
</tr>
<tr>
<td>22 DB X-over/10 healthy F cntrl</td>
<td>BRT</td>
<td>Lormetazepam 1mg; Triazolam 0.25mg; Flunitrazepam 1mg; hs; 1 dose</td>
</tr>
<tr>
<td>23 DB X-over/8 healthy F cntrl</td>
<td>BRT</td>
<td>Midazolam 15mg, one dose Testing 10 hrs post-dose</td>
</tr>
<tr>
<td>24 DB X-over/14 anxious pts</td>
<td>BRT</td>
<td>Medazepam avg 16.5mg x3wks, Testing at various times post-dose</td>
</tr>
<tr>
<td>25 DB parallel /24 GAD pts</td>
<td>Speed Deviation</td>
<td>Diazepam 5mg TID x4wks (1wk plcbl lead-in)</td>
</tr>
<tr>
<td>26 DB X-over/24 F former hypnotic drug users</td>
<td>SDLP</td>
<td>Flurazepam 15mg and 30mg hs</td>
</tr>
</tbody>
</table>
### On Road Studies: Standard Deviation of Lateral Position

#### Study or sub-category

<table>
<thead>
<tr>
<th>N</th>
<th>Treatment Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>SMD (random) 95% CI</th>
<th>Weight %</th>
<th>SMD (random) 95% CI</th>
</tr>
</thead>
</table>
| **01 SDLP on road at dose equivalent <=5mg Diazepam tested in pin**
  - O’Hanlon ’84 (a) 24 | 21.20 (4.60) | 19.00 (4.00) | 0.15 (0.54) [-0.04, 1.12] | 0.54 | 0.54 [-0.04, 1.12] |
  - Volkerst ’92 (a) 18 | 17.76 (2.73) | 17.56 (2.82) | 0.15 (0.07) [-0.68, 0.72] | 0.07 | 0.07 [-0.68, 0.72] |
  - Subtotal (95% CI) 42 | | | 0.30 (0.33) [-0.13, 0.79] | 0.33 | 0.33 [-0.13, 0.79] |
  - Test for heterogeneity: Chi^2 = 1.12, df = 1 (P = 0.29), I^2 = 10.6%
  - Test for overall effect: Z = 1.42 (P = 0.16) |
| **02 SDLP at dose equivalent <=5mg Diazepam tested in am**
  - O’Hanlon ’84 (b) 24 | 22.50 (3.00) | 19.00 (4.50) | 0.15 (0.90) [0.30, 1.50] | 0.90 | 0.90 [0.30, 1.50] |
  - Volkerst ’92 am (b) 18 | 18.76 (2.53) | 17.10 (2.27) | 0.15 (0.58) [0.00, 1.35] | 0.58 | 0.58 [0.00, 1.35] |
  - Subtotal (95% CI) 42 | | | 0.30 (0.80) [0.35, 1.25] | 0.80 | 0.80 [0.35, 1.25] |
  - Test for heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 = 0%
  - Test for overall effect: Z = 3.82 (P = 0.0004) |
| **03 SDLP at doses >=10mg equiv**
  - O’Hanlon ’84 (c) 16 | 21.10 (2.20) | 19.00 (4.50) | 1.25 (1.07) [-0.13, 1.29] | 1.07 | 1.07 [-0.13, 1.29] |
  - O’Hanlon ’95 (c) 16 | 24.60 (1.60) | 22.00 (1.00) | 1.45 (2.08) [1.20, 2.96] | 2.08 | 2.08 [1.20, 2.96] |
  - Verster ’02 20 | 30.60 (1.60) | 21.20 (1.00) | 10.26 (6.91) [5.20, 8.62] | 6.91 | 6.91 [5.20, 8.62] |
  - Subtotal (95% CI) 52 | | | 39.29 (3.07) [3.80, 5.03] | 3.07 | 3.07 [3.80, 5.03] |
  - Test for heterogeneity: Chi^2 = 45.94, df = 2 (P < 0.00001), I^2 = 95.5%
  - Test for overall effect: Z = 2.17 (P = 0.03) |
| Total (95% CI) 136 | | | 100.00 (1.42) [0.53, 2.32] | 1.42 | 1.42 [0.53, 2.32] |
  - Test for heterogeneity: Chi^2 = 63.12, df = 6 (P < 0.00001), I^2 = 90.5%
  - Test for overall effect: Z = 3.11 (P = 0.002) |

#### Other On-Road Driving Variables:
- **3 studies of BRT** – homogeneous, no effect.
- **2 studies of mean speed, deviation from instructed speed**
  - heterogeneous
## Case Control Studies (n=6)

<table>
<thead>
<tr>
<th>Cases</th>
<th>- Controls</th>
<th>Drug ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Matched by</td>
<td></td>
</tr>
<tr>
<td>1 ER</td>
<td>- Randomly selected drivers at gas stations</td>
<td>Blood screen in ER</td>
</tr>
<tr>
<td></td>
<td>- Weekday, hour, location</td>
<td></td>
</tr>
<tr>
<td>2 ER</td>
<td>- ER non-trauma</td>
<td>Blood screen in ER</td>
</tr>
<tr>
<td></td>
<td>- sex and age +/- 1 year</td>
<td></td>
</tr>
<tr>
<td>3 Identified by database</td>
<td>- Random sample</td>
<td>Interview (79.8%)</td>
</tr>
<tr>
<td></td>
<td>- age and sex</td>
<td></td>
</tr>
<tr>
<td>4 Hospital admissions</td>
<td>- From same practice</td>
<td>Prescriptions* issued</td>
</tr>
<tr>
<td></td>
<td>- sex, year of birth</td>
<td>3/12 before injury or reference date</td>
</tr>
<tr>
<td>5 Collision database Nested case control</td>
<td>- Randomly selected</td>
<td>Prescription database, Current Use.</td>
</tr>
<tr>
<td></td>
<td>- None (adjusted for sex and age)</td>
<td></td>
</tr>
<tr>
<td>6 Older drivers who sought treatment within 7 days of MVC injuries</td>
<td>- Randomly selected</td>
<td>Pharmacy database, 6/12 before reference date</td>
</tr>
<tr>
<td></td>
<td>- age, sex and county</td>
<td></td>
</tr>
</tbody>
</table>

*R“minor tranquilizers” (“e.g. Benzodiazepines”)

Rapoport et al, 2009, J Clin Psych*
Case control Studies: Benzodiazepines and MVCs

- Subgroup of older adults: OR 1.36 (95% CI 1.13 - 1.63, p=0.001)

Rapoport et al, 2009, J Clin Psych
Some caveats

- Less effect with age (*Barbone*, 1998)
- Less effect with time (*Neutel*, 1995)
- Less effect with short half-life (*Hemmelgarn*, 1997)
- Greater effect BEFORE prescription (*Oster*, 1990)
What Would You Do?

- Benzodiazepines
  - Uses more than you initially intended.
  - Claims well able to drive.
  - Claims doesn’t drive right after or if they do, only to store, not on hwy or at night.
  - BUT Looks tired in appointment (or roadside).
Discussion

- **Experimental studies**
  - no consistent findings in studies using simulators
  - ability to maintain road position associated with benzodiazepines in on road tests
  - no delay or slowing of brake reaction time using simulators or on road tests
  - mechanism for impaired driving and MVCs remains unclear

- **Epidemiological studies**

  (case control and cohort studies):
  - 60% increased risk of MVC; NNH 26 (approx 4% of tx’d)
  - Not significantly higher for older adults
    - Other patient related factors??
    - Less risky driving patterns??
  - Caution – association
    - Role of other factors?? (eg. Sensation seeking)
Discussion

- Generalizability of Experimental Studies
  - Mostly healthy controls
  - only 10 of 97 outcome measures comparable
  - 4/10 yielded heterogeneity
  - Therefore 6/97.
  - TESI and SDLP – 1 ctr each.
- Mechanism of driving impairment unclear
- Variability in the design of the epidemiological studies

Future Directions:
- need to study patients vs. healthy controls
- Consistent designs
- Impact of intervention.

Clinical Implications:
- consider and inform patients about the impact of benzodiazepines on driving ability.
- Recommending short-term use only likely insufficient
  - risk may be highest within the first month of prescription
Z-Drugs

Non-Benzodiazepine Hypnotics

- Zopiclone (T1/2 = 5-6hr), 5 and 7.5mg available.
  - cyclopyrrolone derivative
  - Imovane
- Zaleplon (T1/2 = 1 hr), no longer available in Canada
  - pyrazolopyrimidine Derivative
  - Starnoc
- Zolpidem (T1/2 = 2 hr), 5 and 10mg available.
  - Ambien/Sublinox
US: FDA 2007

- Requested all hypnosedative manufacturers to modify product labelling to include new safety warnings, esp vis complex behaviors
  - Sleep driving
  - Sleep cooking
  - Sleep eating
  - Sleep conversations
  - Sleep sex

- Lit Review – most (15/17) cases zolpidem.

_Dolder et al, CNS Drugs, 2008, 22 (12), 1021-1036_
Zopiclone 7.5mg and SDLP in Patients Mean age 63
Bedtime Administration; Testing 10-11 hr later

Note: BAC 0.5mg/mL = +2.4cm

Leufkens, Psychopharmacology 2014; 231: 2785-2789
Zolpidem

**Case-crossover**
- Yang et al 2011 OR 1.74 (95% CI 1.25-2.43)
  - but only in males, age 46-64
- Orriols et al 2011 – NS
  - Association with responsibility for collisions among collisions, and only at higher than usual doses (OR 1.29, 95% CI 1.09-1.52).

**Case Series**
- Gibson et al 2009 IRR 5.31 (99% CI 3.55-7.95)
  - up to 4 weeks prior to the rx. NOT after

**Cohort Studies**
- Gustavsen et al 2008 SIR 2.2 (95% CI = 1.4 -3.4)
  - but only for males age 18-34
- Hansen 2015 HR 2.20 (95% CI 1.64-2.95)
  - but only for 30-240 days and >360 days post prescription

Zopiclone

- **Barbone et al, Lancet 1998** Case Crossover
  - OR 4.00 (95% CI 1.31-12.2)
  - No stratified data analysis

- **Gustavsen et al, Sleep Medicine 2008** Cohort
  - SIR 2.3 (95% CI 2.0-2.8)
  - But only age 18-54

- **Gibson et al, Am J Epi 2008** Case Series
  - IRR 6.93 (99% CI 5.83-8.94)
  - But only first four weeks

Two other Case Crossover studies negative

- **Orriols et al, Clin Pharm and Ther 2011**
- **Yang et al, J Epidem 2011**
Clinical reasons for heterogeneous response
Antidepressants
Risk of exposure to medication in the month prior to crash

- Proton Pump Inhibitors
- Antifungals
- Benzodiazepines
- Antipsychotic
- 2nd Generation Antidepressants
- 1st Generation Antidepressants
- All Antidepressants

Adjusted Hazard Ratio (with 95% CI)

Rapoport et al, AJGP 2011
Crash risk stratified by concomitant medications

- No Benzodiazepine
- Benzodiazepine
- No Antipsychotic
- Antipsychotic
- Anticholinergic Index 3+
- Anticholinergic Index 0-2

Adjusted Hazard Ratio (with 95% CI)
Other Epidemiological Studies of Antidepressants and MVC in Older Adults

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meuleners et al. 2011 JAGS</td>
<td>OR 1.8 MVC requiring hospitalization</td>
</tr>
<tr>
<td>Case-crossover, 60+</td>
<td></td>
</tr>
<tr>
<td>Rapoport et al 2008 JAGS</td>
<td>Dementia 66 years plus</td>
</tr>
<tr>
<td>Case Crossover, 66+</td>
<td>OR 1.5</td>
</tr>
<tr>
<td></td>
<td>2\textsuperscript{nd} generation &gt; 1\textsuperscript{st} generation.</td>
</tr>
<tr>
<td>Coupland et al. 2011. BMJ.</td>
<td>Depression 65 years plus.</td>
</tr>
<tr>
<td>Cohort study, 65+</td>
<td>NS for any class</td>
</tr>
<tr>
<td>Hu et al. 1998. AAP.</td>
<td>OR 2.04 males only</td>
</tr>
<tr>
<td>Case-only Panel Analysis, 65+</td>
<td></td>
</tr>
</tbody>
</table>

*Cameron and Rapoport, Canadian Journal on Aging 2016*
Vigilance needed

- Antidepressants second only to benzodiazepines in community-dwelling seniors.
- Newer antidepressants as safe – needs to be questioned.
  - Recently recognized - falls, low sodium, bleeding risk
  - Consider warning of driving risks in first several months of starting an antidepressant concurrently with benzodiazepines or other highly anticholinergic drugs.
Factors increasing risk of impaired driving on antidepressants

- Increasing age
- Initial start up/adjustment
- Rapid escalation/ higher doses
- First week of antidepressant treatment
- Active depressive symptoms
- Comorbid psychotropics, especially benzodiazepines.

Sansone & Sansone, Psychiatry 2009.
Broader Perspective of Licit Drugs
Individual Drug Systematic Review

- Published and Grey Literature 1960-present
- 208 studies of individual drugs and MVCs or Driving Impairment, including 27 w MVC, with 7 focusing on older adults.
- 28% of the medications were associated with increased risk:
  - Buprenorphine, codeine, dihydrocodeine, methadone, tramadol, carisoprodol, insulin
  - Levocitirizine, diazepam, flunitrazepam, nitrazepam, flurazepam, lorazepam, temazepam, triazolam, zolpidem, zopicone, lithium
- 67.9% not significantly associated w MVC (including antidepressants, with 10 individual ATDs by Coupland et al 2011)

Rudisill et al, Accident Analysis Prevention 2016
US Case-Control Study, 50+ years, PDI (potential driving impairing)

- 35/90 PDI drugs had OR >1.2
  - One or two, OR 1.29
  - Three or more, OR 1.87
- 79/200 PDI diseases had OR>1.4
  - One or two, OR 1.49
  - Three or more, OR 2.20

LeRoy, AA.; Morse, ML. Department of Transportation. HS 810 858. Multiple medications and vehicle crashes: analysis of databases. 2008.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>7.50 (2.35, 23.91)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>3.00 (1.05, 8.55)</td>
</tr>
<tr>
<td>Non-narcotic antitussives</td>
<td>2.23 (1.30, 3.82)</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>2.22 (1.98, 2.49)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>2.20 (1.37, 3.52)</td>
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<tr>
<td>Skeletal muscle relaxants</td>
<td>2.09 (1.71, 2.55)</td>
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<tr>
<td>Anti-anxiety drugs (Benzodiazepine)</td>
<td>2.00 (1.72, 2.31)</td>
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<tr>
<td>Anticonvulsants</td>
<td>1.97 (1.64, 2.38)</td>
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<tr>
<td>SARIs</td>
<td>1.90 (1.49, 2.44)</td>
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<tr>
<td>Belladona Alkaloids</td>
<td>1.85 (1.08, 3.19)</td>
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<tr>
<td>Insulins</td>
<td>1.80 (1.45, 2.22)</td>
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<tr>
<td>Hypotensives, sympatholytic</td>
<td>1.79 (1.17, 2.74)</td>
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<tr>
<td>SNRI</td>
<td>1.78 (1.19, 2.66)</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>1.69 (1.17, 2.43)</td>
</tr>
<tr>
<td>Anti-emetic/anti-vertigo</td>
<td>1.63 (1.17, 2.28)</td>
</tr>
</tbody>
</table>

LeRoy, AA.; Morse, ML. Department of Transportation. HS 810 858. Multiple medications and vehicle crashes: analysis of databases. 2008.
<table>
<thead>
<tr>
<th>Disease Groups</th>
<th>Odds Ratio with 95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAD TRAUMA</td>
<td>36.00 (11.09, 116.90)</td>
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<tr>
<td>ACIDOSIS</td>
<td>15.00 (1.75, 128.40)</td>
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<tr>
<td>NEUROTIC DISORDER</td>
<td>12.00 (1.34, 107.37)</td>
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<tr>
<td>DELIRIUM, ACUTE</td>
<td>10.50 (2.18, 50.55)</td>
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<td>CONSCIOUSNESS ALTERATION</td>
<td>9.00 (2.90, 27.91)</td>
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<tr>
<td>PERSONALITY DISORDERS</td>
<td>9.00 (1.82, 44.59)</td>
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<tr>
<td>HEMORRHAGE, UNSPEC</td>
<td>6.00 (1.10, 32.76)</td>
</tr>
<tr>
<td>ALCOHOLISM</td>
<td>5.44 (2.95, 10.01)</td>
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<tr>
<td>DIABETIC KETOACIDOSIS</td>
<td>5.40 (1.81, 16.11)</td>
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<tr>
<td>STRESS DISORDERS</td>
<td>5.40 (1.81, 16.11)</td>
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<tr>
<td>VISUAL DISTURBANCES</td>
<td>4.71 (1.83, 12.16)</td>
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<tr>
<td>DEPRESSION</td>
<td>3.99 (3.19, 4.99)</td>
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<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td>3.72 (2.99, 4.63)</td>
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<tr>
<td>PLEURAL EFFUSION</td>
<td>3.69 (1.78, 7.68)</td>
</tr>
<tr>
<td>EXTRAPYRAMIDAL REACTIONS</td>
<td>3.60 (1.56, 8.33)</td>
</tr>
</tbody>
</table>

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Simulators

- Furlan et al, work in progress
- Last 10 years: 30 simulator psychotropic studies.
- Small samples, various simulators and outcome measures, times-post-dose, few with sample size calculations or age/gender adjustments.
Assessing the Literature

Neuropsychiatric Illness
Antidepressants
Age
Benzodiazepines
Sex/Gender
Limitations

- Meds vs Sx (Indication and Channeling)
- Dementia or Cog Impairment Suicide
- Timing of the Drug, Onset, Route, Kinetic/dynamic, other drugs
- Dose-Response Acute Exposure Classes vs Drugs Adherence
- Age Sex/Gender Health Status Tolerance
- Driving Exposure and Other Unmeasured Confounds
Thank you