Driving under the influence of benzodiazepines

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Benzoïdazepines and crashes

Driving under the influence of drugs, benzodiazepines included, is a type of crime many times forgotten

What evidence do we have to support the notion that benzodiazepine use might increase the risk of causing a traffic accident?

Road traffic crashes are in approximately 90% of the cases related to human factors:

1. Unknown factors
2. Neuropsychological changes
3. Cognitive reductions
4. Sleepiness
5. Bad traffic habits (high speed, etc)
6. Diseases
7. Medicinal drugs (side effects)
8. Drugs of abuse
9. Alcohol

Most knowledge about alcohol
Drugs might cause traffic relevant impairment

Accompanied by increased risk of causing or being involved in a crash (fatal or non-fatal)

• Can be demonstrated in analytical epidemiological studies
• Can be demonstrated as reduced performance in traffic relevant experimental studies

Epidemiological studies

A. Analytical epidemiological studies
B. Blood drug concentration-effect correlations in drivers
C. Drug findings in subsets of drivers
   a. Injured in traffic accidents
   b. Killed in traffic accidents
   c. Involved in traffic accidents
   d. Suspected of driving under the influence

Analytical epidemiological studies

1) Pharmacoepidemiological (cohort) studies
   - Compare accident incidence with non-users
2) Case-control studies
   - Compare drug findings in accident involved drivers (surviving or killed) with drug findings in comparable control group not involved in accident
3) “Culpability”-studies
   - Compare drug findings in drivers (surviving or killed) responsible for crashes with drug findings in crash drivers not responsible for the accident
1. Pharmacoepidemiological studies

FOR MEDICINAL DRUGS A COHORT-MODEL APPROACH CAN BE APPLIED TO OBTAIN INFORMATION ABOUT TRAFFIC ACCIDENT RISK

### Cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design / Population sample</th>
<th>Outcome</th>
<th>Drugs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ray et al (1992)</td>
<td>Cohort + Case crossover; 16,262 (65-84 y) Registry, Crash with personal injury</td>
<td></td>
<td>BZD</td>
<td>RR=1.5 [1.2-1.9]</td>
</tr>
<tr>
<td>Neutel (1998)</td>
<td>Cohort; 323,658 (&gt; 20 y) Registry, Hospitalization for crash injury</td>
<td></td>
<td>BZD</td>
<td>OR=3.1 [1.5-6.2] (OR for single BZD: 1.0 – 5.1)</td>
</tr>
<tr>
<td>Barbone et al (1998)</td>
<td>Case crossover, 410,306 (&gt; 18 y) Registry, 19,386 drivers involved in a first road-traffic crash</td>
<td></td>
<td>BZD</td>
<td>OR=1.6 [1.2-2.1] OR=4.0 [1.3-12.2]</td>
</tr>
</tbody>
</table>

The Norwegian prescription database as background

- To determine whether persons prescribed certain medications were at higher risk for traffic accidents
Materials and methods

Data were retrieved from three Norwegian population-based registries:

- **Norwegian Prescription Database (NorPD)**
  All dispensed prescriptions at pharmacies to individual patients treated in ambulatory care

- **Road Accident Registry**
  Information about accidents involving personal injuries in road traffic accidents

- **Central Population Registry**
  Demographic information on all residents in Norway, including date of birth and death, data of emigration from Norway

Data from the three registries were linked by the unique 11-digit identification number which is assigned to all individuals living in Norway.

Materials and methods

- Natural opium alkaloids
- Benzodiazepine anxiolytics
- Benzodiazepine hypnotics

- Nonsteroid anti-inflammatory drugs (NSAIDs)
  - Antiasthmatics
  - Penicillins
  - Calcium receptor antagonists

- Any drugs
Materials and methods

Subjects 18 – 69 years (3.1 million; 8 144 554 person years)

Study period
2.5 year (April 2004 – September 2006)

Materials and methods

- Calculation of the Standardized Incidence Ratio (SIR)

SIR:
- The incidence of accidents in the exposed person-time was compared with the incidence of accidents in the unexposed person-time by calculation of the standardized incidence ratio
- Exposed period: starting at day after dispensing day
  - 7 days
  - 14 days
  - number of days corresponding to the number of Defined Daily Doses (DDD)

** Unexposed period = all days where persons was unexposed to the medicine in question
Materials and methods

SIR was calculated separately for age groups and sexes

SIR > 1 indicates an increased risk of being involved in an accident as a driver where personal injury is caused to either driver or others

Results

Among 3.1 million study subjects there were 22,405 drivers involved in accidents with personal injuries

Results (both sexes combined)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medicine</td>
<td>1.4 (1.3-1.5)</td>
</tr>
<tr>
<td>Natural opium alkaloids</td>
<td>2.0 (1.7-2.4)</td>
</tr>
<tr>
<td>Benzodiazpine anxiolytics</td>
<td>2.9 (2.5-3.5)</td>
</tr>
<tr>
<td>Benzodiazpine hypnotics</td>
<td>3.3 (2.1-4.7)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.5 (1.0-2.1)</td>
</tr>
<tr>
<td>Anti-asthmatics</td>
<td>1.5 (1.0-2.0)</td>
</tr>
<tr>
<td>Calcium receptor antagonists</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1.1 (0.8-1.5)</td>
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</tbody>
</table>

Exclusion of person-time where the patients received natural opium alkaloids or benzodiazepines at the same time as they received the actual medicine, did not change the results.
### SUMMARY – NOR PD-based studies

<table>
<thead>
<tr>
<th>SIR &gt; 2:</th>
<th>Carisoprodol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Natural opium alkaloids</td>
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<tr>
<td></td>
<td>Benzodiazepine hypnotics</td>
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<tr>
<td></td>
<td>Z-hypnotics (Imidazopyrides)</td>
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<tr>
<td></td>
<td>Benzodiazepines tranquilizers</td>
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<tr>
<td>SIR 1-2:</td>
<td>NSAIDS</td>
</tr>
<tr>
<td></td>
<td>Insulins</td>
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<tr>
<td></td>
<td>Sedating antidepressants (TCA etc)</td>
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<tr>
<td></td>
<td>Nonsedating antidepressants (SSRI etc)</td>
</tr>
<tr>
<td>SIR 1+:</td>
<td>Antiepileptics</td>
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<tr>
<td></td>
<td>Calcium receptor antagonists</td>
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<td></td>
<td>Penicillins</td>
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<tr>
<td></td>
<td>Oral antidiabetics</td>
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<td></td>
<td>Lithium</td>
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<td></td>
<td>Valproat</td>
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<tr>
<td></td>
<td>Salbutamol</td>
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</tbody>
</table>

### LIMITATIONS

- To what extent do drug users drive?
- Was the drug used as prescribed?
- Importance of underlying disease?
- Use of prescription medicine coupled to intake of alcohol, drugs of abuse, etc?
- Problems with the starting point of the exposure period (the day after dispensing)
- To which extent were the accident drivers at fault?
- Only one third of accidents with person injury is reported to the Accident Registry

### Strengths of the model

- A high data quality by using population based registries
- High quality of the linkage using the unique 11-digit person identifier
- Knowledge of the types and amount of drugs that the patients had received
- Data not affected by recall bias
### Analytical epidemiological studies

1) **Pharmacoepidemiological (cohort) studies**
   - Compare accident incidence with non-users

2) **Case-control studies**
   - Compare drug findings in accident involved drivers (surviving or killed) with drug findings in comparable control group not involved in accident

3) **"Culpability"-studies**
   - Compare drug findings in drivers (surviving or killed) responsible for crashes with drug findings in crash drivers not responsible for the accident

### Case-control studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Case</th>
<th>Control</th>
<th>Drug exposure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skegg et al</td>
<td>57</td>
<td>1452</td>
<td>Medicines dispensed last 3 months before</td>
<td>RR: 5.2 [2.1-12.6] (sedatives)</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td></td>
<td>RR: 4.9 [1.8-13.0] (minor tranquillizers)</td>
</tr>
<tr>
<td>Honkanen et al</td>
<td>201</td>
<td>325</td>
<td>Blood samples + interview</td>
<td>OR: 2.3 (mainly diazepam)</td>
</tr>
<tr>
<td>Leveille et al</td>
<td>234</td>
<td>447</td>
<td>Data from prescription databases</td>
<td>OR: 0.9 [0.4-2.0]</td>
</tr>
<tr>
<td>Hemmelgarn et al</td>
<td>5579</td>
<td>55790</td>
<td>Data from prescription databases</td>
<td>RR: 1.5 [1.0-2.0] (long half-life)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR: 1.0 [0.8-1.3] (short half-life)</td>
</tr>
<tr>
<td>Dussault et al</td>
<td></td>
<td></td>
<td>Blood sample</td>
<td>OR: 2.5 [1.4-4.3]</td>
</tr>
<tr>
<td>Mura et al</td>
<td>900</td>
<td>900</td>
<td>Blood samples (urine, sweat)</td>
<td>OR: 1.7 [1.2-2.4]</td>
</tr>
<tr>
<td>Movig et al</td>
<td>110</td>
<td>816</td>
<td>Blood samples (urine samples)</td>
<td>OR: 5.0 [1.8-14.0]</td>
</tr>
<tr>
<td>McGwin et al</td>
<td>901</td>
<td>&gt;65</td>
<td>Questionnaire</td>
<td>OR: 5.2 [0.9-30.0]</td>
</tr>
</tbody>
</table>

### NON-ALCOHOL DRUGS (MEDICINAL + ILLEGAL) IN CASE-CONTROL STUDIES

- Observational data have been difficult to obtain since the case-control approach used for alcohol is hampered by
  - less comprehensive analysis of NAD in accidental drivers
  - post-mortem blood drug concentration changes in killed drivers
  - difficult to obtain representative data for blood drug concentrations in control population drivers
Analytical epidemiological studies

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   - Compare drug findings in drivers (surviving or killed) responsible for crashes with drug findings in crash drivers not responsible for the accident

Culpability-studies

Benzodiazepines:

3398 killed drivers, Australia OR: 1.3 (0.5 - 3.3)
2500 injured drivers, Australia OR: 2.0 (1.1 - 3.9)
482 killed drivers, Canada OR: 3.6 (0.5 – 28.2)

Epidemiological studies

A. Analytical epidemiological studies
B. Blood drug concentration-effect correlations in drivers
C. Drug findings in subsets of drivers
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Handling of drunken and drugged driving cases in Norway

- Blood samples
  - Alcohol
  - Amphetamines
  - Benzodiazepines
  - Opioids
  - Cocaine
  - THC
  - CNS-stimulants

- Urine samples
  - Benzodiazepines
  - Opioids
  - Cocaine
  - CNS-stimulants

- Hair samples
  - Benzodiazepines
  - Opioids
  - Cocaine
  - CNS-stimulants

- Report to the police
- Expert witness statement
- Expert witness statement (DFTDA)
- Court

- Blood (and urine) samples - clinical examination (by police physician)
- Evidential breath sample

Analyses:
- Alcohol, amphetamines, cocaine, THC, cannabinoids, opiates, THC, BZDs, corticosteroids, and other substances based on police report and clinical examination

Primary evaluation based on analytical results and clinical examination

Primary evaluation based on analytical results

Benzodiazepines
Alcohol

Individual blood-concentration – effect variation

Fig. 2. Percentage of impaired drivers who were determined "not impaired". Only values represent the medians of all values (not mean values). The black columns represent the reference group whose only variable was noted. In the study group significant differences in the percentage were observed for "low" impaired. (Fig. 2A) Alcohol Blood concentrations were divided into therapeutically, mildly elevated, moderately elevated, and highly elevated groups. The percentage of impaired drivers showed significant differences between all groups. (Fig. 2B) Therapeutic level 0.025–0.050%, mildly elevated 0.051–0.100%, moderately elevated 0.101–0.150%, highly elevated >0.150%.

Individual blood-concentration – effect variation

Fig. 3. The graph shows the average blood concentrations of benzodiazepines in a group of drivers who were classified as "not impaired". The black columns represent the reference group whose only variable was noted. The white columns show the percentage of drivers impaired in relation to the blood concentration of benzodiazepines. The number of drivers in each group is shown at the base of the columns. (Fig. 3A) Therapeutic level 0.025–0.050%, mildly elevated 0.051–0.100%, moderately elevated 0.101–0.150%, highly elevated >0.150%.

I. Gustavsen, Accident Analysis and Prevention 2009
Epidemiological studies

A. Analytical epidemiological studies

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Frequency (%) of BZDs total, some commonly single BZDs and illegal drugs detected in blood samples from apprehended drivers in Norway during 2000-2005
CONTROLLED EXPERIMENTAL STUDIES

A. Laboratory experiments
- Psychomotor skills
- Cognitive tests

B. Driving simulator experiments

C. Car driving
- On closed circuits
- In real traffic (under some supervision)

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J. Ingum et al.,
Psychopharmacology 1992
Summary

• Analytical epidemiological studies indicate that benzodiazepine prescription and use are associated with increased crash risk.
• In subsets of drivers killed or apprehended after risky or careless driving, benzodiazepines are overrepresented and drug blood concentration - effect relationships are found.
• Benzodiazepines in therapeutic or supratherapeutic doses decrease performance in series of experimental studies of different types.
• Taken together this evidence strongly support the notion that use of benzodiazepines (in developed countries) represents a considerable risk factor in roadside traffic.