Medicines and Driving: How to improve information for patients and health care professionals?

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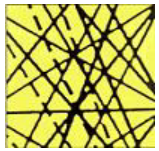
DRUID

Social Pharmacy
Pharmacoepidemiology
and Pharmacotherapy



Content

- Road Safety in Europe
- What about DRUID (Driving under the Influence of Drugs, Alcohol and Medicines)?
- How to improve information for patients/drivers and health care professionals?

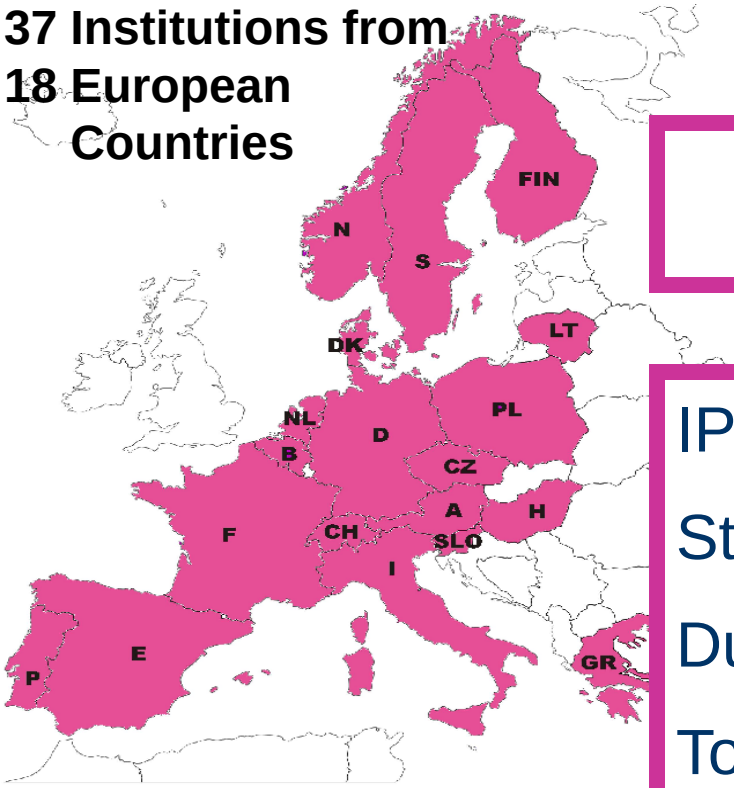
Road Safety in Europe

- 46,700 persons killed (2003)/year in EU-25
- Nearly 2.0 million injured
- Main cause of death < 45 y
- € 200 billion/year cost to society, 2% of GDP
- 1 inhabitant/3 will be hospitalised during his life because of a crash
- European Road Safety Action Programme: saving 25,000 lives on EU roads by 2010

Background

- High number of DUI accidents, drugs and medicines proportionally increasing
- Insufficient knowledge of prevalence and risk of illegal drugs and medicines in traffic
- Difficulties in detecting illegal drug and medicine consumption by drivers

DRUID - Overview



37 Institutions from 18 European Countries

17 EU Member States

+ Norway

IP - EU 6th Framework-Programme

Start: October, 15th, 2006

Duration: 48 Months

Total Budget: ~ 26 Mio €

EU-funding: 19 Mio €

7 co-operative Work Packages

DRUID

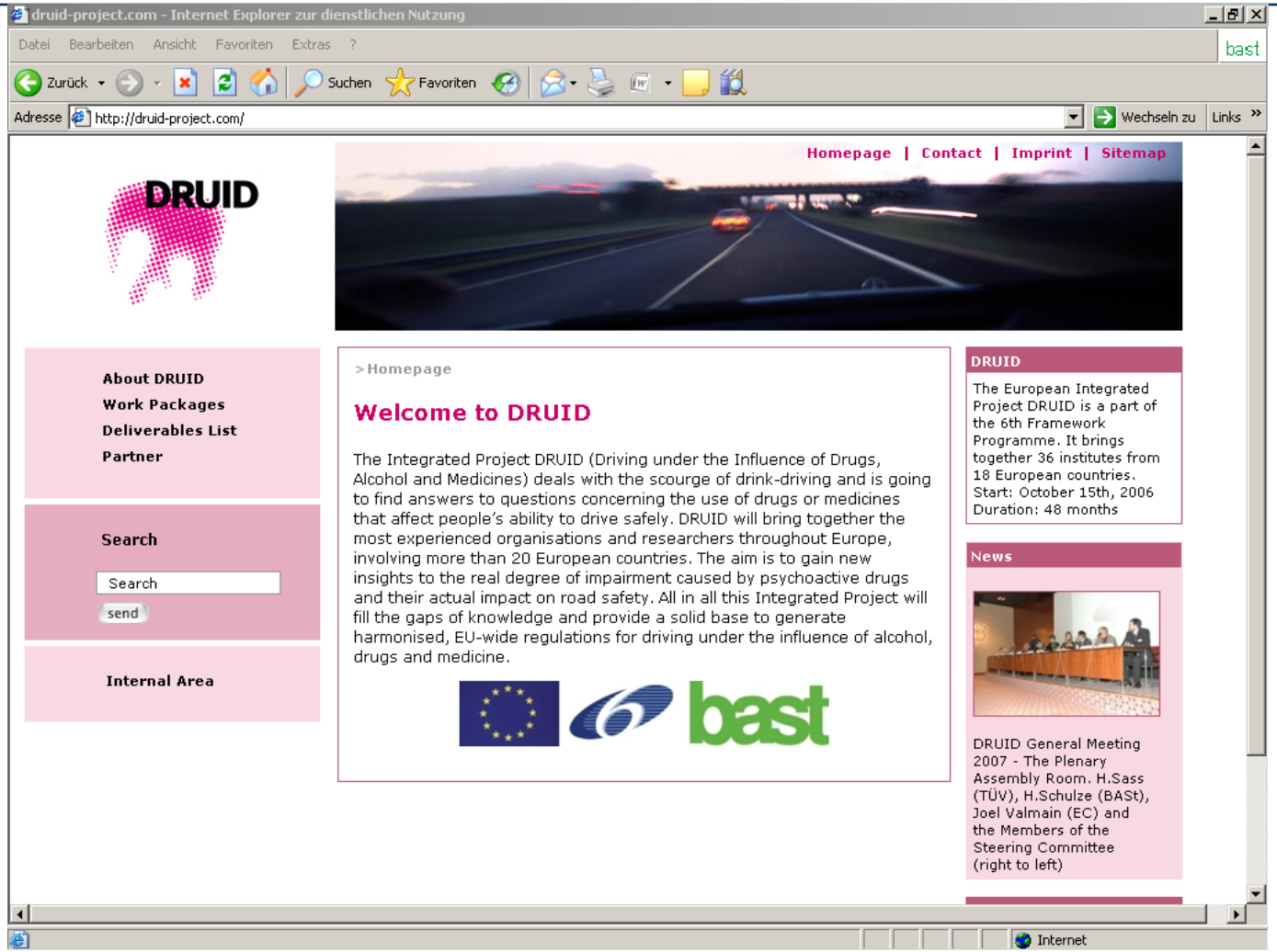
Objectives

- Enhance the knowledge about the influence of psychoactive substances on driving
- Establishment of risk thresholds for relevant psychoactive substances
- Information and guidelines for various key actors and drivers
- Recommendations for legislation, enforcement and rehabilitation measures

DRUID Workpackages

- WP 1 Methodology (BASt, D)
- WP 2 Epidemiology (DTU, DK)
- WP 3 Enforcement (SWOV, NL)
- WP 4 Classification (UVa, E)
- WP 5 Rehabilitation (KfV, A)
- WP 6 Withdrawal (DRSC, SL)
- WP 7 Dissemination (RUGPha, NL)

http://druid-project.eu



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Scope of the problem

- Prevalence and epidemiology (data from Australia, EU, North America)
- Behavioural toxicity and impairment (experimental studies)
- Risk communication

Illicit drugs and road traffic

Drug	General driver pop.	Collision & Involved	Fatally Injured	
Cannabis	**6.7%**	**2.2%**	**13.5%**	**19.5%**
Opiates	**1.2%**	**3.2%**	**4.9%**	**1.4%**
Amphet.	**0.1%**	**2.7%**	**1.7%**	**0.8%**
Cocaine	**1.1%**	**5.2%**	**0.2%**	**6.8%**
(Benzo's	**3.6%**	**3.4%**	**4.1%**	**8.5%)**

Dussault et al., 2002
N=5,931 and 482 killed

Del Rio & Alvarez, 2002
N=5,745 killed

Drummer et al.,2003
N=3,398 killed

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Behavioural toxicity and impairment

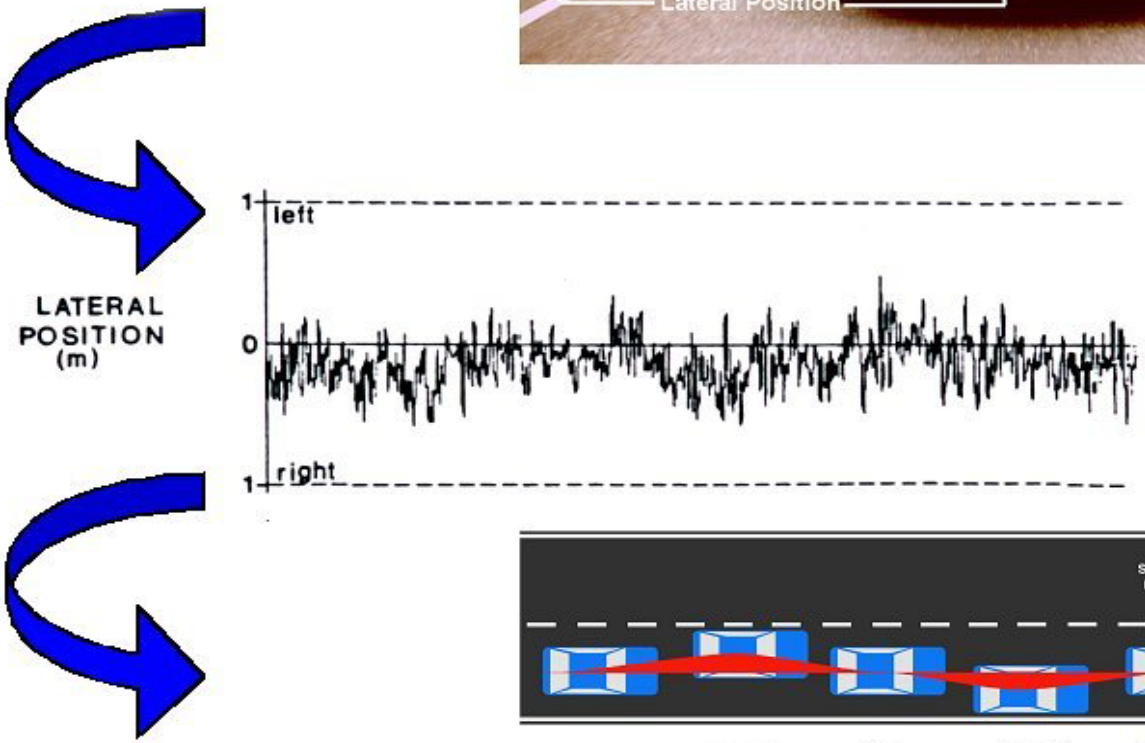
Standard driving test (developed in the NL in 1982)

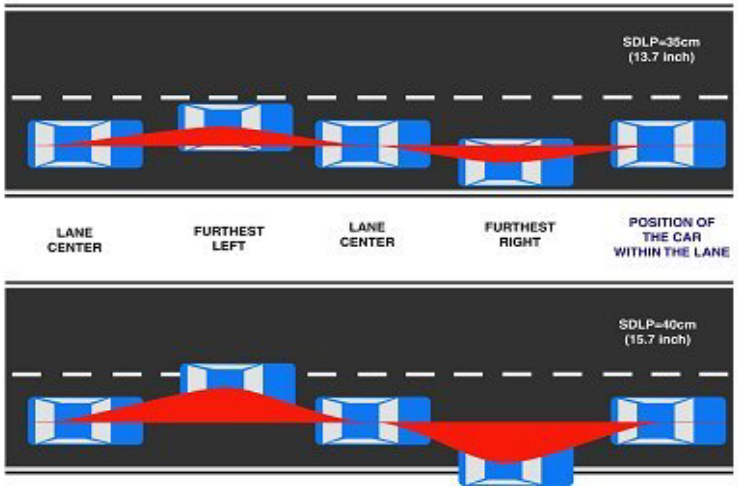
- Applied in > 50 major (published) studies with psychiatric and neurological patients, impaired elderly and healthy volunteers
- Recognized as valid for assessing safety of anxiolytics and hypnotics

Standard driving test

- Safety is supervised by instructor with access to redundant controls.
- Subject operates instrumented vehicle over 100 km primary highway circuit in traffic.
- Speed and lateral position are recorded.
- Standard deviation of lateral position (SDLP) is the primary outcome variable.

The instrumented test vehicle has a camera for lateral position measurements. The camera is equipped with two infrared lights, to enable recording during the night and dark weather circumstances. Data (speed and lateral position) are continuously recorded on a board computer with a sampling rate of 2 Hz. The raw data is edited off-line to remove data that were disturbed by extraneous events (e.g. overtaking and traffic jams).



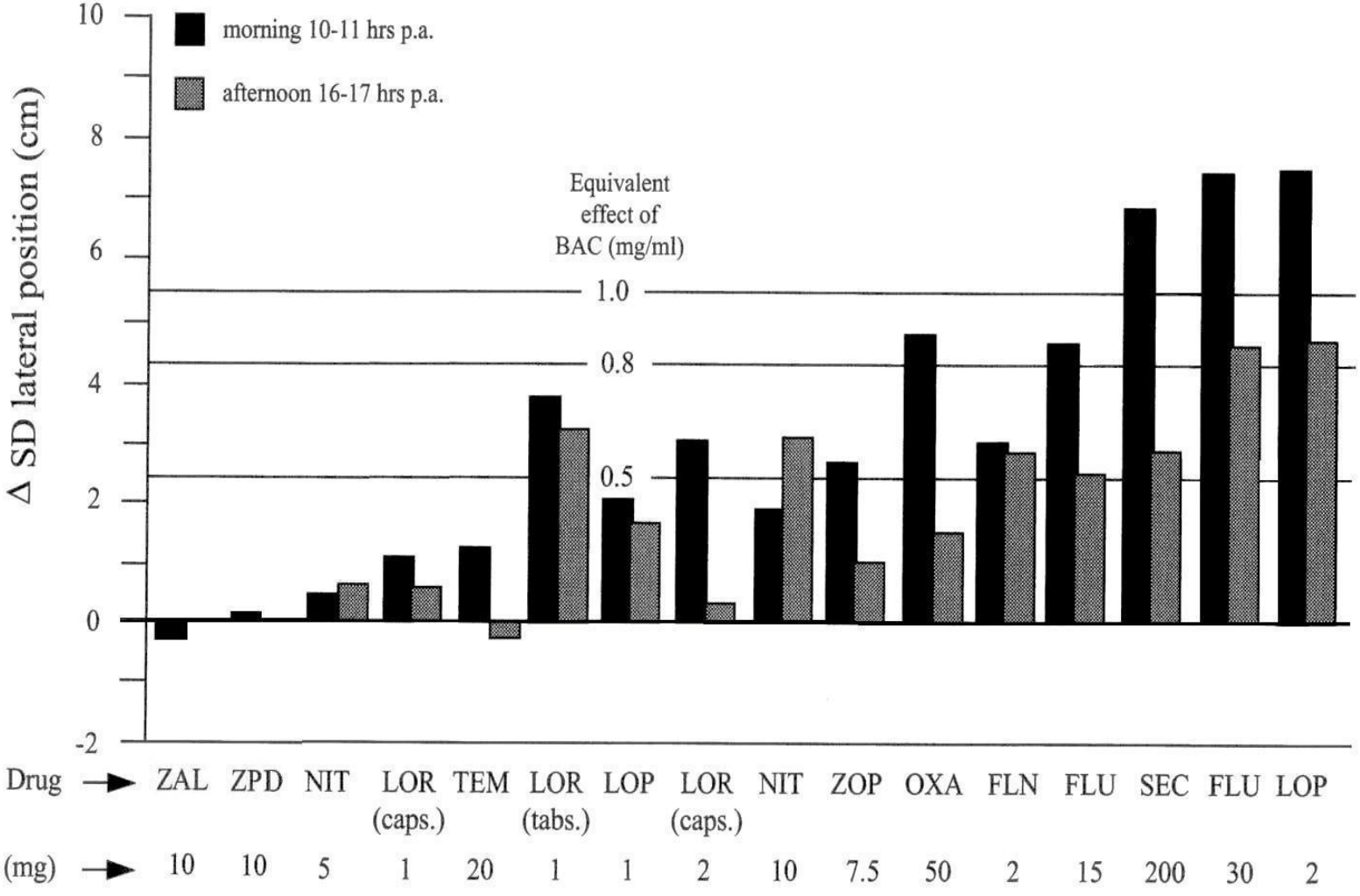


The Standard Deviation of Lateral Position (SDLP) is computed, expressing the weaving of the car.

Hypnotic series (1982-1998)

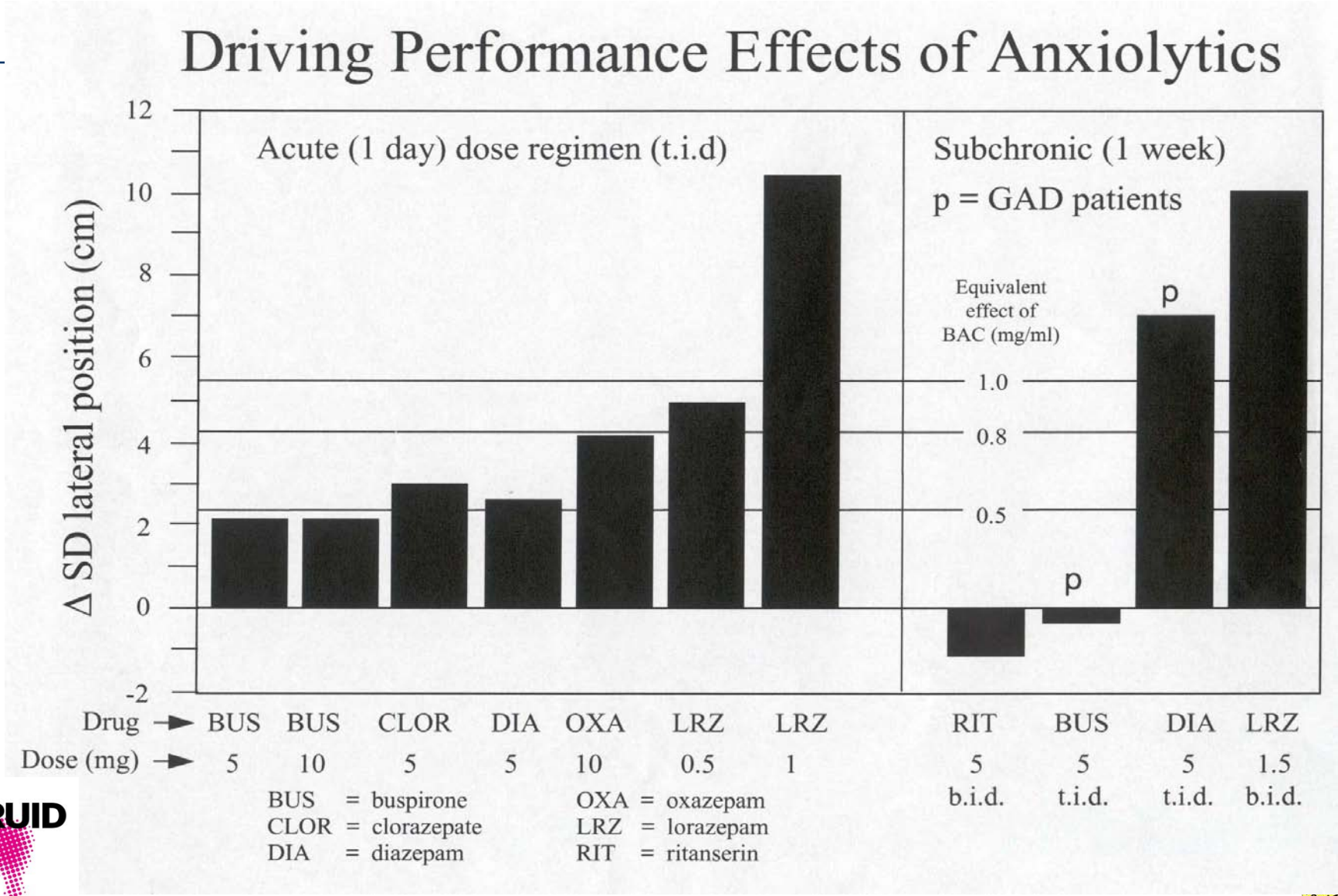
- Purpose: evaluate residual sedation after sleep at times 5-17h post-dosing
- Subjects: primary insomnia patients (DSM III-R), shiftworkers and healthy volunteers
- Design: double-blind, placebo and active controlled, cross-over (N = 14-24)
- Power: > 90% for detecting ($p \leq .01$) the same ΔSDLP as for BAL = 0.5 mg/ml

Driving Performance Effects of Hypnotics



ZAL = zaleplon
ZPD = zolpidem
LOR = lormetazepam
LOP = loprazolam
FLN = flunitrazepam
NIT = nitrazepam
ZOP = zopiclone
SEC = secobarbital
TEM = temazepam
OXA = oxazepam
FLU = flurazepam

Driving Performance Effects of Anxiolytics



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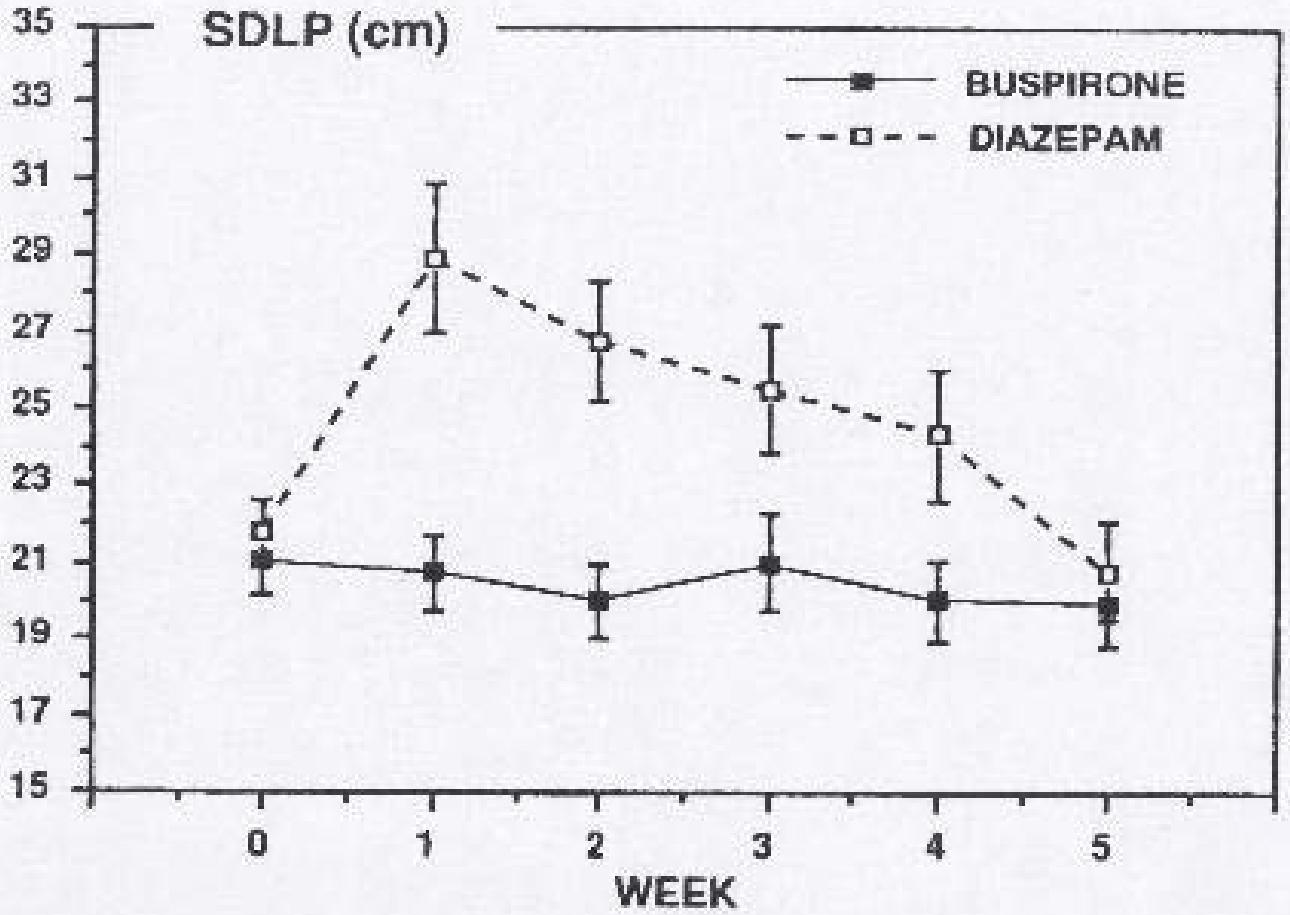
Safer alternatives exist



4. Mean (±SE) of SDLP in each treatment week in the buspirone the diazepam group.

Van Laar, Volkerts and Van Willigenburg, 1992

Conclusions

derived from experimental psychopharmacology

- Differences exist between benzodiazepines
- Safer alternatives exist for benzodiazepines, e.g:

  - Buspiron (anxiolytics)

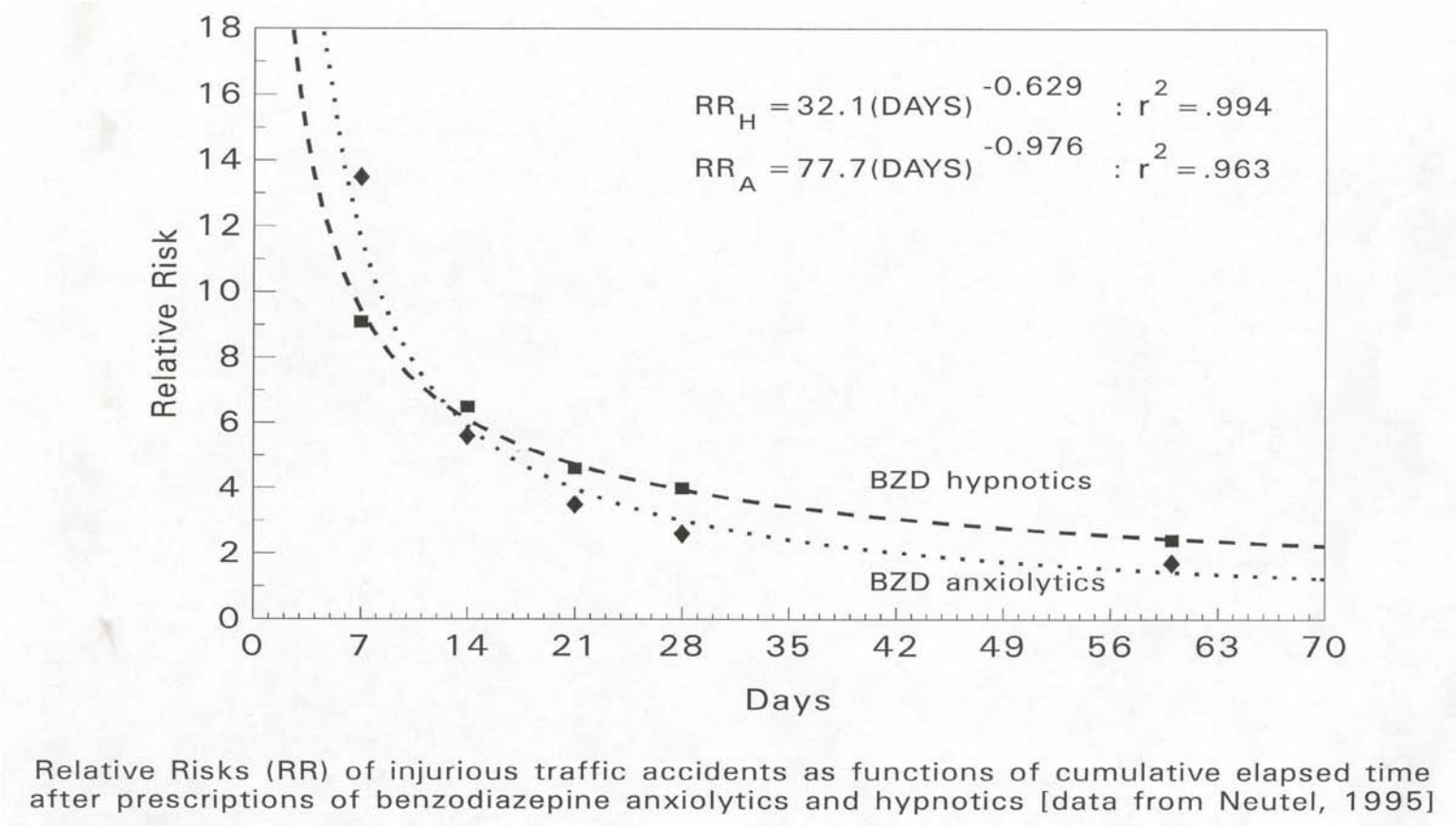
  - Zaleplon (hypnotics)
- Similar results could be presented for antihistamines and antidepressants

Risk of traffic accidents: what is our present knowledge?

- Case control designs
  - Linkage of drug use and Rxs from medication records in injured drivers (pharmacoepidemiology)
  - Match drug use in crashes with random matched persons
- Responsibility studies

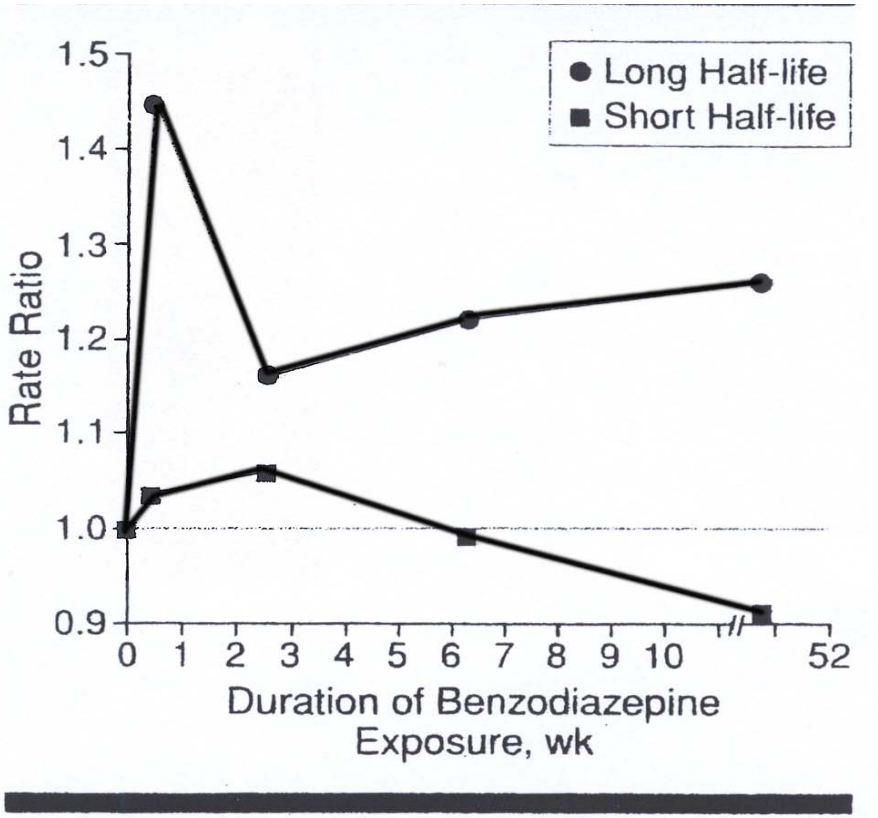
  Effect of drug use on proportion culpable

Benzodiazepines:
Risk at the start of treatment



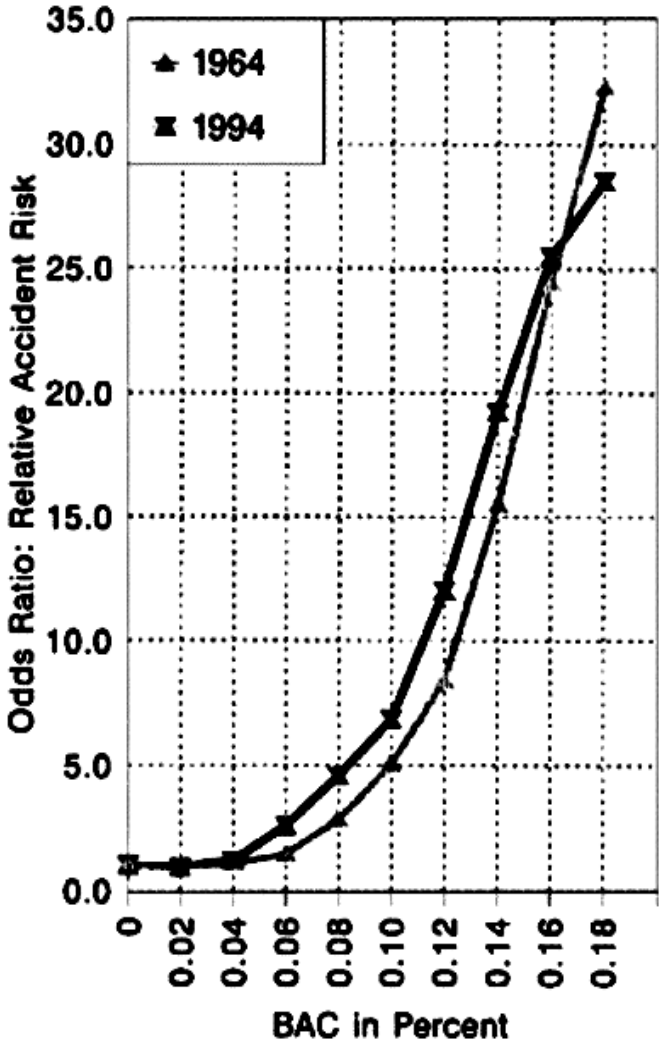
Relative Risks (RR) of injurious traffic accidents as functions of cumulative elapsed time after prescriptions of benzodiazepine anxiolytics and hypnotics [data from Neutel, 1995]

Long versus short half-life BZ's



Adjusted rate ratio of motor vehicle crashes by duration of continuous exposure to long– and short–half-life benzodiazepines.

A classic study
alcohol use and the risk of accidents



Borkenstein, 1974

Relative risks associated with the use of hypnotic and anxiolytic drugs

Drug	Relative Risk	Comparable to BAC (%)	Reference
Diazepam	**3.1**	**.08**	Neutel, 1998
Flurazepam	**5.1**	**.10**	Neutel, 1998
Lorazepam	**2.4**	**.07**	Neutel, 1998
Oxazepam	**1.0**	**< .05**	Neutel, 1998
Triazolam	**3.2**	**.08**	Neutel, 1998
Zopiclone	**4.0**	**.09**	Barbone et al.,1998

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Dose-response Relationship for Benzodiazepines

Barbone et al. 1998: Odds ratio for traffic accident by dose:

Low dose		Intermediate dose		High dose	
N	**Odds ratio (95% CI)**	**N**	**Odds ratio (95% CI)**	**N**	**Odds ratio (95% CI)**
63	**1.27** (0.80-2.01)	84	**1.68** (1.13-2.49)	42	**2.67** (1.33-5.39)

Case control studies

Dussault et al 2002 482 fatally injured drivers 11,952 survey drivers	Benzodiazepines OR 2.5 (1.4-4.3)
Mura et al 2003 900 injured drivers 900 patients (controls)	Benzodiazepines OR 1.7
Movig et al 2004 110 injured drivers 1029 controls	Benzodiazepines OR 5.05 (1.82-14.04)

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Conclusions derived from risk analyses

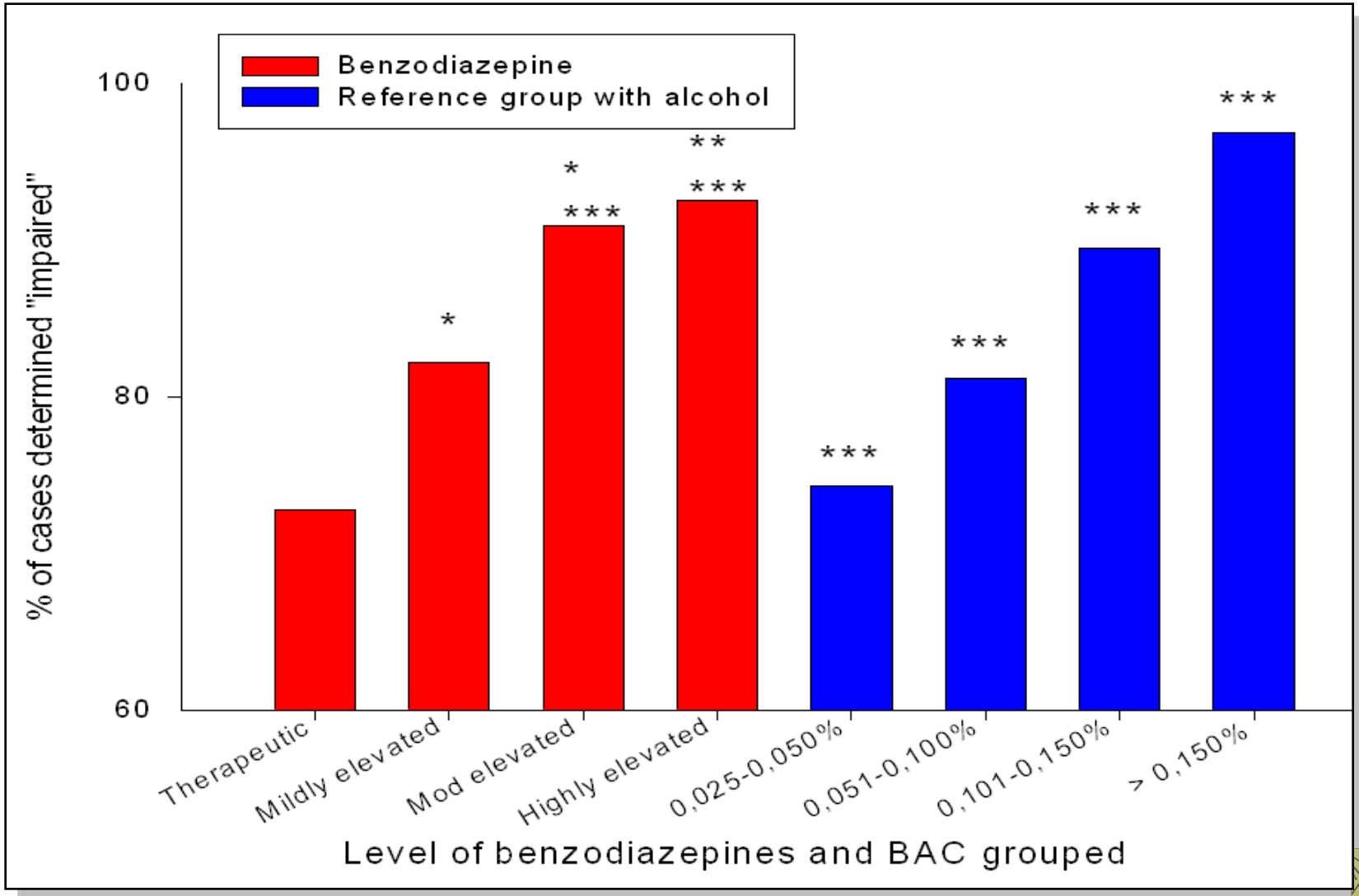
- Benzodiazepines (BZs) are the most extensively analysed medicinal drugs regarding risk assessment in traffic.
- BZs, particularly long half-life acting drugs, in higher therapeutic doses and / or at the start of treatment are most likely to cause an increase in crash risk.
- Increased risk of BZs at least similar to (but probably more than) BAC levels above the legal limit (0.05 – 0.08%).

Assessment of fitness to drive

- Bramness et al 2002:

  - 818 samples containing only 1 BZ, impaired drivers had significantly higher blood levels of diazepam, oxazepam, flunitrazepam than those not impaired, with ORs for being assessed as impaired of 1.61, 3.65 and 4.11 for the three supratherapeutic drug levels

Bramness et al 2002



Three-tier Categorization System for Communicating Risk

Category	Impairment description (Wolschrijn et al., 1991)	Comparison with BAC (Dutch driving studies)
I	Presumed to be safe or unlikely to produce an effect	Equivalent to BAC < 0.5 g/l (< 0.05%)
II	Likely to produce minor or moderate adverse effects	Equivalent to BAC 0.5-0.8 g/l (0.05-0.08%)
III	Likely to produce severe effects or presumed to be potentially dangerous	Equivalent to BAC >0.8 g/l (> 0.08%)

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Categorization System for Communicating Risk

- Application in Germany, Belgium, Spain and France to inform health care professionals and patients
- ICADTS guidelines for prescribing and dispensing of medicines affecting driving performance (see www.icadts.org)
- FIP Statement of Professional Standards: The Supply of Medicines Affecting Driving Performance (see www.fip.org)

French Law for labeling since 2005

Niveau 1

Soyez vigilant !
Médicament pouvant modifier vos capacités de conduite. Respectez les mises en garde et ne prenez pas le volant sans avoir lu attentivement la notice

Niveau 2

Soyez très prudent !
Risque possible lors de la conduite automobile. Demandez l'avis d'un professionnel de santé

Niveau 3

Attention danger !
Ne pas conduire après la prise de ce médicament. Pour la reprise de la conduite, demandez l'avis de votre médecin

French Regulation Aug 3rd 2005
AFSSAPS (French Medical Agency)

Conclusions

- Prescribing and dispensing guidelines for medicinal drugs and driving impairment exist, but need to be implemented
- Selecting the least impairing medication for drivers based on a categorisation system is feasible
- Instructions for patients by using clear warning symbols will guide patients to a safer use of their medicines