

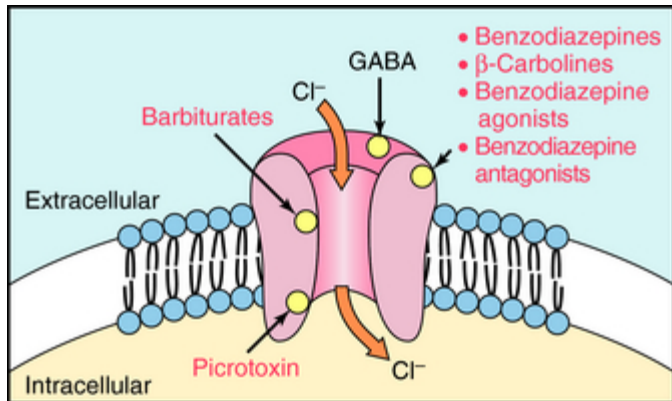
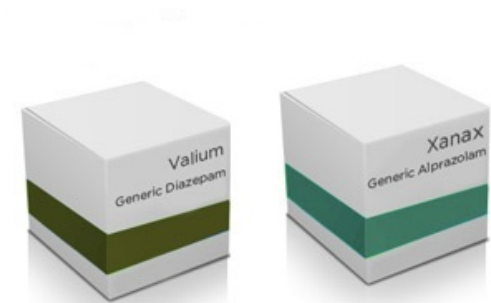
# An explorative approach to observing the impairing effects of chronic benzodiazepine use on driving in a clinical population

**Frederick R.J. Vinckenbosch**

Department of neuropsychology and psychofarmacology  
Division drugs and driving  
Maastricht University, The Netherlands



# Benzodiazepines:



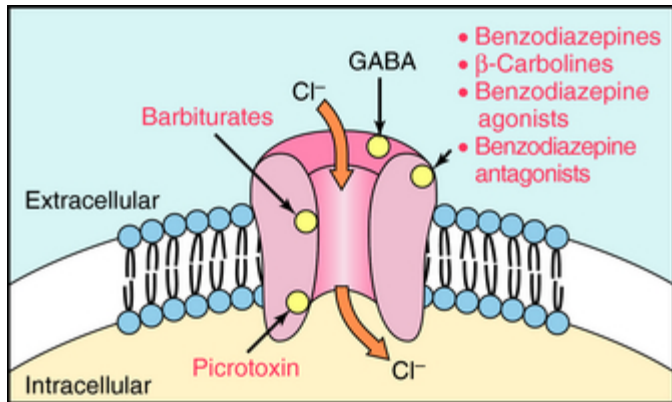
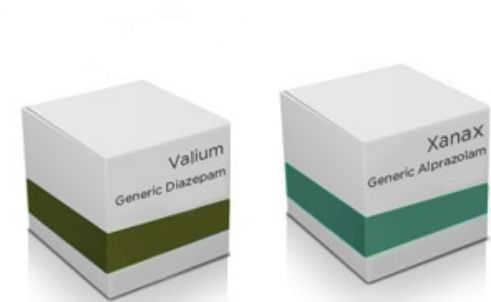
- Sedation (insomnia)
- Anxiolysis
- Muscle relaxation
- Antiepileptic

Illustrations:

<https://basicmedicalkey.com/treatment-of-anxiety-and-insomnia/>

<https://www.healthline.com/health/mental-health/valium-vs-xanax>

# Benzodiazepines:



- Decreased vigilance
- Psychomotor impairment
- Anterograde amnesia

Illustrations:

<https://basicmedicalkey.com/treatment-of-anxiety-and-insomnia/>

<https://www.healthline.com/health/mental-health/valium-vs-xanax>

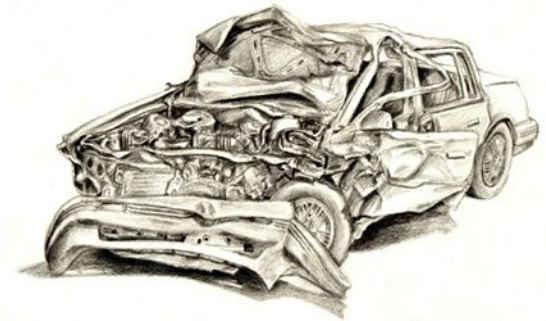
# Benzodiazepines, driving impairment and traffic accidents:

Lines of evidence:

Case-control studies:

Gjerde et al. (2011):

- 204 fatally injured drivers
- 10540 controls (road side testing)
- Benzodiazepines significantly more prevalent in fatally injured drivers (adj. OR:11.4)
- Even more evident in single vehicle crashes (N=68; adj. OR: 16.4)



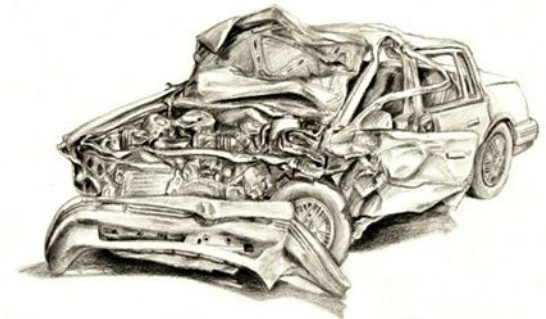
# Benzodiazepines, driving impairment and traffic accidents:

Lines of evidence:

Randomized placebo controlled cross-over trials:

Jongen et al. (2018):

- 23 healthy volunteers
- Treatments: placebo, Diazepam 10mg, Oxazepam 10mg, Oxazepam 30mg
- Impaired performance neurocognitive test battery (PVT, ANT, DSST, DAT, UFOV)
- Impaired road tracking during on-the-road driving test



# On-the-road driving test:

task:

- 100km drive on highway
- Steady speed of 95km/h
- Steady position in middle of right traffic lane

Data:

- Lateral position relative to lane demarcation
- Speed

Outcomes:

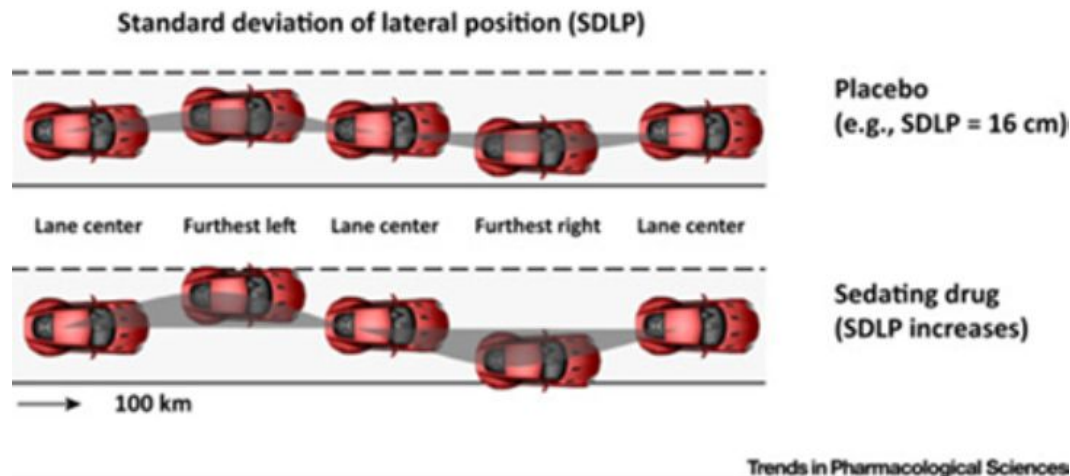
- Standard deviation of the lateral position (SDLP)
- Standard deviation of speed (SDSP)



# On-the-road driving test:

The Standard Deviation of the Lateral Position:

- a.k.a. Lane weaving/swerving/road tracking
- Sensitive to drug effects



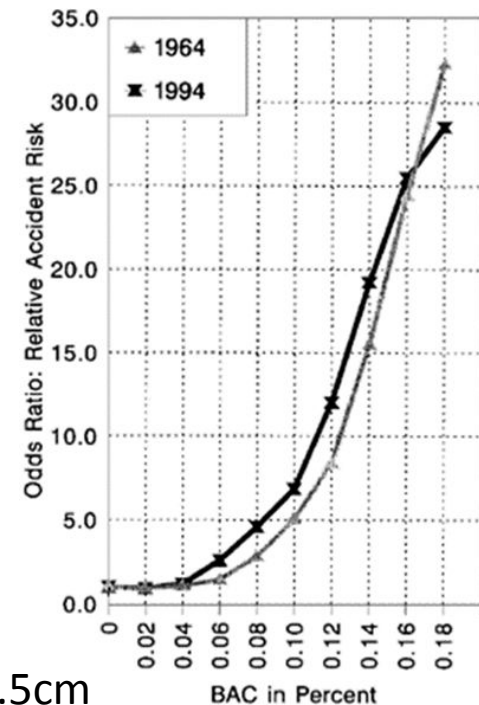
# On-the-road driving test:

The Standard Deviation of the Lateral Position:

- a.k.a. Lane weaving/swerving/road tracking
- Sensitive to drug effects

How much weaving is too much?

- Increase of 2.5cm at BAC of 0.5g/L
- Significant increase in accident risk at BAC of 0.5g/L
- Significant increase in accident risk at SDLP increase of  $\geq 2.5\text{cm}$

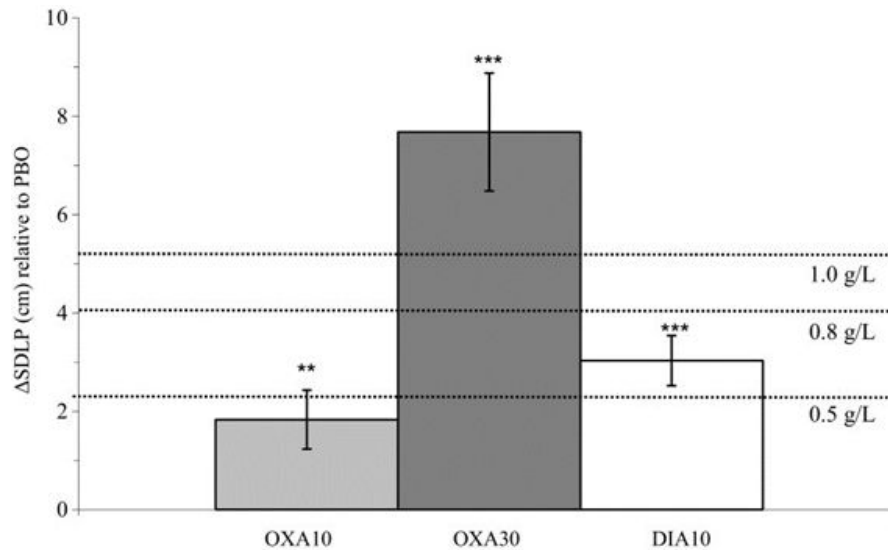




# Benzodiazepines, driving impairment and traffic accidents:

Randomized placebo controlled clinical trials:

Jongen et al. (2018):



# Benzodiazepines, driving impairment and traffic accidents:

Conclusions:

- Benzodiazepines are associated with an **increased accident risk**, especially single-vehicle accidents.
- Benzodiazepines have the potential to **impair cognition and psychomotor performance**.
- Benzodiazepine can induced **road tracking impairment**  $\geq$  Impairment at BAC 0.5g/L.
- Hence: **Benzodiazepines can cause cognitive impairment and traffic accidents.**



# Benzodiazepines in the clinical population

However: Conclusions limited to short-term effects in a drug naïve population

What about a clinical population where long-term use is common?

- Tolerance?
- Clinical condition?

Relevance:

- Advise: When are benzodiazepines dangerous?
- Treatment: Discontinuation of use?
- Policy: Should we prohibit patients to drive?



# Benzodiazepines in the clinical population

Case control-study:

- 55 patients using benzodiazepines  $\geq 6$  months for at least 3 times per week.
- 76 control participants.
- All participants completed neuropsychological test battery and on-the-road driving tests.

# Benzodiazepines in the clinical population

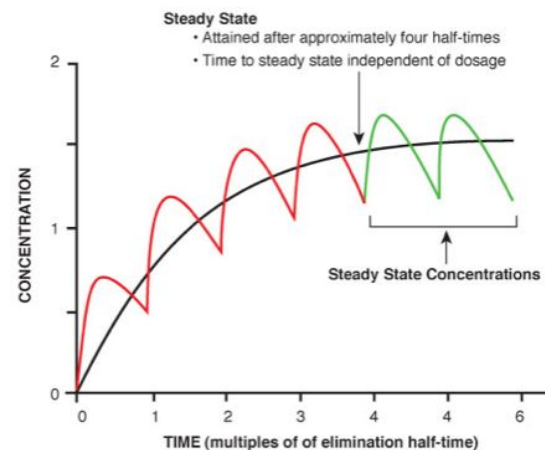
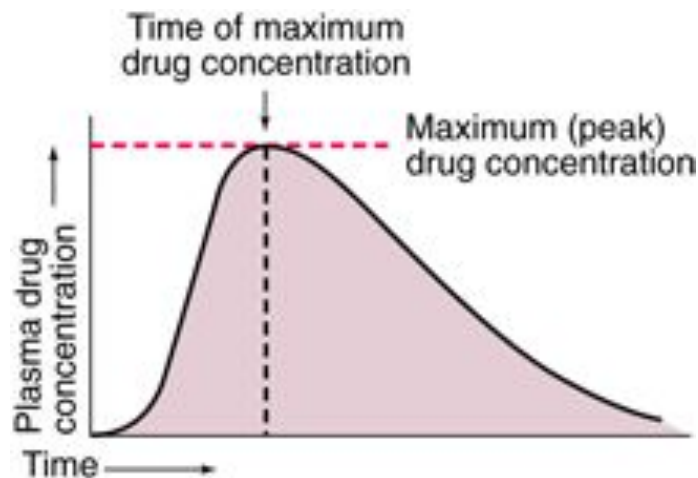
Quantifying treatment intensity:

Medication	Dose (mg)	Body weight	Time since last use	Frequency
Zolpidem	10	58	12	1/day
Oxazepam	30	110	14	1/day
Oxazepam	5	83	3	3/day
Lorazepam	1	76	10	1/day
Midazolam	15	67	12.5	1/day

- What is the plasma concentration at start of testing?
- What is the average plasma concentration over time?
- Are these concentrations (still) relevant (therapeutic/toxic range)?

# Benzodiazepines in the clinical population

Quantifying treatment intensity:



# Benzodiazepines in the clinical population

## Quantifying treatment intensity:

Concentration at start testing after multiple doses:

$$C_{ss}(t) = \frac{F * D * K_a}{V_d * (K_a - K_{el})} * \left( \frac{e^{-K_{el}*t}}{1 - e^{-K_{el}*\tau}} - \frac{e^{-K_a*t}}{1 - e^{-K_a*\tau}} \right)$$

- $C_{ss}(t)$  = concentration at time “t” after steady state has been reached
- F = Bioavailability
- D = dose
- $K_a$  = absorption rate constant
- $V_d$  = apparent volume of distribution
- $K_{el}$  = elimination rate constant
- $\tau$  = Administration interval

# Benzodiazepines in the clinical population

## Quantifying treatment intensity:

Average plasma concentration at steady state:

$$C_{ss}(\text{mean}) = \frac{F \cdot D}{CL \cdot \tau}$$

- $C_{ss}(\text{mean})$  = Average plasma concentration at steady state
- F = Bioavailability
- D = dose
- Cl = clearance rate
- $\tau$  = Administration interval



# Benzodiazepines in the clinical population

## Sample description:

	Control Participants	Patients (low)	Patients (high)
<b>N</b>	76	31	19
<b>Gender [F:M]</b>	35:41	19:12	9:10
<b>Mean age (SD)</b>	55.6 (12.7)	52.8 (12.0)	56.5 (11.4)
<b>Mean annual distance (SD)[km]</b>	13499 km (9276)	12798 km (8886)	15553 km (24189)
<b>Mean Equivalent plasma concentration (SD)[ng/ml]</b>	-	46.9 (57.3)	257.2 (574.1)
<b>Mean Equivalent steady state plasma concentration (SD) [ng/ml]</b>	-	46.7 (49.7)	245 (529.5)
<b>Duration of use[years]</b>	-	8.6 (8.4)	6.9 (7.0)
<b>CNS co-medications:</b>	-	23	15
TCA	-	3	4
SSRI/SNRI	-	13	9
Lithium	-	2	1
Antipsychotic	-	5	1
Opioid	-	4	1
Analgesic	-	3	4
Antiepileptic	-	2	-
Trazodone	-	1	-
Methylphenidate	-	-	-
Pramipexol	-	1	-
Melatonin	-	-	-
MAOI	-	1	-

# Benzodiazepines in the clinical population

## Tasks and outcome measures:

Task	Outcome measure	Factor loading	Principal component
Trailmaking	Part A: completion time	.802	<b>Higher order functioning</b>
	Part B: completion time	.879	
	Difference completion time part A & B	.727	
Digit symbol substitution test	Correct responses	-.733	
Determination test	Average reaction time	.727	
	Correct responses	-.704	
Highway driving test	Standard deviation of the lateral position	.338	<b>Low level functioning</b>
	Standard deviation of speed	.351	
Psychomotor vigilance test	Median reaction time	.721	
	Lapses (RT > 500ms)	.767	
Reaction test	Part 1: Average reaction time	.855	
	Part 2: Average reaction time	.781	
Reaction test	Part 3: Average reaction time	.637	<b>Go/no-go decision time</b>
Adaptive Tachistoscopic Traffic Perception Test	Response accuracy	.191	

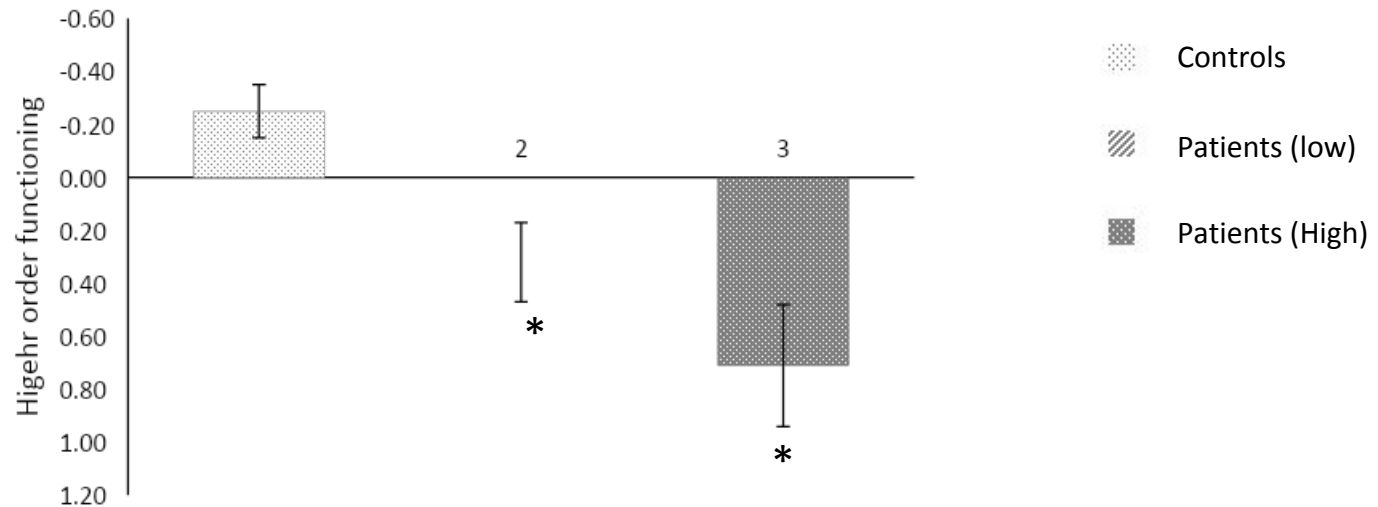
# Benzodiazepines in the clinical population

Tasks and outcome measures:

Complaint questionnaire	Factor loading
Beck's depression inventory	.840
State-trait anxiety inventory	.871
Pittsburgh sleep quality index	.882
Groningen sleep quality scale	.693

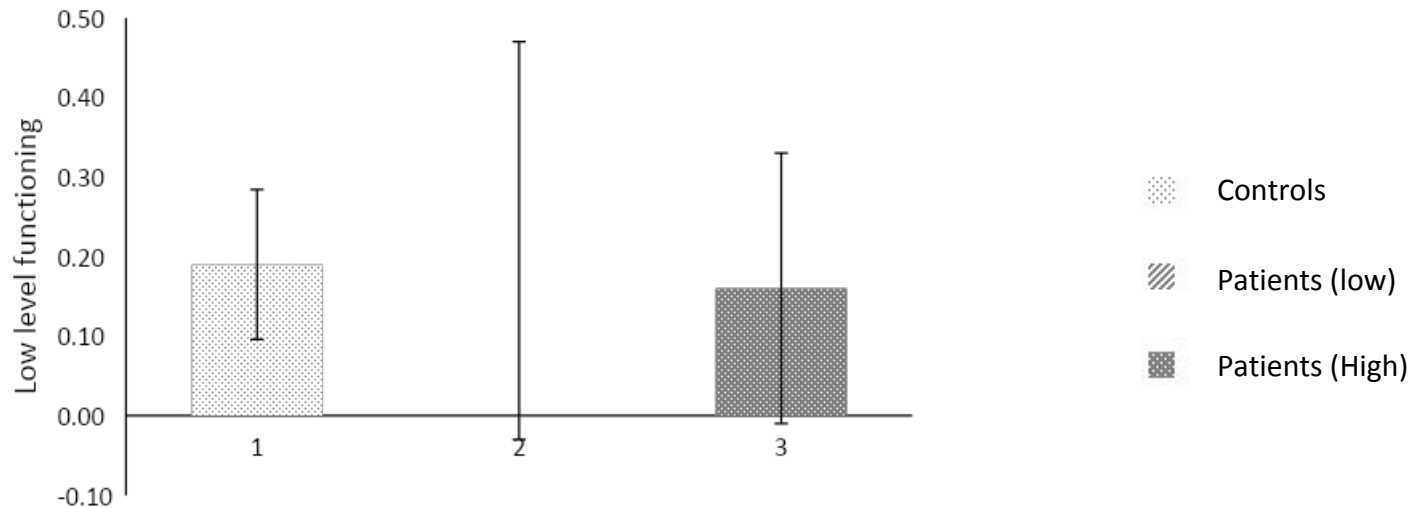
# Benzodiazepines in the clinical population

Results:



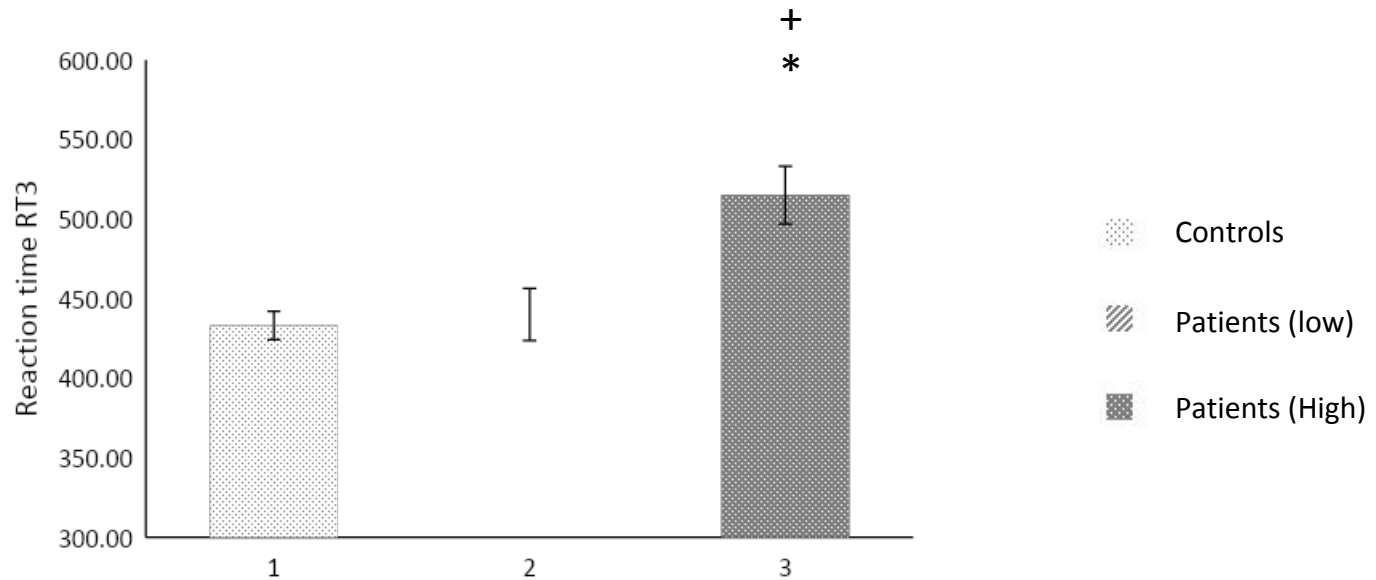
# Benzodiazepines in the clinical population

## Results:



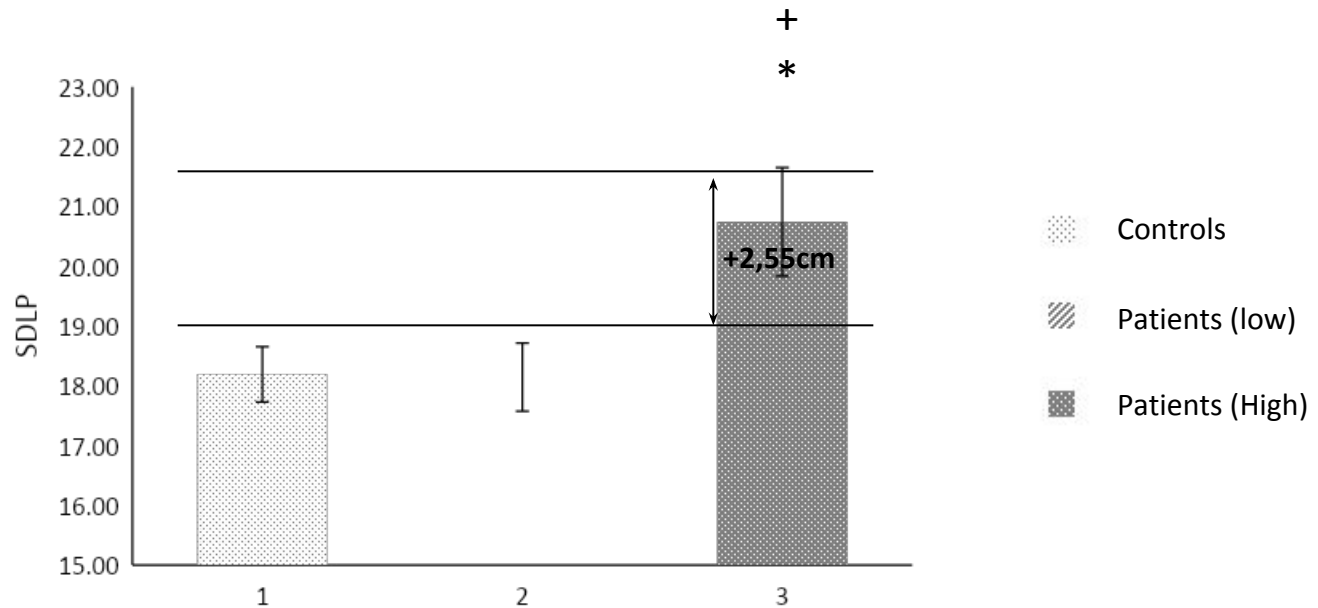
# Benzodiazepines in the clinical population

Results:



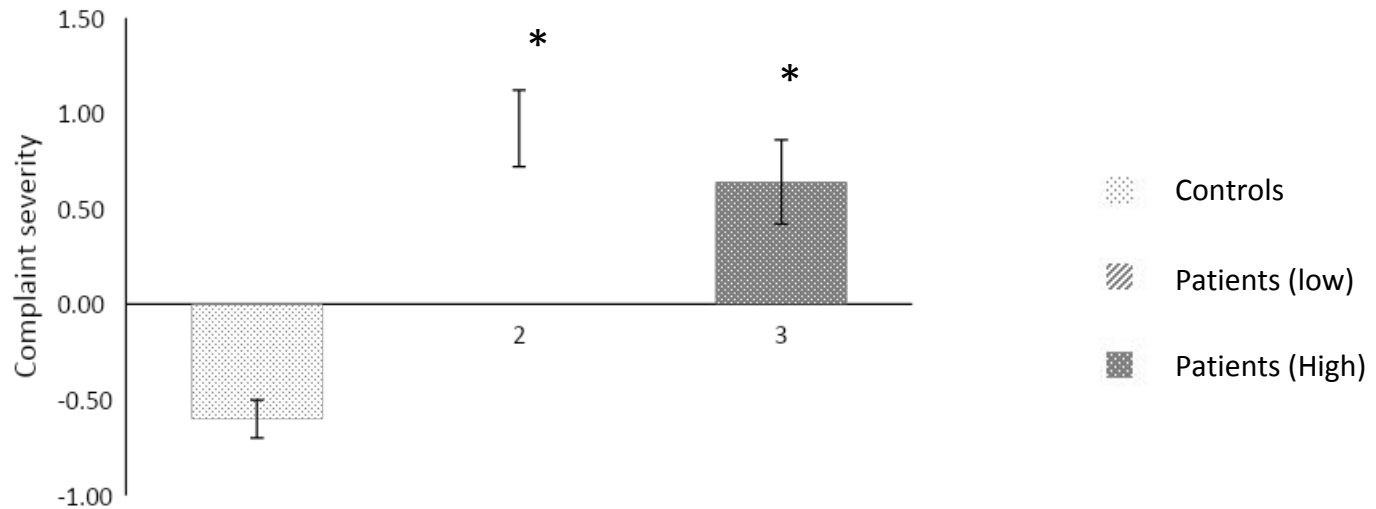
# Benzodiazepines in the clinical population

Results:



# Benzodiazepines in the clinical population

Results:





# Benzodiazepines in the clinical population

## Results and discussion:

- **Higher order functioning:**

- Controls > Patients
- Low dose = High dose

=> Clinical condition

=> Relevance: complex/stressful situations

- **Low level functioning:** Inconclusive

- **Go/No-go decision time:**

- Controls = low dose > high dose

=> Benzodiazepines

=> Relevance: Uncertain

- **SDLP:**

- Controls = Low dose < High dose
- High dose  $\geq$  BAC 0.5 g/L

=> Benzodiazepines

=> Relevance: Increased accident risk

# Benzodiazepines in the clinical population

## Limitations:

- Small sample size = low statistical power (.60)
  - No controlling for age
  - No controlling for duration of use
- No actual blood concentrations
- No controlling for co-medications (effects? Interactions?)

# Benzodiazepines in the clinical population

## Conclusions:

- Benzodiazepines still appear to significantly impair road tracking at therapeutic concentrations in long-term users.
- Clinical condition (anxiety) appears to affect complex decision making under pressure, hence might affect driving performance in complex or busy traffic situations.
- Future research recommendations:
  - Increase sample size
  - Blood samples
  - Include measure of task related stress

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