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

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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

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.

- Meds: Theophylline, Ventolin, Fluticasone, Atrovent, Norvasc, Lipitor, Altace, Plavix, Losec.

- 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
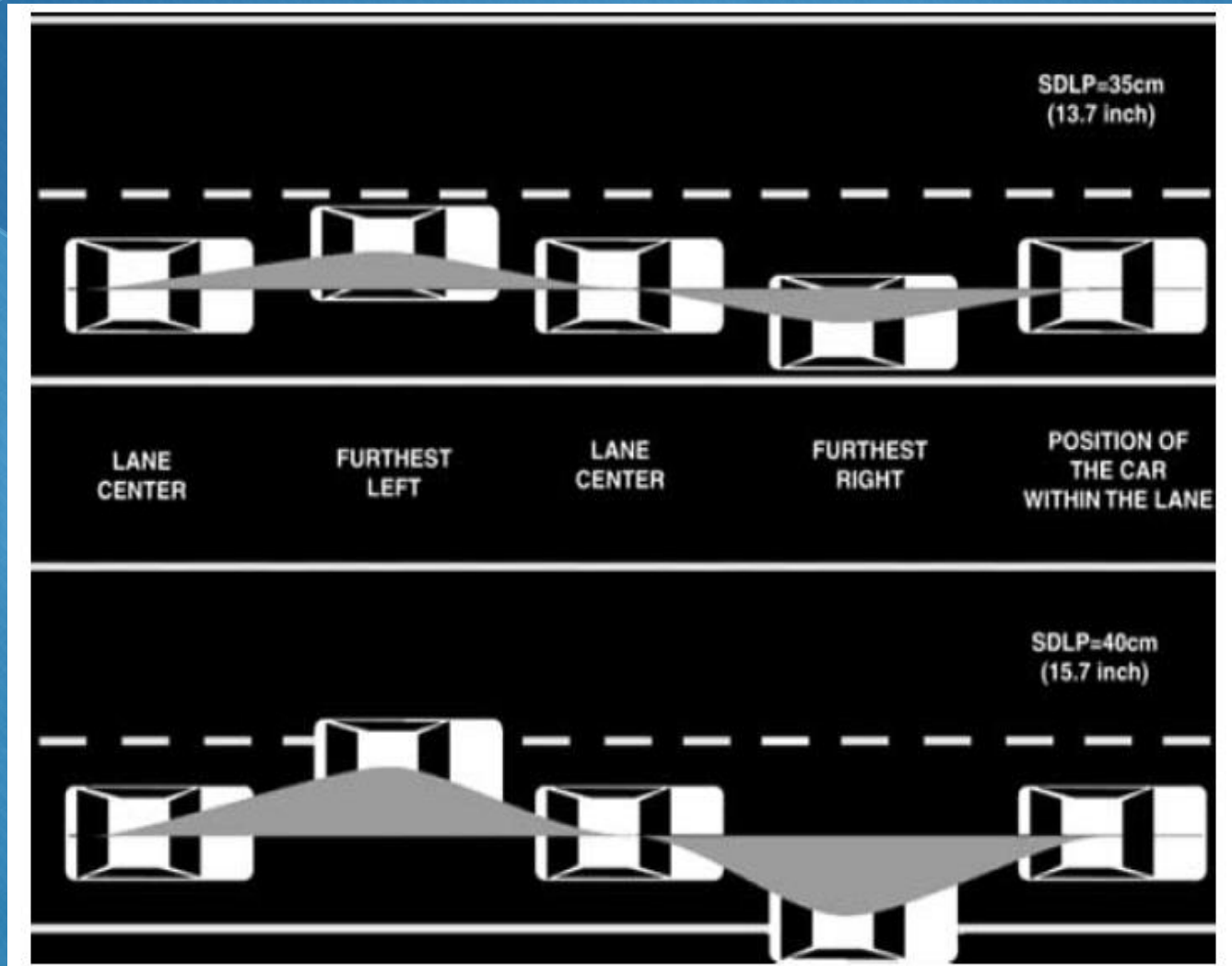
Verster, 05

On Road Studies – Verster, 05

Subjects	Design	Time[1]	Treatment	Day 1	Day 8
9 HV,m	C, Pc	1h, e	diazepam 5 mg	NS	------
			diazepam 10 mg	*	------
16 HV,b	C, Pc	1-2h,e	diazepam 5 mg tid	*	*
			ondansetron 1 mg bid	NS	NS
			ondansetron 4 mg bid	NS	NS
18 HV,b	C, Pc	2-3h,a	suriclone 0.2 mg tid	*	*
			lorazepam 0.5 mg tid	*	*
19 AO,b	B, Pg	3-4h,m	alpidem 50 mg bid	*	*
18 AO,b	B, Pg	3-4h,m	lorazepam 2 mg bid	*	*
12 AO,b	B, Pb	1-2h,e	diazepam 5 mg tid	*	*
			buspirone 5 mg tid	NS	NS
18 HV,m	C, Pc	3h,a	lorazepam 1.5 mg bid	-----	*
			ritanserin 5 mg bid	-----	NS
20 HV,b	C, Pc	1h	alprazolam 1 mg	*	-----
18 HV,m	C, Pc	10h[2]	oxazepam 50 mg	*	-----
17 HV,w	C, Pc	10h[2]	zolpidem 10 mg	NS	-----
30 HV,b	C, Pc	4h[6]	zolpidem 10 mg	*	-----
			zolpidem 20 mg	*	-----

Verster 04
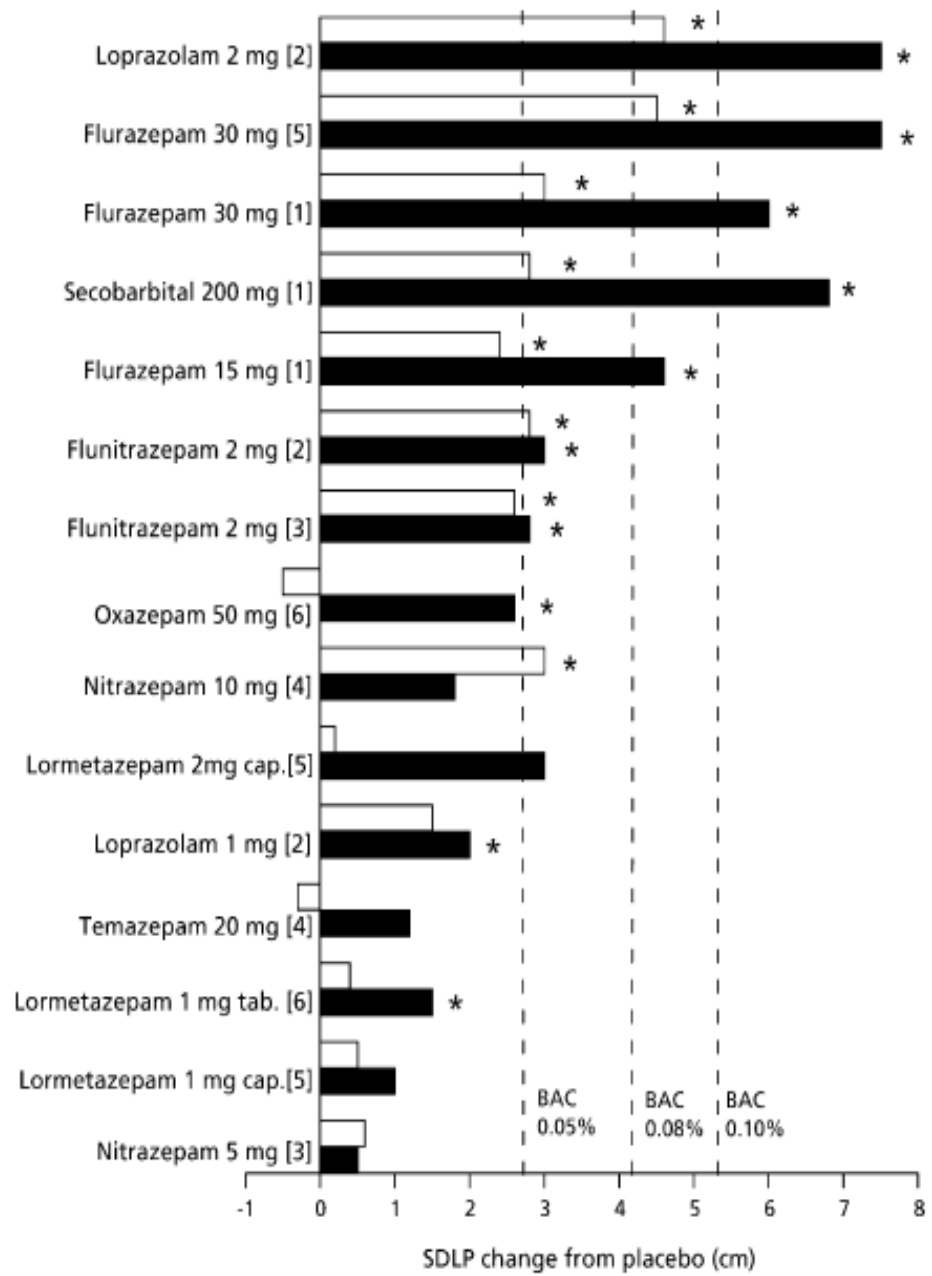
Meta-Analysis

- **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

Rapoport et al (2009) J Clin Psychiatry

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

Articles

404 studies obtained

376 studies excluded

28 studies included

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)

11 epidemiological

17 experimental

6 case-control studies

3 cohort studies

2 case-control culpability studies

9 computer-simulated driving tests

8 on road driving tests

Among the experimental driving studies, only 10 of 97 outcome variables were comparable.

Study design/Cases	Outcome variable	Drug
10 DB X-over/9 healthy	Tracking errors and severity	Diazepam 10mg hs; Testing 1.5 and 3 hrs post-dose
11 DB X-over/12 healthy	Tracking errors and severity	Diazepam 15mg; Testing 1 and 3.5 hrs post-dose
12 DB parallel/54 healthy, 6 per group	BRT (brake reaction time) Abs speed deviation	Diazepam 5, 10, 20mg; Chlorazepate 10, 20, 40mg ‖ 2 nights, testing 2hrs post-dose
13 DB Parallel/60 healthy male	BRT	Diazepam avg 7 or 14mg (1 dose) Testing shortly post-dose
14 DB X-over/18 healthy	BRT	Lormetazepam 1mg, Oxazepam 50mg 2 consec nights, testing 7 & 16hrs post-dose
15 DB parallel/70 drivers	# of collisions	Diazepam 25mg; Testing 30mins post-dose
16 DB X-over/19 women with insomnia	Deviation from instructed speed	Temazepam 20mg/Placebo (1 dose) Testing 5.5 hrs post-dose
17 DB X-over/23 patients with insomnia	Speed deviation, # of collisions	Lormetazepam 1mg/plcb; 1 & rpt'd doses Testing 9-11 hrs post-dose
18 DB X-over/12 anxious male patients	BRT	Chlorazepate 20mg hs x7d Testing on days 3, 10, 17; 8 hrs post-dose

Simulator Studies: Tracking Error Severity Index for Diazepam

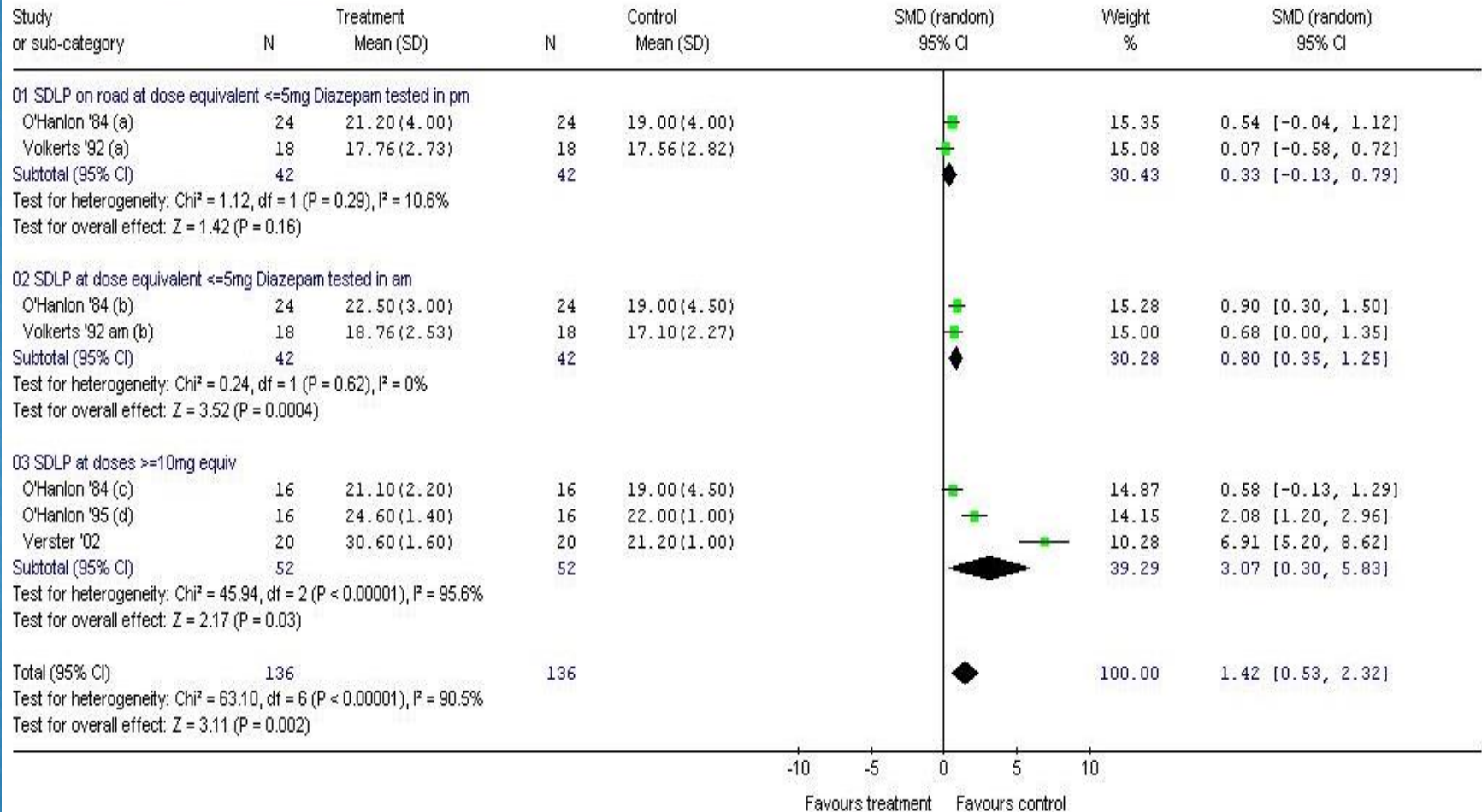| Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 Testing within 1.5 hours of dose							
Mattila '88 1.5hr	9	49.00 (10.00)	9	33.00 (4.00)		24.86	2.00 [0.82, 3.18]
Mattila '98 1 hr	12	35.00 (6.00)	12	15.00 (2.00)		22.26	4.32 [2.76, 5.88]
Subtotal (95% CI)	21		21			47.11	3.10 [0.83, 5.37]
Test for heterogeneity: Chi² = 5.39, df = 1 (P = 0.02), I² = 81.4%							
Test for overall effect: Z = 2.68 (P = 0.007)							
02 Testing at 3 or 3.5 hours post-dose							
Mattila '88 3hr	9	37.00 (9.00)	9	27.00 (4.00)		25.71	1.37 [0.31, 2.42]
Mattila '98 3.5 hr	12	15.00 (3.00)	12	14.00 (3.00)		27.18	0.32 [-0.48, 1.13]
Subtotal (95% CI)	21		21			52.89	0.79 [-0.23, 1.81]
Test for heterogeneity: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total (95% CI)	42		42			100.00	1.90 [0.42, 3.38]
Test for heterogeneity: Chi² = 21.34, df = 3 (P < 0.0001), I² = 85.9%							
Test for overall effect: Z = 2.52 (P = 0.01)							

-10   -5   0   5   10
Favours treatment   Favours control

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

Study design/Cases	Outcome variable	Drug
19 DB X-over/ 20 healthy	SDLP (Std Dvtn Ltr Pstn) Speed Deviation	Alprazolam 1mg; 1 dose Testing 1 hr post-dose
20 DB X-over/ 18 healthy	SDLP	Lormetazepam 1mg; Oxazepam 50mg 2 nights, testing 7 & 16 hrs post-dose
21 DB X-over/ 16 healthy	SDLP	Diazepam 5mg TID x8d (Lorazepam 0.5mg TID separate n=19) ‖ testing 1-2hrs post-dose on days 1 and 8
22 DB X-over/10 healthy F cntrl	BRT	Lormetazepam 1mg; Triazolam 0.25mg; Flunitrazepam 1mg; hs; 1 dose ‖ testing 10hrs post-dose
23 DB X-over/8 healthy F cntrl	BRT	Midazolam 15mg, one dose Testing 10 hrs post-dose
24 DB X-over/14 anxious pts	BRT	Medazepam avg 16.5mg x3wks, Testing at various times post-dose
25 DB parallel /24 GAD pts	Speed Deviation	Diazepam 5mg TID x4wks (1wk plcb lead-in) ‖ Testing 1.5hrs post-dose
26 DB X-over/24 F former hypnotic drug users	SDLP	Flurazepam 15mg and 30mg hs ‖ 2 nights; testing 10-11 hrs and 16-17 hrs post-dose

On Road Studies: Standard Deviation of Lateral Position

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 SDLP on road at dose equivalent <=5mg Diazepam tested in pm							
O'Hanlon '84 (a)	24	21.20(4.00)	24	19.00(4.00)		15.35	0.54 [-0.04, 1.12]
Volkerts '92 (a)	18	17.76(2.73)	18	17.56(2.82)		15.08	0.07 [-0.58, 0.72]
Subtotal (95% CI)	42		42			30.43	0.33 [-0.13, 0.79]
Test for heterogeneity: Chi² = 1.12, df = 1 (P = 0.29), I² = 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)	24	19.00(4.50)		15.28	0.90 [0.30, 1.50]
Volkerts '92 am (b)	18	18.76(2.53)	18	17.10(2.27)		15.00	0.68 [0.00, 1.35]
Subtotal (95% CI)	42		42			30.28	0.80 [0.35, 1.25]
Test for heterogeneity: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%							
Test for overall effect: Z = 3.52 (P = 0.0004)							
03 SDLP at doses >=10mg equiv							
O'Hanlon '84 (c)	16	21.10(2.20)	16	19.00(4.50)		14.87	0.58 [-0.13, 1.29]
O'Hanlon '95 (d)	16	24.60(1.40)	16	22.00(1.00)		14.15	2.08 [1.20, 2.96]
Verster '02	20	30.60(1.60)	20	21.20(1.00)		10.28	6.91 [5.20, 8.62]
Subtotal (95% CI)	52		52			39.29	3.07 [0.30, 5.83]
Test for heterogeneity: Chi² = 45.94, df = 2 (P < 0.00001), I² = 95.6%							
Test for overall effect: Z = 2.17 (P = 0.03)							
Total (95% CI)	136		136			100.00	1.42 [0.53, 2.32]
Test for heterogeneity: Chi² = 63.10, df = 6 (P < 0.00001), I² = 90.5%							
Test for overall effect: Z = 3.11 (P = 0.002)							

-10   -5   0   5   10

Favours treatment   Favours control

Other On-Road Driving Variables:

-3 studies of BRT – homogeneous, no effect.

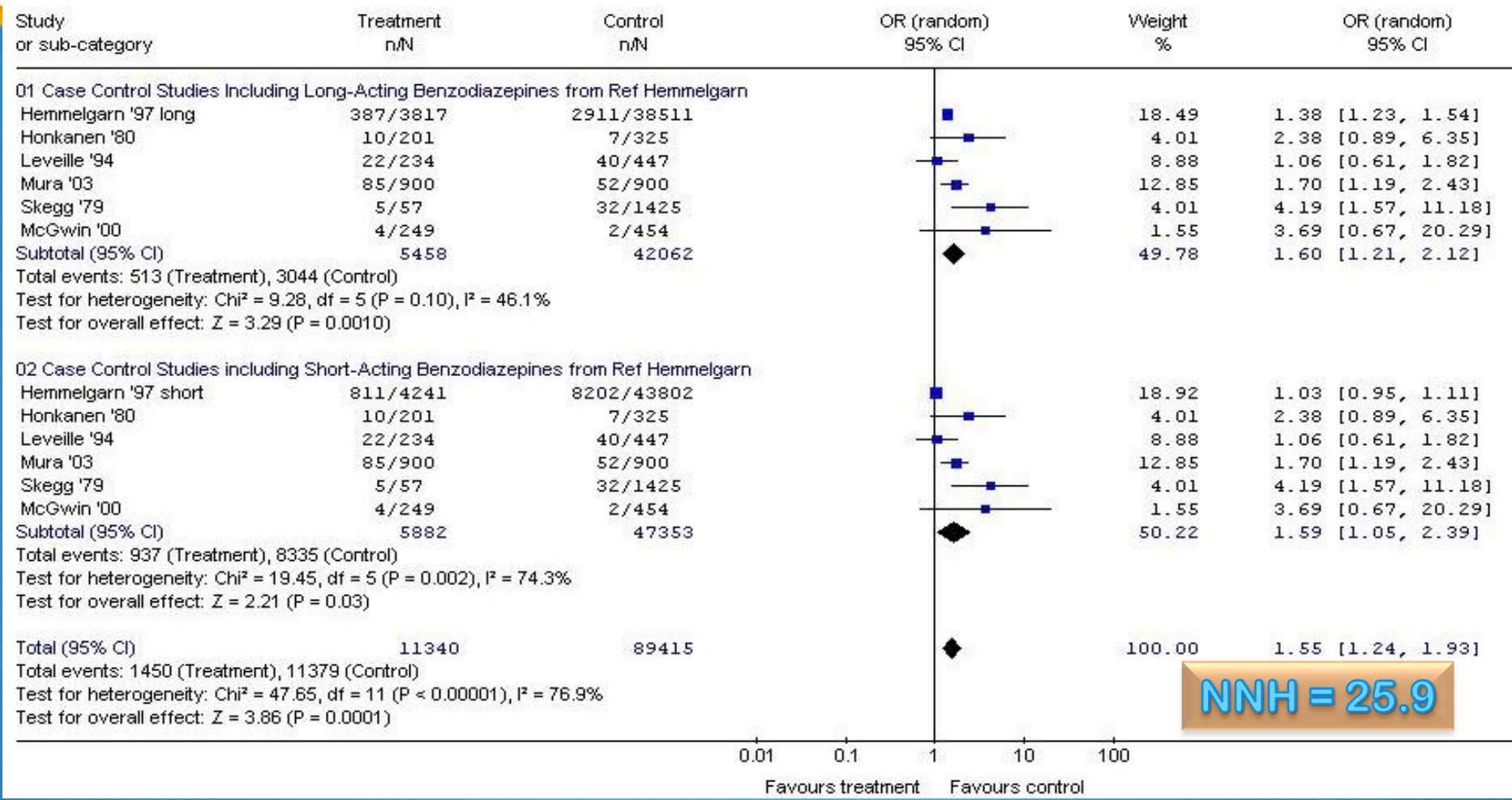-2 studies of mean speed, deviation from instructed speed

  - heterogeneous

Case Control Studies (n=6)

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

*"minor tranquilizers" ("e.g. Benzodiazepines")

Rapoport et al, 2009, J Clin Psych

Case control Studies: Benzodiazepines and MVCs

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Case Control Studies Including Long-Acting Benzodiazepines from Ref Hemmelgarn					
Hemmelgarn '97 long	387/3817	2911/38511		18.49	1.38 [1.23, 1.54]
Honkanen '80	10/201	7/325		4.01	2.38 [0.89, 6.35]
Leveille '94	22/234	40/447		8.88	1.06 [0.61, 1.82]
Mura '03	85/900	52/900		12.85	1.70 [1.19, 2.43]
Skegg '79	5/57	32/1425		4.01	4.19 [1.57, 11.18]
McGwin '00	4/249	2/454		1.55	3.69 [0.67, 20.29]
Subtotal (95% CI)	5458	42062		49.78	1.60 [1.21, 2.12]

Total events: 513 (Treatment), 3044 (Control)
Test for heterogeneity: Chi² = 9.28, df = 5 (P = 0.10), I² = 46.1%
Test for overall effect: Z = 3.29 (P = 0.0010)

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
02 Case Control Studies including Short-Acting Benzodiazepines from Ref Hemmelgarn					
Hemmelgarn '97 short	811/4241	8202/43802		18.92	1.03 [0.95, 1.11]
Honkanen '80	10/201	7/325		4.01	2.38 [0.89, 6.35]
Leveille '94	22/234	40/447		8.88	1.06 [0.61, 1.82]
Mura '03	85/900	52/900		12.85	1.70 [1.19, 2.43]
Skegg '79	5/57	32/1425		4.01	4.19 [1.57, 11.18]
McGwin '00	4/249	2/454		1.55	3.69 [0.67, 20.29]
Subtotal (95% CI)	5882	47353		50.22	1.59 [1.05, 2.39]

Total events: 937 (Treatment), 8335 (Control)
Test for heterogeneity: Chi² = 19.45, df = 5 (P = 0.002), I² = 74.3%
Test for overall effect: Z = 2.21 (P = 0.03)

| Total (95% CI) | 11340 | 89415 | | 100.00 | 1.55 [1.24, 1.93] |

Total events: 1450 (Treatment), 11379 (Control)
Test for heterogeneity: Chi² = 47.65, df = 11 (P < 0.00001), I² = 76.9%
Test for overall effect: Z = 3.86 (P = 0.0001)

NNH = 25.9

0.01 0.1 1 10 100
Favours treatment   Favours control

- Subgroup of older adults: OR1.36 (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

Regulatory Perspective

US: FDA 2007

○ **Requested all hypnosedative manufactuers 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
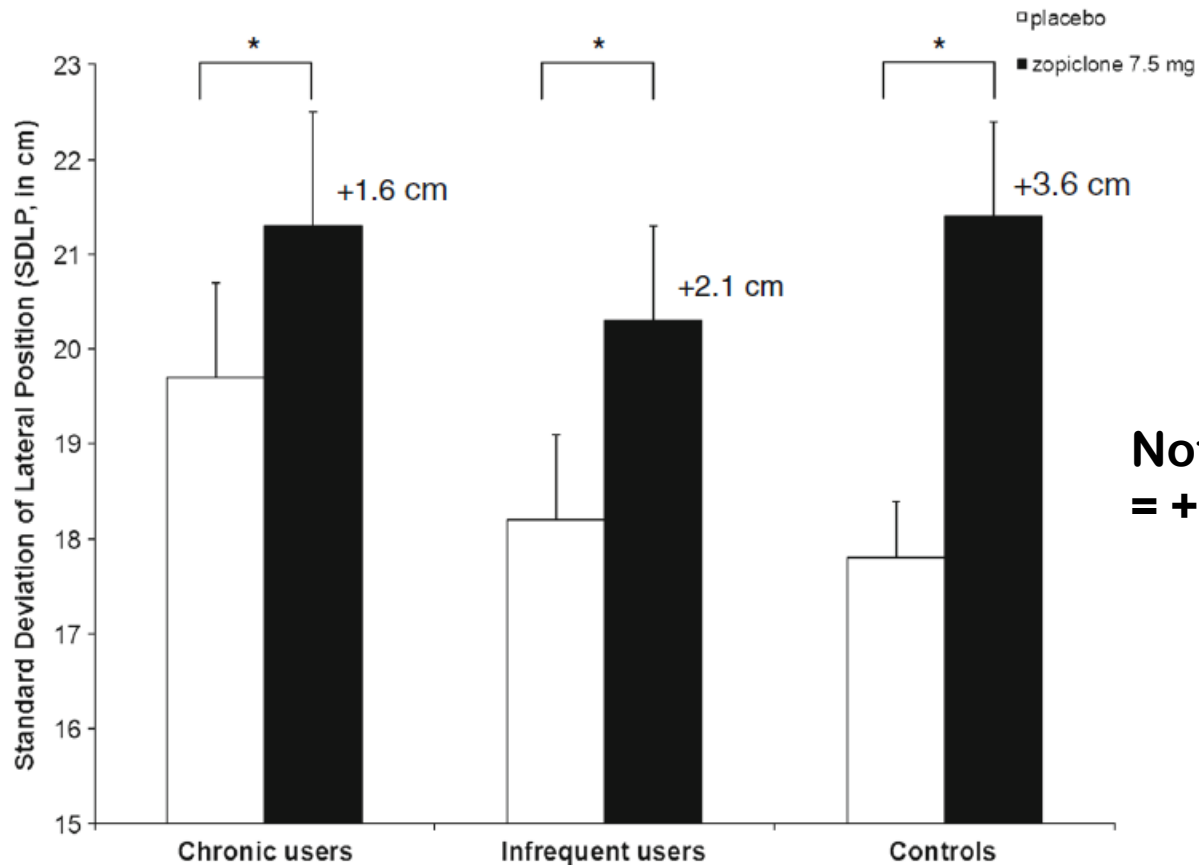
Zolpidem

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 30-240days and >360 days
        post prescription

*Gibson et al, Am J Epidemiology 2009; Orriols et al, Clin Pharm Ther 2011;
Yang et al, J Epidemiology 2011; Gustavsen et al, Sleep Medicine 2008;
Hansen et al Am J Public Health 2015.*

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
Orriiols et al Clin Pharm and Ther 2011
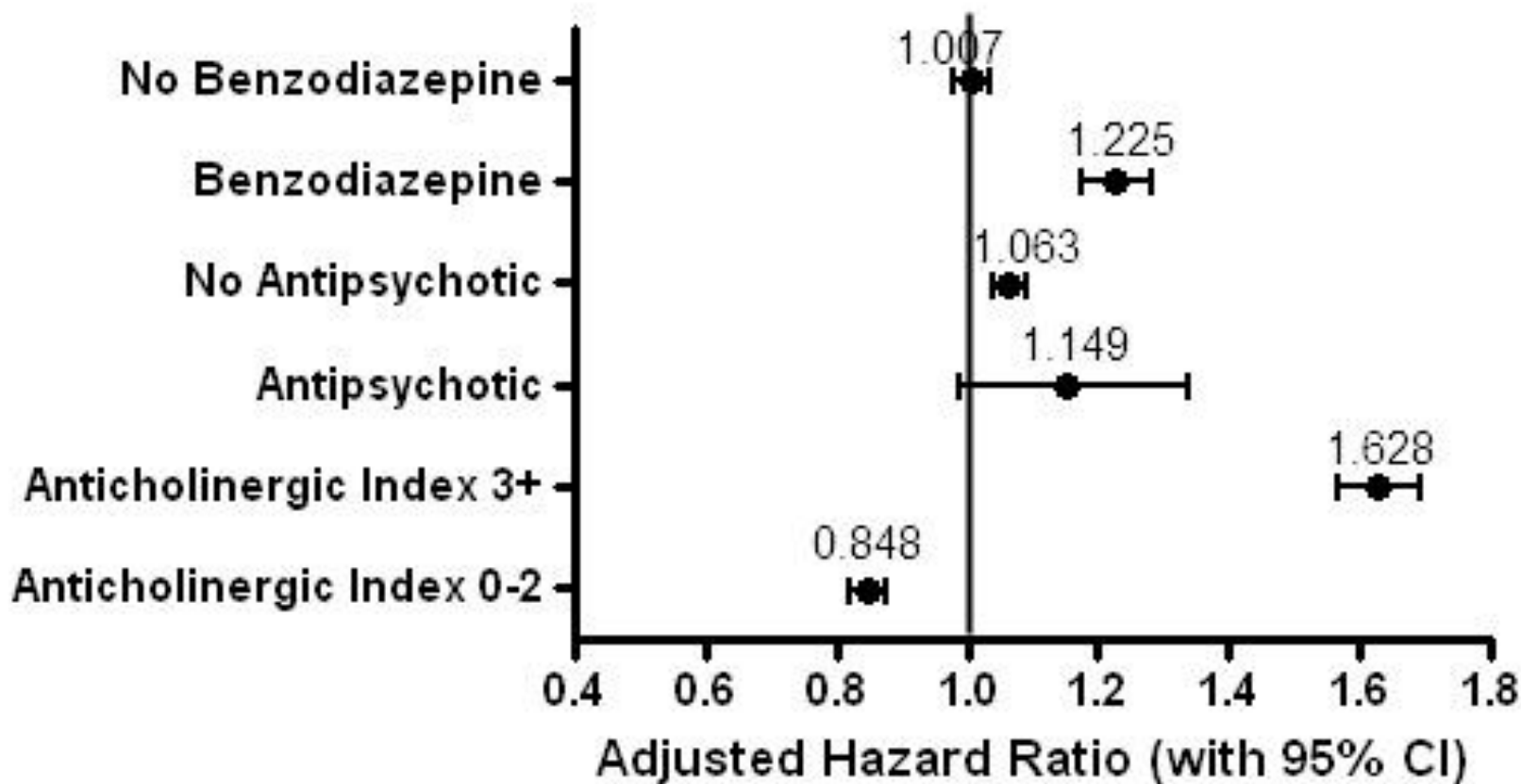*Yang et al J Epidem 2011*

Clinical reasons for heterogeneous response

Antidepressants

Risk of exposure to medication in the month prior to crash

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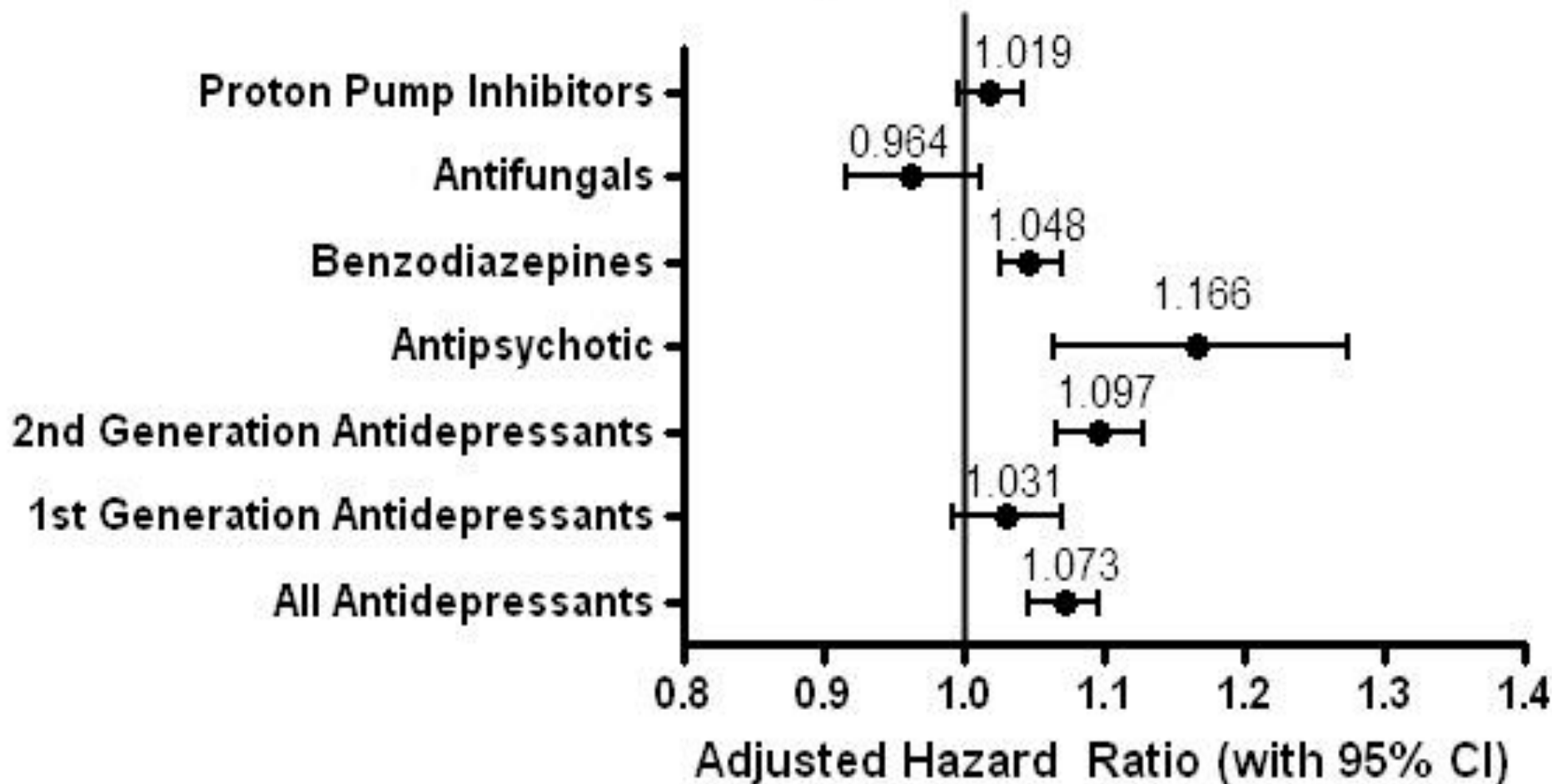
Crash risk stratified by concomitant medications

Other Epidemiological Studies of Antidepressants and MVC in Older Adults

Study/Design	Findings
Meuleners et al. 2011 JAGS Case-crossover, 60+	OR 1.8 MVC requiring hospitalization
Rapoport et al 2008 JAGS Case Crossover, 66+	Dementia 66 years plus OR 1.5 2nd generation > 1st generation.
Coupland et al. 2011. BMJ. Cohort study, 65+	Depression 65 years plus. NS for any class
Hu et al. 1998. AAP. Case-only Panel Analysis, 65+	OR 2.04 males only

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, flurazaepam, 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.

Drug Class	OR (95% CI)
Barbiturates	7.50 (2.35, 23.91)
Antihistamines	3.00 (1.05, 8.55)
Non-narcotic antitussives	2.23 (1.30, 3.82)
Narcotic analgesics	2.22 (1.98, 2.49)
Antipsychotics	2.20 (1.37, 3.52)
Skeletal muscle relaxants	2.09 (1.71, 2.55)
Anti-anxiety drugs (Benzodiazepine)	2.00 (1.72, 2.31)
Anticonvulsants	1.97 (1.64, 2.38)
SARIs	1.90 (1.49, 2.44)
Belladona Alkaloids	1.85 (1.08, 3.19)
Insulins	1.80 (1.45, 2.22)
Hypotensives, sympatholytic	1.79 (1.17, 2.74)
SNRI	1.78 (1.19, 2.66)
Platelet aggregation inhibitors	1.69 (1.17, 2.43)
Anti-emetic/anti-vertigo	1.63 (1.17, 2.28)

Top 15

LeRoy, AA.; Morse, ML. Department of Transportation. HS 810 858. Multiple medications and vehicle crashes: analysis of databases. 2008.

Disease Groups	Odds Ratio with 95% C.I.	
HEAD TRAUMA	36.00 (11.09, 116.90)	
ACIDOSIS	15.00 (1.75, 128.40)	
NEUROTIC DISORDER	12.00 (1.34, 107.37)	
DELIRIUM, ACUTE	10.50 (2.18, 50.55)	
CONSCIOUSNESS ALTERATION	9.00 (2.90, 27.91)	
PERSONALITY DISORDERS	9.00 (1.82, 44.59)	
HEMORRHAGE, UNSPEC	6.00 (1.10, 32.76)	
ALCOHOLISM	5.44 (2.95, 10.01)	
DIABETIC KETOACIDOSIS	5.40 (1.81, 16.11)	
STRESS DISORDERS	5.40 (1.81, 16.11)	
VISUAL DISTURBANCES	4.71 (1.83, 12.16)	
DEPRESSION	3.99 (3.19, 4.99)	
PSYCHIATRIC DISORDERS	3.72 (2.99, 4.63)	
PLEURAL EFFUSION	3.69 (1.78, 7.68)	
EXTRAPYRAMIDAL REACTIONS	3.60 (1.56, 8.33)	

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Simulators

- Furlan et al, work in progress

- Last 10 years: 30 simulator psychotropic stuides.

- Small samples, various simulators and outcome measures, times-post-dose, few with sample size calculations or age/gender adjustments

Limitations

Meds vs Sx (Indication and Channeling)
Dementia or Cog Impairment
Suicide

Dose-Response
Acute Exposure
Classes vs Drugs
Adherence

Timing of the Drug, Onset, Route, Kinetic/ dynamic, other drugs

Age
Sex/Gender
Health Status
Tolerance

Driving Exposure and Other Unmeasured Confounds

Thank you