Do minor tranquilisers (benzodiazepines) increase risk of collision in which the driver is injured?

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ABSTRACT

Drivers taken to hospital in Victoria after a collision must provide blood for analysis for the proscribed drugs (cannabis, MDMA, methamphetamine). A longitudinal study is examining a range of other substances including benzodiazepines, opiates, and other psychotropic medication and matching toxicology results to police collision reports. Each driver is assigned a degree of responsibility according to the method of Robertson. If a substance causes impairment, then drivers in whom the substance is found are likely to be "responsible" for the collision than those who are drug or alcohol free.

1802 samples have been analysed to date. Of the alcohol-positive drivers, 96% were responsible for their collision.

This paper focuses on the benzodiazepine tranquilisers. Benzodiazepines were detected in 10.2% of samples (n=184). Preliminary evidence suggests there is a dose relationship with small increase in collision risk at therapeutic levels and high risk at toxic levels. Abuse of prescription drugs is a road safety issue worthy of specific study and targeted interventions.

The combination of benzodiazepines and alcohol was associated with increased responsibility for collision even when the prescribed drugs were present at therapeutic levels. Combining drugs increased the likelihood of responsibility for collision;

- drug-free drivers - 45% were responsible,
- with 1-2 drugs - 80% were responsible,
- with 3 drugs - 94% were responsible and
- with 4+ drugs - 96% were responsible.

It is now possible to test for benzodiazepines at the roadside. An enforcement measure that may improve road safety would be to adopt zero tolerance for alcohol when benzodiazepines are prescribed. The ongoing study will continue to examine dose relationships and specific drug interactions, which will inform development of targeted counter-measures.

KEYWORDS: Benzodiazepines, drugs, alcohol, collision, responsibility analysis, injury, driver.

INTRODUCTION

Road safety strategies often focus on the road toll because toxicology has traditionally been available for all deceased drivers and the collisions are often thoroughly investigated by specialist investigators. For every fatality there are 25 collisions in which road users are seriously injured with devastating effects for communities and very substantial economic costs. Coronial data indicates that 25% of fatal collisions are related to driving under the influence of alcohol and 32% of deceased drivers test positive for other drugs that can cause impairment. Whilst good evidence exists associating various drug classes with responsibility for fatal collision, there has been little data linking drug use with non-fatal collisions.

Benzodiazepines

The benzodiazepine family of minor tranquillisers, sedatives, anticonvulsants and hypnotics have largely taken the place of the barbiturates in the treatment of anxiety and insomnia because of their safety and efficacy. Representative members of the group are diazepam (Valium, Ducene), oxazepam (Serepax), nitrazepam (Mogadon) and flunitrazepam (Rohypnol).

The benzodiazepines act to depress the central nervous system in qualitatively different ways. Some are better at relieving anxiety and are classified as tranquillisers. Others are more sedating and used to treat insomnia. Some members of the group are primarily used as anticonvulsants. There is no sharp distinction between any of these effects and higher doses of any of the benzodiazepines induce sedation and coma. There is a twentyfold variation in dose equivalence.

Name	Duration of action	Dose equivalent	Trade names in Australia
Alprazolam	short	0.5 – 1 mg	Alprax, Kalma, Xanax, Zamhexal
Bromazepam	intermediate	3 – 6 mg	Lexotan
Clobazam	intermediate	10 – 15 mg	Frisium
Clonazepam	long	0.25 – 0.5 mg	Rivotril
Diazepam	long	5 mg	Antenex, Ducene, Ranzepam, Valium, Valpam
Flunitrazepam	intermediate	1 – 2 mg	Hypnodorm
Lorazepam	intermediate	0.5 – 1 mg	Ativan
Nitrazepam	long	5	Alodorm, Mogadon
Oxazepam	short	15 – 30 mg	Alepam, Murelax, Serepax
Temazepam	Short	10 – 20 mg	Normison, Temaze, Temtabs
Triazolam	very short	0.25 mg	Halcion

Different benzodiazepines have different abuse potential; the more rapid the absorption, the greater the intoxicating effect and the more open to abuse the drug becomes. The speed of onset of action of a particular benzo correlates well with the ‘popularity’ of that drug for abuse. The two most common reasons for preference for abuse are that a benzodiazepine is ‘strong’ and that gives a good ‘high’.

METHOD

The *Road Safety Act Victoria (1986)* requires a person over the age of 15 years, who is taken to hospital following a motor vehicle collision, to furnish a blood sample for analysis. The sample is divided into three aliquots: a 'screening' sample, a 'patient' sample which is given to the patient and an 'evidential' sample which is stored and transported subject maintaining continuity. The screening sample was subject to further analysis for this study.

The Act proscribes driving with a blood alcohol concentration >0.00% or >0.05% depending on licence status. Delta-9-tetrahydrocannabinol, methamphetamine and methylene-dioxy-methamphetamine (MDMA) are proscribed at any concentration.

The first 936 samples were screened by Victorian Forensic Sciences Centre (VFSC). Subsequent blood samples (n=1801) were screened at the Victorian Institute of Forensic Medicine (VIFM). Both services are accredited by the National Association of Testing Authorities (NATA) in the provision of Toxicology for Forensic Science (ISO/IEC 17025:2005). 935 samples were excluded from the study because the sample was not from an injured driver: e.g. blood taken from passengers when the identity of the driver was uncertain, non-injured drivers requesting blood samples after breath analysis, or where the collision was on private property.

Under the *Road Safety Act,* the practitioner taking the blood sample completes a certificate bearing a unique Certificate Number that is the only identifier for toxicology processing, ensuring confidentiality of the drivers' details. The results are returned to Victoria Police where the Certificate Number is matched to a collision report.

Responsibility Analysis

Analysis of responsibility for collision was carried out using the method developed Robertson and Drummer (1994). A value between 1 and 4 is assigned to eight factors which might explain the collision: road condition, vehicle condition, driving conditions, collision type, witness observations, compliance with road laws, task difficulty and level of driver fatigue (see Appendix 1 for scoring guidelines). The higher the value given, the more the extenuating factor is likely to have contributed to the collision. A driver with a low aggregate low score (score <13) is judged to be 'responsible' for the collision, a driver with a mid-range score (≥13 and ≤15) is defined as 'contributing' to the collision, and a driver with a high score (15 and above) is defined as 'not responsible' for the collision. Responsibility analysis was carried out blinded to knowledge of the toxicology to avoid expectant bias.

The study initially encountered a bias in sample selection by hospital practitioners. In 1990 the focus of road safety interventions was on alcohol. Victoria Police and emergency physicians agreed that doctors could perform preliminary breath tests (PBT) on patients to determine the need for a blood sample. If the patient returned a negative PBT they were not required to furnish a sample, unless there was a clinical reason to suspect drug use. Victoria Police formally requested hospitals and members of the College of Emergency Medicine to stop using preliminary tests, allowing more alcohol-negative samples to be available for drug analysis. Since the request was made, compliance has been rising steadily, resulting in a growing

proportion of alcohol negative drivers in each batch of results made available and a more reliable control sample.

Table 1: Proportion of samples received that had a blood alcohol concentration of 0.000%

	1st 450 samples		2nd 450 samples		3rd 450 samples		4th 450 samples	
Alcohol Negative	274	60.1%	330	73.3%	337	74.9%	351	78.0%

The control sample (50.3% of the total) was the group of drivers in whom no impairing drugs or alcohol was detected. The odds ratio for the control group being responsible for the collision was defined as 1. Cases in which the driver "contributed" to the collision (n=237) were excluded from final analysis.

RESULTS

The toxicology results from two thousand seven hundred and thirty seven drivers were received by the project team during the period 2009-2011. 1802 were included in this analysis. Samples were excluded in the following circumstances:

- if sample was not from a driver (i.e. if it were from a pedestrian or passenger),
- if the driver had not been injured in the collision,
- if the driver had attempted suicide by driving,
- if the driver had died within 30 days due to injuries sustained in the collision, or
- there was insufficient data in the collision report to analyse responsibility.

Demographics

Injured drivers were 62.8% male with a mean age of 36.8 years (range 14-91).

Chart 1: % of total drivers in each age range

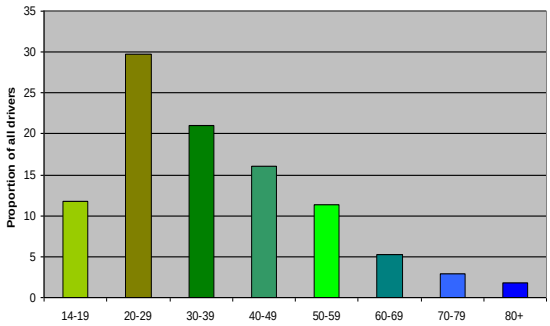
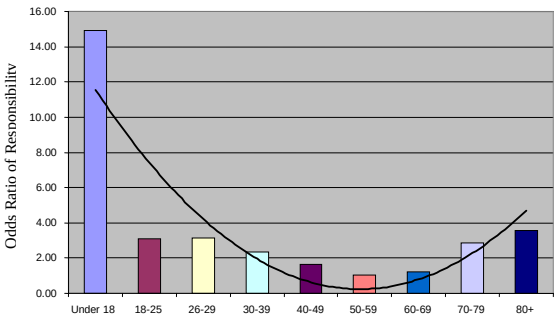


Chart 2: Risk associated with drivers of each age range



There were 40 drivers (8 female) below the legal driving age of 18 years; 12 were drugs and alcohol free. Twenty six (65%) of the underage drivers had a blood alcohol concentration (BAC) between 0.011% and 0.198% (mean of 0.091%). Other drugs detected in the underage drivers include stimulants (n=4), benzodiazepines (n=1), delta-9-tetrahydrocannabinol (n=7) and antidepressants (n=1). Ketamine was detected in one 15 year old male driver in association with a blood alcohol concentration of 0.099%.

The results for the whole group are summarised in table 2.

Table 2: Summary of responsibility level by driver group

Group	Responsibility Analysis			Total	Culpability Ratio	Odds Ratio	95% CI
	Responsible	Contributory	Not Resp.				
Control (drug & alc. free)	412	163	332	907	1.24	1.00	0.82 - 1.23
Drug and/or alcohol pos.	731	74	90	895	8.12	6.55	5.04 - 8.51
Drug positive/alcohol neg.	244	56	87	387	2.80	2.26	1.70 - 3.00
Drug positive/alcohol pos.	237	10	2	249	118.50	95.49	23.57 - 386.93
Drug negative/alcohol pos.	250	8	1	259	250.00	201.46	28.12 - 1443.42
Stimulants alone	25	2	4	31	6.25	5.04	1.74 - 14.62
Stimulants alone/in comb.	92	5	7	104	13.14	10.59	4.85 - 23.15
Single benzo only	19	3	6	28	3.17	2.55	1.01 - 6.46
Benzodiazepines alone	23	3	6	32	3.83	3.09	1.24 - 7.67
Benzos alone/in comb.	154	16	14	184	11.00	8.86	5.03 - 15.61
THC alone	24	8	11	43	2.18	1.76	0.85 - 3.64
THC alone/in comb.	173	22	14	209	12.36	9.96	5.67 - 17.49
Opiates alone	54	15	38	107	1.42	1.15	0.74 - 1.78
Opiates alone/in comb.	159	30	50	209	3.18	2.56	1.81 - 3.63
Ketamine alone/in comb.	13	1	3	17	4.33	3.49	0.99 - 12.36
Antidepressants alone	20	8	11	39	1.82	1.47	0.69 - 3.10
Antidep's alone/in comb.	89	13	16	118	5.56	4.48	2.58 - 7.78
Antipsychotics alone	1	0	1	2	1.00	0.81	0.05 - 12.93
Antipsych's alone/comb.	14	4	2	20	7.00	5.64	1.27 - 24.99

There have been other studies of drug prevalence in Victoria (Longo 2000, Ch'ng 2007, Drummer 2004) which showed a similar prevalence of drivers injures or killed where benzodiazepines were identified as the only drug present.

Drug prevalence

Table 3: Comparison of results from similar studies

	Longo et al. (n=2500)	Ch'ng et al. (n=436)	Drummer et. al.(n=3398)	Current Study (n=1802)
Drug and Alcohol Neg	77.4%		50.1%	50.3% (n=907)
Alcohol Positive	12.4%		23.2%	28.2% (n=508)
Stimulants only	0.8%	4.1% (alone/in comb.)	1.6%	1.7% (n=31)
Benzodiazepines only	1.8%	15.6% (alone/in comb.)	1%	1.8% (n=32)
Cannabinoids only	7.1%	4.6% (Δ9-THC only)	1.7%	2.4% (n=43)

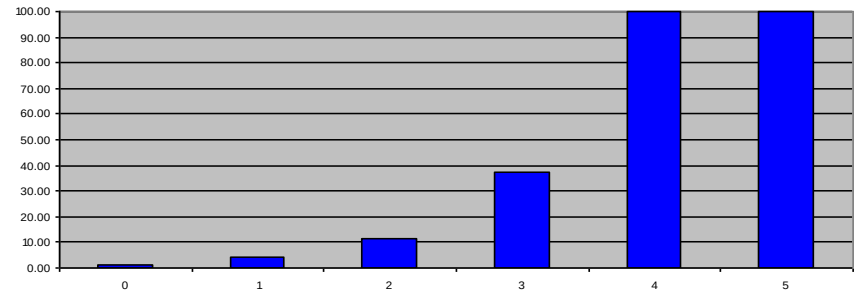
It is important to identify drivers in whom a single substance was present to understand the contribution of that substance to collision risk. The interaction of the variable is so complex that when 4 or more drugs are present *every* driver is culpable (Chart 3, Table 4). Variable interactions will be studied further as data accumulates.

Drugs in combination

Table 4: Culpability ratio (drivers responsible to those not responsible), odds ratios and 95% confidence limits relating to number of substances present in sample.

Drugs Present*	Total	Responsible	Contributory	Not Resp.	Culpability Ratio	OR	95% CI
0	907	412	163	332	1.24	1.00	0.82 - 1.23
1	525	407	45	73	5.58	4.49	3.37 - 5.99
2	252	213	24	15	14.20	11.44	6.65 - 19.70
3	93	87	4	2	43.50	37.47	9.17 - 153.20
4	24	23	1	0	--	--	--
5	1	1	0	0	--	--	--

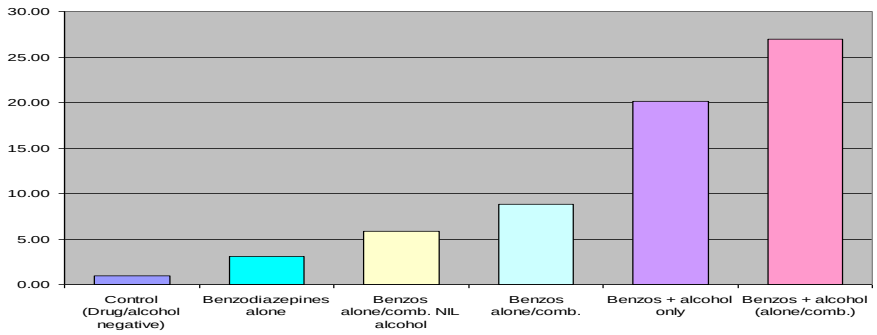
Chart 3: Odds ratios for drugs in combination



NB. No driver under the influence of 4-5 drugs was deemed 'not responsible' for their collision; therefore the columns 4 and 5 are arbitrarily set at 100.

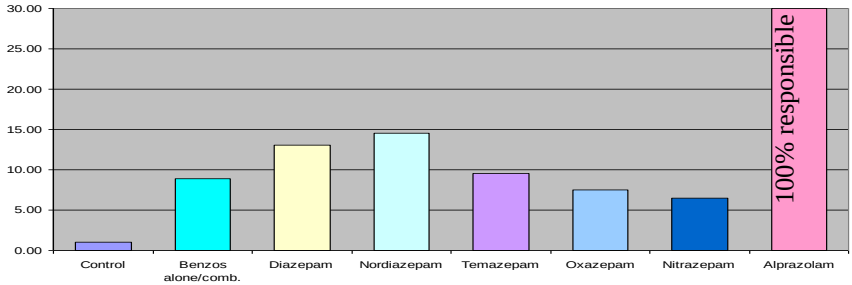
Benzodiazepines (BZD)

Chart 4: Odds ratio of being responsible for collision by presence/absence of a BZD alone or in combination



The data show that using benzodiazepines increases the odds ratio of a driver being responsible for a collision. The relative risk for a BZD alone is 1.43 (95%CI 1.18-1.74). This risk increases again when another substance is used (RR=1.59), and again when alcohol is introduced (RR=1.75).

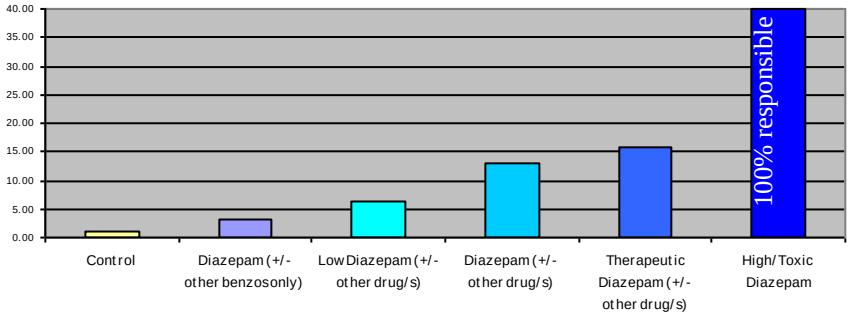
Chart 5: Comparison of odds ratios for individual benzodiazepines



NB. Calculations for categories include all drivers testing positive to the substance, not positive to *only* that substance.

Diazepam and alprazolam were the most common benzodiazepines detected in injured drivers (as well as nordiazepam, a metabolite of diazepam). They also carried a higher probability of being responsible for the collision.

Chart 6: Odds ratios for diazepam level found and presence/absence of other drug/s.



NB. All 26 drivers with diazepam levels in the high/toxic range caused their collision; therefore the odds ratio displayed is representative only.

Early data indicates that there is a dose relationship with diazepam.

Alprazolam

Table 4: Summary of responsibility for drivers testing positive to alprazolam

Group	Responsibility Analysis			Total
	Responsible	Contributory	Not Resp.	
Alprazolam (+/- other benzos only)	8	0	0	8
Alprazolam (+/- other drugs)	41	3	0	44
Low (<0.02mg/l)	5	1	0	6
Therapeutic (0.02-0.04mg/l)	9	1	0	10
High (0.041-0.075mg/l)	3	1	0	4
Toxic (>0.075mg/l)	24	0	0	24

Only 1 of the 44 alprazolam-positive drivers had a level of the drug considered low or therapeutic and had no other drugs in their system.

DISCUSSION

There is a well-recognised increased risk of personal injury crashes among drivers using anti-anxiety drugs compared with the rest of the population [1] and this is exacerbated by alcohol and other sedatives.[2] There is a hangover effect and a small dose of any sedative the following day can potentiate the risks. There is a decrement in tasks requiring vigilance at low doses and tolerance is only occasionally noted. The opposite effect, exaggerated impairment, has also been documented. [3] A meta-analysis of over 500 studies showed that the serum level of each benzodiazepine studied related to the degree of impairment in the laboratory.[4]

The benzodiazepine group has been shown to impair driving skills to a similar degree and in similar ways to alcohol. In general terms, the risk of collision is doubled for patients taking benzodiazepines. The impairment and collision risk are greatest in the first two weeks of treatment. [5] The ICADTS working group concluded that patients should be warned not to drive in the first two weeks of treatment. [6] Although treatment with benzodiazepine tranquillisers will improve clinical anxiety, there is no improvement in their driving ability. [7]

This study shows that benzodiazepines significantly increase the risk of collision particularly when the drugs are misused or combined with alcohol. The increased risk

of combining alcohol and benzodiazepines could be mitigated by introducing roadside testing in conjunction zero tolerance for alcohol.

Alprazolam is of particular concern. Twenty four of the 44 drivers who tested positive (64%) had levels considered either high or toxic. In fact, only one driver had a level of alprazolam in the low-therapeutic range and no other substances. The only reasonable conclusion is that the other 43 drivers were taking the drug irresponsibly, recreationally, or in excess of the prescribed dose. All alprazolam-positive drivers were either responsible for, or contributed to the collision in which they were injured. The road safety implication is that alprazolam should be considered for special controls on prescription and supply.

CONCLUSION

This study provides evidence that benzodiazepines impair driving in a dose-related manner. Potential road safety interventions for consideration include:

- Road-side drug screening for benzodiazepines
- Education of consumers to reduce recreational use
- Education for prescribers of benzodiazepines

The road safety issues need to be conveyed to specific target groups, including doctors, pharmacists and users.

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APPENDIX 1 - **Scoring Guidelines for Responsibility/Culpability Analysis**

Mitigating Category			Score
1. Condition of the road			
	Sealed Road*		
	Two or more lanes and smooth		1
	Divided Road		1
	Two or more lanes and rough		2
	Unmarked, thin and smooth		2
	Unmarked , thin and rough		3
	Unsealed road		
	Smooth		2
	Rough and/or corrugated		3
2. Condition of the Vehicle			
	Roadworthy		1
	Unroadworthy (contributed to accident unclear)		2
	Unroadworthy (contributing to accident)		4
3. Driving Conditions			
	Day		
	Clear and/or cloudy		1
	*Fog and/or mist, clear and windy (>40 kph)		2
	*Visibility good and road wet		3
	Showers and/or rain		
	Night		
	†‡Clear		1
	‡Cloudy		2
	Fog/mist/showers/rain/ice/wind		3
4. Type of Accident			
	Single vehicle		
	No Influence from other vehicles		1
	Influence from other vehicles		3
	Multi-vehicle		
	Striking vehicle attempting to avoid		2
	Striking vehicle not attempting to avoid		1
	Struck vehicle in the wrong		1
	Struck vehicle in the right		3
5. Witness Observations			
	No apparent reason		1
	Reckless -	Swerving	1
		Irregular driving	1
	Negligent -	Witnessed road infringement	1
		Lack of road sense	1
	Vehicle fault		3
	Driver not to blame		4
6. Road Law Obedience			
	Was driver obeying road laws?	Yes	3
		No	1
7. Difficulty of Task Involved			
	Straight road or sweeping bend		1
	§ Across lanes in	Heavy traffic	2
		Light traffic	1
	Winding road/sharp bend/ U-turn		2
	Overtaking		2
	Avoiding unexpected traffic		3
8. Level of Fatigue			
	Only if mentioned in police reports		2

*Add 1 if road has been newly resurfaced
†If in heavy traffic, add 1 point.
‡If not lighted, add 1 point
§Scores 1, if under the guidance of traffic signals.