FURTHER PUBLIC SUBMISSIONS ON THE PROPOSED AMENDMENTS TO THE POISONS STANDARD

Regulation 42ZCZQ, Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary of the Department of Health and Ageing publishes herein all valid public submissions made in response to the invitation for further public submission on the proposed amendments to the Poisons Standard. These submissions are in response to the delegates' interim decisions. The interim decision takes into account the original application, submissions received in any consultative phase and advice from the March 2013 Advisory Committee on Chemicals Scheduling (ACCS) #7, the Advisory Committee on Medicines Scheduling (ACMS) #8 and the joint ACCS and ACMS #5.

In accordance with the requirements of subsection 42ZCZQ of the Regulations these submissions have had confidential information removed.

Material claimed to be commercial-in-confidence was considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework (SPF), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Discrete submissions have been grouped by substance. A submitter provided a submission that related to multiple substances and this has been separately grouped.

LIST OF SUBMISSIONS

Substance	**Total number of public submissions**
Benzodiazepines	37*
Adrenaline, bupivacaine and lignocaine	6
Eubacterium species	1

*3 submissions have not been published due to confidential information.

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra, ACT 2601

By email SMP@health.gov.au

6 June 2013

Dear Sir/Madam,

Interim decision to reschedule alprazolam to Schedule 8 – Regulation 42ZCZK of the Therapeutic Goods Regulations 1990

We write to support the interim decision of the committee to reschedule alprazolam for reasons outlined in our original submission of 17 January 2013.

This interim decision is consistent with subsection 52E (1) of the Therapeutic Goods Act 1989 which includes consideration being given to:

(a) the risks and benefits of the use of a substance;
(b) the purposes for which a substance is to be used and the extent of use of a substance;
(c) the toxicity of a substance;
(d) the dosage, formulation, labelling, packaging and presentation of a substance;
(e) the potential for abuse of a substance.

While we acknowledge some concerns expressed in earlier submissions from aged care and pharmacy bodies regarding additional administrative costs of rescheduling all benzodiazepines, the potential public health benefit of improving the quality of supply of these potentially addictive medications by rescheduling to S8 would outweigh these costs. In any case, given the ACMS interim decision to selectively reschedule alprazolam only at this stage we believe this significantly allays such concerns.

Please see attachment 1 for our recently published manuscript that provides further evidence of the need to reschedule alprazolam in order to improve public health. Attachment 2 contains our original 17 January 2013 submission to the ACMS by way of background.

Sincerely,

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Attachment 1: Rintoul, A. C., M. Dobbin, et al. (2013). "Recent increase in detection of alprazolam in Victorian heroin-related deaths." MJA 198(4): 206-209.

Attachment 2: Our **o**riginal submission 17 Jan 2013 ‘Regulation 42ZCZK of the Therapeutic Goods Regulations 1990’

Recent increase in detection of alprazolam in Victorian heroin-related deaths

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Abstract

Objectives: To examine the rate of detection of alprazolam among cases of heroin-related death (HRD) in Victoria, including the relationship between alprazolam supply and HRDs.

Design and setting: Population-based study of community alprazolam supply in Victoria and HRDs reported to the Victorian coroner from January 1990 to December 2010.

Main outcome measures: Number of prescriptions for alprazolam supplied; defined daily dose (DDD) per 1000 population per day of alprazolam; number of cases of HRD in which alprazolam was detected through postmortem toxicological testing.

Results: Alprazolam supply increased by 1426%, from 0.42 DDD/1000/day in 1990, to 6.41 in 2010. For every 1 unit increase in DDD/1000/day, the proportion of cases of HRD in which alprazolam was detected increased at an incidence rate ratio of 2.4 (95% CI, 2.1–2.8; $P < 0.001$). Alprazolam was detected among increasing proportions of HRDs, from 5.3% in 2005 to a peak of 35.3% in 2009.

Conclusion: The increase in detection of alprazolam among cases of HRD, particularly since 2005, and the disproportionate increase in prescribing of the high-dose 2 mg formulation compared with other formulations suggest a need to examine alprazolam prescribing and to identify inappropriate prescribing and the circumstances of diversion from licit to illicit use.

The use of benzodiazepines by opioid-dependent people is widespread.[1-4] The 2011 Victorian Illicit Drug Reporting System (IDRS), a sentinel survey of people who inject drugs (PWID), reported 92% lifetime and 71% recent (in the past 6 months) use among PWID.[5] PWID use benzodiazepines for a number of reasons: to enhance the intoxicating effects of heroin or other opioids, manage anxiety, or manage withdrawal symptoms.[3]

The contribution of benzodiazepines to heroin overdose is well established.[6,7] Alprazolam is a benzodiazepine registered in Australia for short-term treatment of anxiety and panic disorder. It is not recommended as first-line treatment because of concerns about risks of dependence and its potential for misuse.[4,8]

Alprazolam, like other commonly misused drugs, has a rapid onset and offset of action and high potency.[8] Alprazolam may also be more toxic in overdose than other benzodiazepines.[9] Laboratory-based studies have found that in combination with methadone, alprazolam has significant effects on respiration.[10] A review of the interaction concluded that most evidence suggests the interaction is pharmacodynamic in nature.[11]

Victorian IDRS reports showed recent alprazolam use increased from 8% in 2005[12] to 69% in 2011.[5] Alprazolam is now the most commonly injected benzodiazepine,[5] with a reported street price of three tablets for $10.[13] Alprazolam use is associated with disproportionate levels of harm, including amnesia, violent outbursts of rage in otherwise non-violent individuals, and theft.[1,13-15] In Victoria, most alprazolam (81%) used by PWID in 2011 was obtained from illicit sources.[5]

Given the increased number of episodes of serious harm associated with alprazolam use, we aimed to examine its public health impact, to inform prescribing and to guide appropriate policy responses. We investigated trends in alprazolam prescribing and its detection in heroin-related deaths (HRDs) in Victoria. Our hypothesis was that increased mean consumption of alprazolam is likely to have significant effects on heroin users,[16] a population already vulnerable to drug toxicity.

Methods

Victorian prescription estimates

Estimates of prescription numbers for all dose formulations of alprazolam dispensed in Victoria for each calendar year, 1990–2010, were calculated from national supply data, Australian Statistics on Medicines (ASM), published by the Pharmaceutical Benefits Advisory Committee Drug Utilisation Sub-Committee. We determined the annual proportion of Pharmaceutical Benefits Scheme (PBS) supply to Victoria using data from Medicare Australia and applied this proportion to the annual ASM data. The ASM data provide a more complete estimate of alprazolam supply, as they include both private non-PBS prescriptions (those that do not attract a PBS subsidy) and PBS prescription numbers.

A defined daily dose per 1000 population per day (DDD/1000/day) for Victoria was calculated for each year using the same Victorian proportions derived from the PBS figures, the DDD for alprazolam (1 mg),[17] the base number of estimated alprazolam prescriptions in Victoria, the usual pack size (50 tablets) for each dose formulation and Victorian population data.

Alprazolam detection in heroin-related deaths

Annual aggregate numbers of HRDs and annual numbers of cases of HRD in which alprazolam was detected were extracted from the Victorian Institute of Forensic Medicine toxicology database. Cases reported to the Victorian coroner in the 21-year period 1990–2010 that were classified as drug-related deaths, involved heroin and had been subjected to toxicology testing were included. All cases had results for a full range of toxicology tests, including for ethanol and common drugs of misuse. All presumptive detections had been confirmed by appropriate analytical techniques. Alprazolam had been tested for, using both immunoassay class tests on urine or blood (depending on availability of specimens) and gas chromatography–mass spectrometry on blood. All detections had been confirmed and quantified in blood using validated methods.

1 Heroin-related deaths (HRDs) and detection of alprazolam, Victoria, 1996–2010*

Parameter	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Total number of HRDs	147	157	265	362	331	47	51	90	84	57	26	36	76	51	96
Alprazolam detected, no. (%)	2 (1.4%)	1 (0.6%)	3 (1.1%)	7 (1.9%)	4 (1.2%)	0 (0.0)	2 (3.9%)	4 (4.4%)	2 (2.4%)	3 (5.3%)	3 (11.5%)	6 (16.7%)	13 (17.1%)	18 (35.3%)	27 (28.1%)
No. of alprazolam prescriptions ('000s)	95	100	119	119	134	145	150	161	174	179	188	217	236	246	240
Alprazolam prescriptions per 100 000 population†	2087	2170	2559	2533	2828	3012	3074	3257	3488	3526	3653	4146	4431	4528	4327
Defined daily dose/1000 population/day	2.06	2.22	2.68	2.86	3.25	3.52	3.70	4.00	4.36	4.54	4.77	5.48	6.06	6.58	6.41

*1990–1995 not shown (there were no HRDs involving alprazolam during this period). † The proportion dispensed in Victoria was estimated using national Medicare data on Pharmaceutical Benefits Scheme supply of all formulations and this was applied to Australian Statistics on Medicines supply data (see Methods). ◆

Ethics approval was granted by the Victorian Institute of Forensic Medicine Research Advisory Committee.

Statistical analysis

We used a Poisson regression model to assess the relationship between estimated trends in alprazolam supply and HRDs involving alprazolam. All statistical tests adjusted for annual fluctuations in HRDs. Data were analysed using Stata, version 11 (StataCorp).

Results

Alprazolam prescribing

Alprazolam supply increased by 1426% from 0.42 DDD/1000/day in 1990 to 6.41 DDD/1000/day in 2010 (Box 1). The estimated number of Victorian prescriptions for alprazolam increased by 611%, from 609/100 000 population in 1990 to 4327/100 000 population in 2010 (Box 1). The most remarkable change was in prescriptions for the 2 mg formulation, which increased from 4.1% to 27.9% of the population-adjusted rate for alprazolam prescriptions between 1998 and 2010. Box 2 shows trends in total DDD/1000/day for the four alprazolam dose formulations. A large proportion of alprazolam prescriptions were private; in 2009, private prescriptions accounted for 37.2% of all prescriptions.

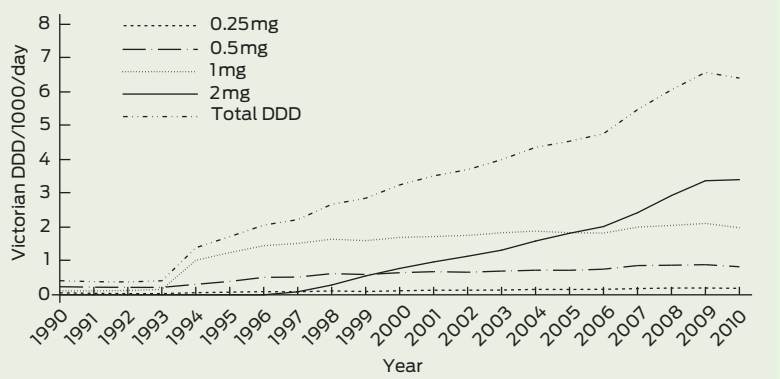
Heroin-related deaths

There were 2392 HRDs in Victoria from 1990 to 2010. The annual number varied considerably over this time, with a large increase in HRDs per year from 1993, peaking at 362 deaths in 1999 (Box 1). A large decrease in HRDs reflected a reduction in heroin supply in 2001, and numbers subsequently fluctuated between 26 and 76 HRDs per year from 2001 to 2009, increasing to 96 in 2010 (Box 1, Box 3).

The number of alprazolam detections increased steadily from 2004, reaching a peak in 2010. Detection fluctuated between 0 and 4.4% of HRDs from 1990 to 2004, with a large increase from 5.2% in 2005 to 35.3% in 2009, decreasing to 28.1% in 2010 (Box 1, Box 3).

The Poisson regression model showed that for every 1 unit increase in DDD/1000/day, HRDs involving alprazolam increased at an incidence rate ratio of 2.4 (95% CI, 2.1–2.8; $P < 0.001$). Box 4 shows a log linear relationship between supply and the proportion of HRDs in which alprazolam was detected.

2 Estimated alprazolam defined daily dose (DDD) per 1000 population per day, by dose formulation, Victoria, 1990–2010

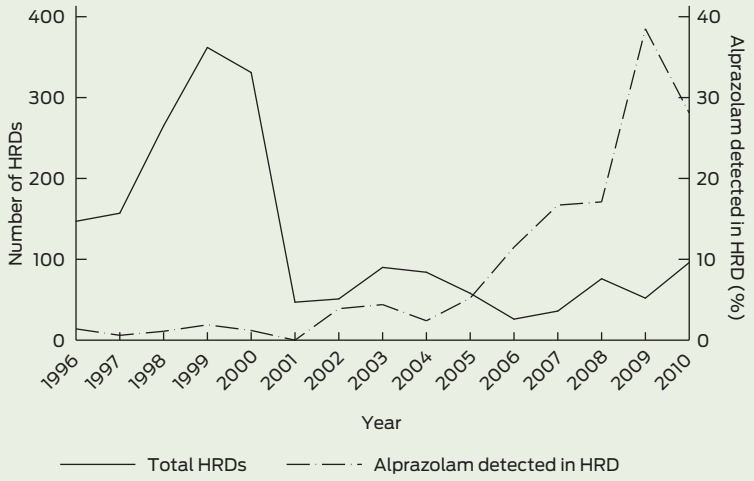


Discussion

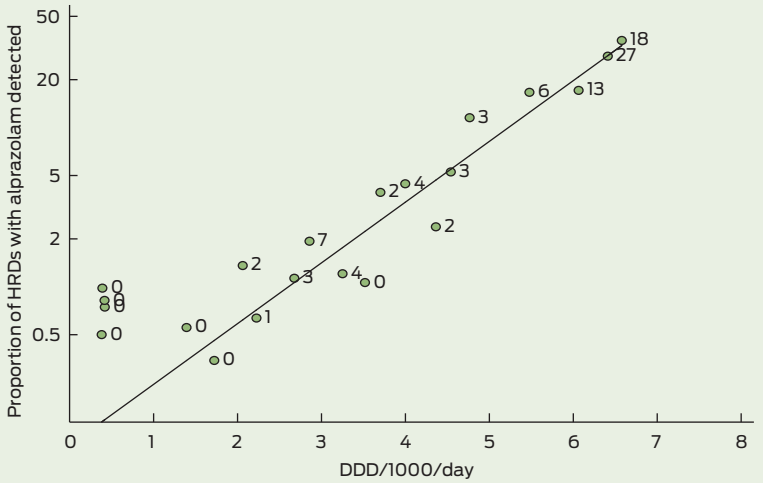
Our study over the 21 years from 1990 to 2010 showed a number of interesting trends in alprazolam prescribing and supply and its relationship to HRDs in Victoria. First, the supply of alprazolam increased despite its status as a second-line treatment for its approved indications; second, the increase in the supply of the high-dose formulation was disproportionate to the increase in other formulations; and third, the rate of detection of alprazolam in HRDs increased more rapidly after 2005, concurrently with other reports of increasing harm among PWID.[13] The association between the detection of alprazolam in HRDs and alprazolam supply was strong and significant. While alprazolam may be more toxic in overdose than other benzodiazepines,[9] the accelerated rate of detection in this population since 2005 could reflect an increased preference for and use of alprazolam,[1] particularly the high-dose formulation, among heroin users.

This raises questions about the increased prescribing of a drug not preferred for treatment of its primary indication,[8,18] and for which little evidence exists for effectiveness beyond short-term use.[4] This is especially important given that it may be more toxic in overdose.[9] We have shown that the proportion of HRDs in which this benzodiazepine was detected increased over time as supply

3 Number of heroin-related deaths (HRDs) and proportion of cases in which alprazolam was detected, Victoria, 1996–2010



4 Relationship between annual proportion of heroin-related deaths (HRD) in which alprazolam was detected and the annual defined daily dose (DDD) per 1000 population per day, Victoria, 1990–2010*



* Yearly figures are plotted and labelled with the number of alprazolam-detected HRD in that year; any years with zero alprazolam-detected HRD deaths had the number of alprazolam HRD set to 0.5 and the proportion of all HRD calculated from this. ◆

increased. Understanding the reasons for the increasing average population-level consumption of alprazolam may help to decrease its supply and the harmful effects seen among PWID. This would be consistent with a previous study that showed that the average consumption of potentially harmful products such as salt and alcohol predicts the number of people affected in the statistically "deviant" tail end of a population distribution.[16,19]

The number of HRDs has remained fewer than during the heroin glut in the late 1990s,[20] which led to the peak in deaths shown in 1999. The lower numbers are likely to reflect trends in heroin supply and should not be interpreted as evidence that alprazolam is relatively safe.

A relative strength of our study is the reporting of all Victorian HRDs spanning a 21-year period, enabling the identification of long-term trends in alprazolam used shortly before death. These data provide valuable information for the future prevention of deaths among people who use heroin. In addition, the prescription data and DDD calculations are estimates of the total number of prescriptions dispensed, based on data from the ASM and Medicare. Incorporating the ASM data improves the accuracy of total prescription volume through the inclusion of private prescriptions.

The finding of a strong and statistically significant association between detection of alprazolam in cases of HRD and its supply in the community is useful for generating a hypothesis about possible causes of increasing detection of this drug in cases of HRD. However, this does not mean a causal relationship exists between the increasing alprazolam supply and such deaths. The contribution of alprazolam to deaths involving multiple drugs is difficult to determine, and it is therefore not possible to specify the proportion of cases of drug toxicity due to combined drugs where alprazolam contributed directly to death.[21] We used detection of alprazolam as an indication of use by PWID, rather than contribution to death per se.

The absolute number and rate of cases of HRD in which alprazolam was detected has increased substantially since 2005. Concern about the misuse of alprazolam in 2010 led to a request to the Australian National Drugs and Poisons Schedule Committee to reschedule it to the more restrictive Schedule 8.[22] Among the committee's stated reasons for not doing so at that time was that there was insufficient evidence of a problem.

This study provides further evidence of the increasing problem, perhaps involving high-dose formulations, of use of diverted medications among PWID.[1] Given the growing concerns with alprazolam use among PWID and its increasing involvement in HRDs, supply control measures — such as better monitoring and surveillance (including real-time prescription monitoring), rescheduling to Schedule 8, and education of health professionals — are warranted. Provision of information about the risks of concurrent use of opioids and alprazolam to PWID is also essential.

Acknowledgements: We are grateful to Damien Jolley and Rory Wolfe of Monash University for providing statistical advice; the PBAC Drug Utilisation Sub-Committee for extracting ASM national prescription volume data; and Katayoon Yazdani for assisting in the compilation of Medicare Australia data.

Angela Rintoul is currently funded through an Australian Postgraduate Award scholarship. Some of this work was completed during her participation in the Victorian Public Health Training Scheme, funded by the State of Victoria through the Department of Health, while on placement with the Drugs Policy Unit at the Victorian Department of Health.

The views and conclusions in this article are ours and do not necessarily represent those of the Department of Health.

Competing interests: Suzanne Nielsen has worked in an unpaid capacity as an investigator on projects funded by

untied educational grants from Reckitt-Benckiser (RB). She has not received any direct funding. Louisa Degenhardt has received untied educational grants from RB to undertake postmarketing surveillance of suboxone tablet and film products in Australia. Malcolm Dobbin has received an honorarium from Pfizer for lectures, which was donated to charity. Neither RB nor Pfizer had knowledge of, or input into, this paper.

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The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra, ACT 2601

17 January 2013

Dear Sir/Madam,

Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 – Proposal to amend benzodiazepines from Schedule 4 to 8

We write as both experienced health professionals with significant research experience in the area of pharmaceutical drugs and related harms. I (A. Rintoul) am a Doctor of Public Health Candidate at Monash University. Over the past three years I have conducted studies on trends in prescription drug supply and detection deaths in Victoria, with a particular focus on populations who use opioids. My colleague (Dr S Nielsen) is a pharmacist and current NHMRC Research Fellow has focused her research for the past 10 years on pharmaceutical drugs including benzodiazepine related harms. It is with this experience that we write to support the proposal to move benzodiazepines from Schedule 4 to Schedule 8.

Firstly, Schedule 8 is reserved for classes of drugs that have potential to cause addiction, there is clear evidence in the medical and scientific literature that demonstrates the addictive potential of benzodiazepines.

Clinical guidelines recommend if a pharmaceutical treatment is indicated, benzodiazepines should only be prescribed for short term use. Current prescription volume data suggests a disconnect between prescribing practices and clinical guidelines, particularly in relation to alprazolam (see **Appendix 2**). Moving benzodiazepines to Schedule 8 would be a relatively simple and effective mechanism to support improved quality in the supply of benzodiazepines due to the additional scrutiny provided to drugs in this schedule. A Schedule 8 classification would encourage clinicians to hesitate before writing a benzodiazepine prescription. This move could also function as a reminder that there is no evidence of the effectiveness of long term use of benzodiazepines in the treatment of anxiety.

Opioid dependent people are a population already at risk of drug toxicity. One study found use of a benzodiazepine within 12 hours of using heroin resulted in a 28 fold increase in risk of overdose when compared with instances where benzodiazepines were not used [1]. Despite this risk, the use of benzodiazepines by opioid-dependent people is known to be widespread. The 2011 Victorian Illicit Drug Reporting System (IDRS), a sentinel survey of people who inject drugs (PWID), reported 92% lifetime and 71% recent use (in the past 6 months) among PWID [2]. PWID use benzodiazepines for a number of reasons; to manage anxiety, manage withdrawal symptoms or to enhance the intoxicating effects of heroin or other opioids [3].

We recently conducted research investigating trends in the detection of benzodiazepines in heroin related deaths (HRD) in Victoria over the period 1990-2010, with a particular focus on alprazolam [4]. Over this 21 year period, at least one benzodiazepine was detected in over half (54%) of all

HRD, however the highest proportion detected was in the most recent year of our study with over three quarters of these deaths (78%) involving at least one benzodiazepine (see **Table 1** and **Figure 1**). Similarly, in a study investigating drug toxicity deaths involving oxycodone in Victoria in the decade to 2010, we found 75% of all oxycodone involved drug toxicity deaths involved at least one benzodiazepine, with an increasing share of these deaths involving alprazolam (*forthcoming, unpublished data relating to this study [5]*).

However, not all benzodiazepines are alike. Alprazolam is increasingly reported to be associated with disproportionate level of harm including poor physical health [6], amnesia, traffic injuries, violent crime, and theft [7, 8]. In Australia, alprazolam is approved for short term treatment of panic disorder, but only as a second line option because of concerns about tolerance, dependence and misuse. Alprazolam has a rapid onset and offset of action and is more potent than other benzodiazepines [9]. In a study examining alprazolam and its relationship with crime, a consistent and concerning theme was the use of alprazolam being associated with serious and often uncharacteristic crime, in addition to its common link with minor crimes and other harms [10] (**see Appendix 4**).

Despite being a second line treatment, alprazolam is increasingly prescribed. In Victoria the base supply of alprazolam increased 1,432% between 1990 and 2010 [4]. Of particular concern, was the increase in supply of the 2mg dose formulation - the strongest dose available (see **Appendix 2, Figure 2**). Reasons for the increase in supply of the 2mg formulation are not clear from our study, but this does indicate potentially inappropriate prescribing.

The increase in base supply of alprazolam is occurring despite evidence that it is not more effective than other benzodiazepines in the treatment of panic disorder [9]. It is also occurring in a context of converging evidence of harms at the population level. For instance, our study that investigated trends in the detection of alprazolam in HRD showed a strong and statistically significant, linear relationship between supply and detection of alprazolam in HRD [4]. While this study does not suggest causation between increasing community supply and increased detection in HRD, it does indicate a concerning trend in alprazolam use amongst a population already vulnerable to drug toxicity. Combining the use of opioids and benzodiazepines increases the risk of overdose, but as alprazolam is known to be relatively more toxic in overdose than other benzodiazepines [11] this is of particular concern.

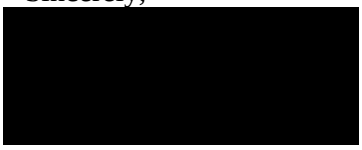
We did not seek to determine the source of the alprazolam for the deceased in this study, but the IDRS report that a large proportion of PWID obtain alprazolam from diverted sources. However, ultimately the supply chain starts with prescribers, and therefore moving alprazolam and other benzodiazepines to schedule 8 would be a useful way to improve the quality of supply of benzodiazepines in the community.

There are useful precedents that demonstrate the success in restricting supply of benzodiazepines (see **Appendix 3**). In 1993, flunitrazepam was moved to Schedule 8 after concerns including a high detection rate in HRD and the role of flunitrazepam in facilitating rape. **Figure 3** shows the relationship between the reduced supply of flunitrazepam and decreased detection in HRD. Similarly, the popularity of temazepam gel cap injection among PWID in the late 1990s and 2000 resulted in serious injection wounds among this population. As a consequence, temazepam gel caps became authority required in May 2002 and were ultimately withdrawn by the manufacturer, Sigma, in 2004. **Figure 4** shows the decline in temazepam supply at the time of these changes, and a corresponding decrease in HRD.

Rescheduling all benzodiazepines to schedule 8 would better reflect the addictive potential of these drugs, that have no evidence of medical benefit beyond short term use. However, if the committee decides not to reclassify the entire class of benzodiazepines, there is evidence of benefit in selectively rescheduling problematic benzodiazepines as demonstrated by the success of reducing the detection of flunitrazepam and temazepam in HRD.

In conclusion, there would be considerable public health benefits in moving benzodiazepines from Schedule 4 to Schedule 8 and we strongly support the proposal for the rescheduling of these drugs. In the event that rescheduling all benzodiazepines is not supported by the committee, we would at the very least strongly encourage selective rescheduling of alprazolam which has become particularly problematic over the past several years.

Sincerely,



Angela Rintoul, BA MSocSci VPHTS DrPH (candidate)
Doctor of Public Health Candidate, Department of Epidemiology & Preventive Medicine
Monash University

and

Dr Suzanne Nielsen, BPharm BPharmSc(Hons) PhD MPS
NHMRC Research Fellow (Early Career)
Discipline of Addiction Medicine, The University of Sydney

References

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7. Drugs and Crime Prevention Committee, *Inquiry into the misuse/abuse of benzodiazepines and other forms of pharmaceutical drugs in Victoria* 2007, Parliament of Victoria Melbourne.
8. Loxley, W., *Benzodiazepine use and harms among police detainees in Australia.* Trends and Issues in Crime and Criminal Justice, 2007(336).
9. Moylan, S., et al., *The efficacy and safety of alprazolam versus other benzodiazepines in the treatment of panic disorder.* J Clin Psychopharmacol, 2011. **31**(5): p. 647-52.
10. Jones, K., et al., *'A Pinch in Every Bottle': Expert Perspectives of Alprazolam Use and its relationship to offending. Poster Presentation, Australasian Professional Society on Alcohol and other Drugs Conference; November 13-16th 2011; Hobart, Australia.* 2011.
11. Isbister, G.K., et al., *Alprazolam is relatively more toxic than other benzodiazepines in overdose.* British Journal of Clinical Pharmacology, 2004. **58**(1): p. 88-95.

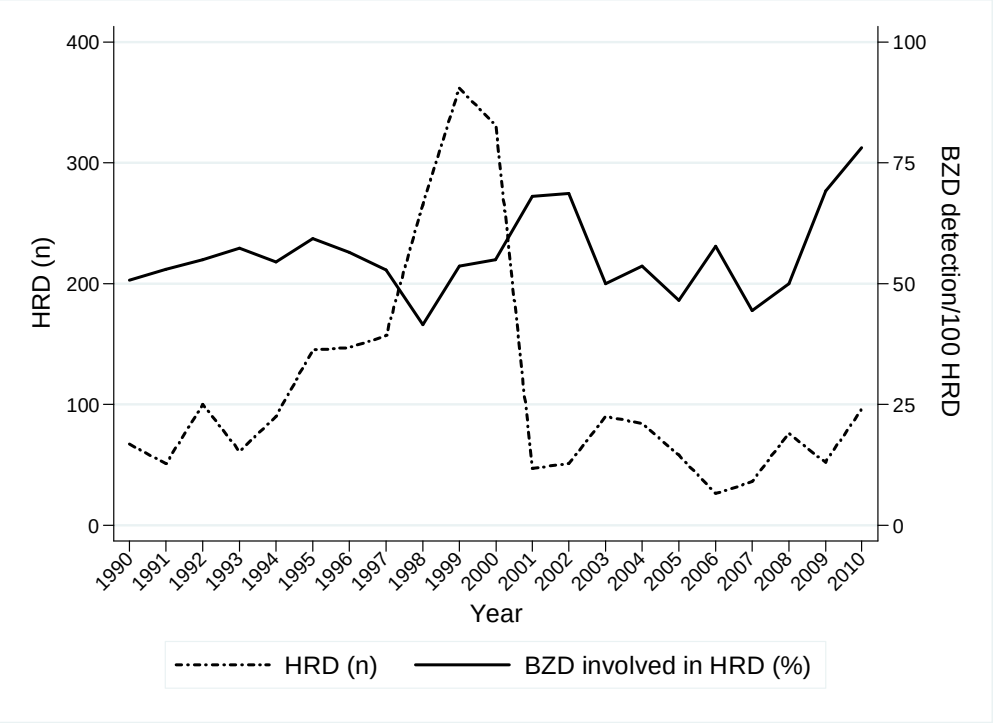
Appendix 1

Table 1: Victorian heroin related deaths and detection of benzodiazepines from 1990 – 2010* - 78% of all Victorian HRD in 2010 involved at least one benzodiazepines

	1990	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Total no. HRD deaths	67	51	100	61	90	145	147	157	265	362	331	47	51	90	84	58	26	36	76	51	96
Total no. HRD where BZD detected	34	27	55	35	49	86	83	83	110	194	182	32	35	45	45	27	15	16	38	35	75
HRD involving a BZD (%)	50.7	52.9	55.0	57.4	54.4	59.3	56.5	52.9	41.5	53.6	55.0	68.1	68.6	50.0	53.6	46.6	57.7	44.4	50.0	68.6	78.1
Diazepam	19	10	29	17	33	55	54	57	90	160	152	26	26	36	37	24	13	15	31	20	46
Alprazolam	0	0	0	0	0	0	2	1	3	7	4	0	2	4	2	3	3	6	13	18	27
Oxazepam	15	7	13	8	14	16	14	19	16	35	23	5	3	6	8	1	2	2	3	4	10
Clonazepam	2	2	4	0	4	10	5	6	4	6	4	2	2	3	2	1	0	0	0	2	10
Temazepam	0	1	3	3	5	12	7	7	3	23	23	9	6	6	1	1	1	1	3	4	3
Flunitrazepam	16	11	25	10	8	16	22	12	9	1	1	0	1	0	0	0	0	0	0	1	0
Nitrazepam	1	2	0	2	2	4	5	2	9	24	16	1	6	0	2	0	0	1	1	0	2
Lorazepam	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Flurazepam	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0

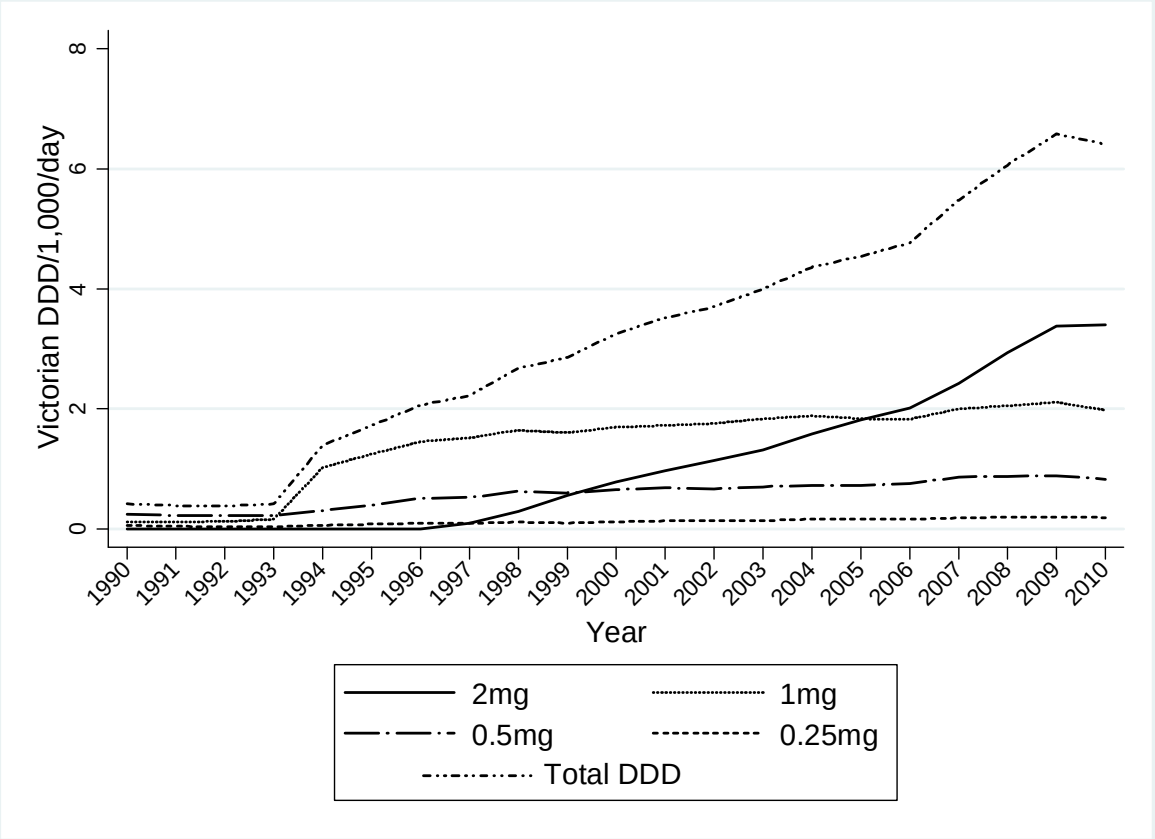
* more than one benzodiazepine may have been detected meaning columns may sum > 100 %

Figure 1: Trends in HRD and the detection of benzodiazepines in HRD, Victoria 1990-2010



Appendix 2: Alprazolam base supply has increased 1,426% since 1990*, the 2mg formulation has increase disproportionately

Figure 2: Defined daily dose of alprazolam by dose formulation, Victoria 1990-2010



*Forthcoming article can be supplied upon request for detail on how Victorian DDD was calculated
Rintoul, A.C., et al., *Recent increase in detection of alprazolam in Victorian heroin-related deaths* Med J Aust, 2013 **(in press)**.

Appendix 3: Success in rescheduling problematic benzodiazepines, Victoria 1990-2010

Figure 3: When flunitrazepam was moved to Schedule 8 in 1993, detection in heroin related deaths rapidly decreased

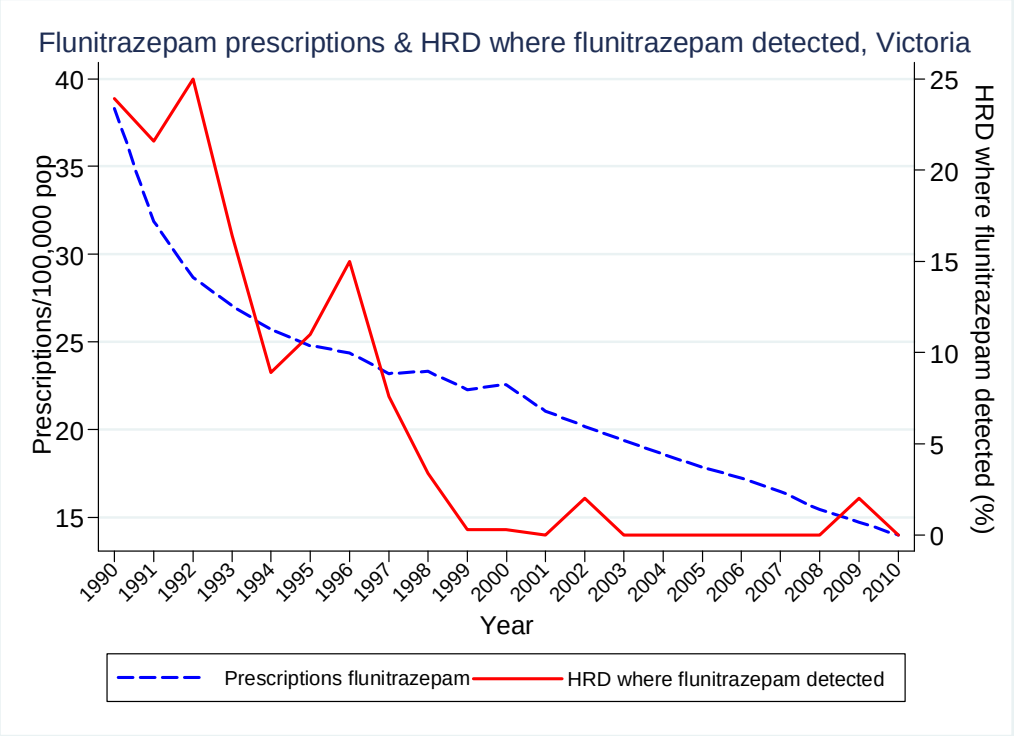
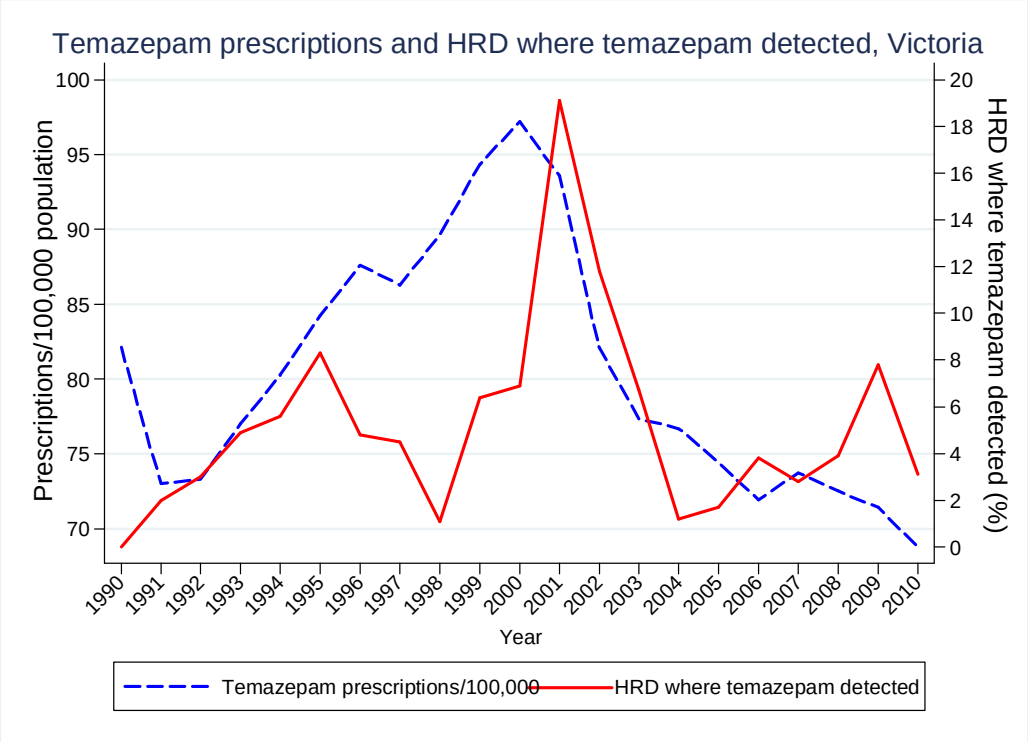


Figure 4: Heroin related deaths where temazepam was detected decreased rapidly when gel caps became authority required.



Submission about rescheduling of alprazolam [SEC=No Protective Marking]
Malcolm.Dobbin to: SMP 31/05/2013 13:46

No Protective Marking

The Secretary
Medicines and Poisons Scheduling Secretariat
GPO Box 9848
CANBERRA SCT 2601

Dear Secretary

I support the rescheduling of alprazolam to Schedule 8.

For the information of the Committee, I have attached a scanned photocopy of the Australian NUAA User's News, Autumn 2013 issue.

On the third page there is an article describing the limited effectiveness of injecting alprazolam.

It describes that in the ACT and Northern Territory people who inject drugs were asked about the effectiveness of inserting Xanax rectally, and suggesting that this was the quickest and most effective way to absorb the drug
.

(See attached file: NUAA news - rectal alprazolam. Autumn 2013.pdf)

Kind regards

Malcolm

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(Embedded image moved to file: pic00067.jpg)

Dr Malcolm Dobbin PhD MBBS DRANZCOG MPH FAFPHM
[redacted]
Adjunct Senior Research Fellow
Department of Forensic Medicine
Monash University

NUAA news - rectal alprazolam. Autumn 2013.pdf  pic00067.jpg  pic30739.jpg

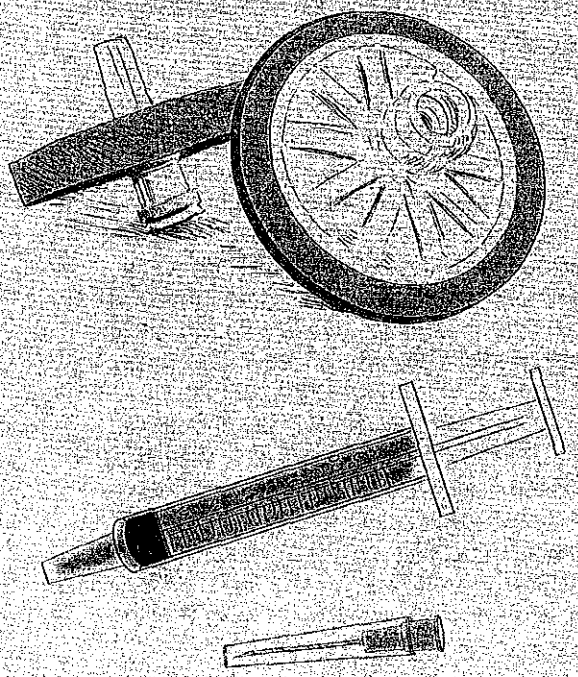
No Protective Marking

User's News
UN 72
Autumn 2013

THE POLY EDITION
Choosing harm reduction

Pharmy FAQs
part 1: pharmaceuticals

We asked peers to give their best answers to some Frequently Asked Questions about using pharmaceuticals, then got our UN Technical Committee of doctors and pharmacists to check the answers. Here is Part 1 of a series on harm reduction and pharmaceuticals. Please note that the much awaited resource on Fentanyl will be released by mid-year, so look out for that.



Q: Whenever I try and mix up pills, the solution turns into a real mess. What am I doing wrong?
A: It's hard to know without more info on the pill but pills are always tricky to mix up and there are nearly always tricks to the trade. Ask around your peer group how they do it. NUAA can help you access the right information for specific pills. When confronted with a new pill go through these steps. Find out what it is. Ring NUAA or get on the web and do your research. Obtain the right equipment you will need. Then, the most important thing to remember is that practice makes perfect. Also, the utensils you use can make a big difference. Always use a stainless steel spoon. The shape of the spoon can be important too. Most people agree that a soup spoon is the best for mixing in, and a teaspoon best for crushing (in the soup spoon). Another trick is to add the water a little bit at a time. Just like mixing a cake, this will make sure that the mix is smooth and has no lumps. Just keep adding more water. Ideally you should use 3ml of water for every pill. Other tricks are to never heat and that the longer you leave the mix to sit, the more potent it will be. Remember, wheel filters are your best friend.

Most pills are safer, work as well but slower (and at times, longer) if they are swallowed. Don't forget – if injecting, go slow and get the taste first if you are not sure of the drug or its strength – and don't use alone.

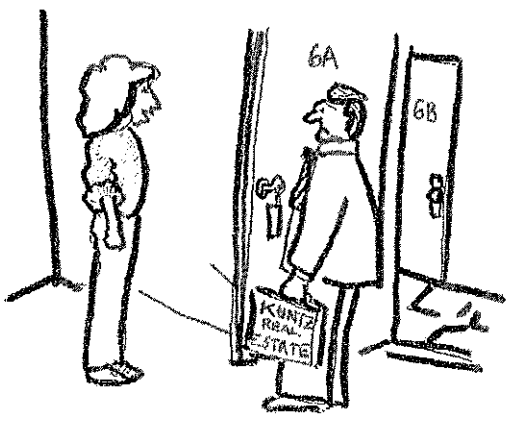
Q: What is the coating on pills, is it toxic and should I get rid of it before IV use?
A: Yes, get rid of it. It is basically a mixture of colouring agents (usually metallic) and slow release agents. To remove that colourful coating on the outside of your pill, the best technique is to apply tape; it will come off when you pull the tape away. Alternatively, you can use a swab. It is called an enteric coating and is designed to stop the pill dissolving until it passes through the stomach and is in your small intestine. It has no active ingredient in it whatsoever, but can cause health problems if injected.

Q: I hear you are not supposed to heat pills. Why and are there any exceptions?
Heating pills is dangerous and unnecessary. The reason it is dangerous is that when you heat the pill,

the inactive ingredients in the pill change. The best example is when you heat oxycontin. Oxycontin has binders (also known as fillers or wax) throughout the pill that act as a slow release mechanism. As you heat oxycontin, the binders liquify and soften. This means they will go straight through a wheel filter and may end up in your mix. Complications can occur after Injection, once the binders have cooled and separated.

Many people use heat because they think they are getting more of the active Ingredient out. However, research has shown that cold water extraction – where you crush up the pill very finely and then let soak in water for 5 minutes – is just as effective as hot techniques and a lot safer. "Yes but there Is less residue in my spoon, so I must have got more out of it" I hear you say. Not so, there is less residue in your spoon because you have melted all of the binders and they are now in your mix and may soon lodge in your lungs, kidneys, spleen or brain.

It seems there are no exceptions with pills. Cold water extraction is best practice across the board as far as we know. One barrier to using cold over hot is that cold is slower. If, after reading this, you are still going to go with heat, then cool your mixture down while in the spoon before filtering it. You can rub an ice-cube on the bottom of the spoon to quicken the process if you want. This will re-solidify any binder that has melted so it doesn't end up in your mix. It's not perfect but better that shooting all those binders.



NO HOT WATER? THAT'S OK – NUAA SAYS COLD IS BEST!

Q: People say it is dangerous to inject Xanax®. Why? Is there a safer way?

A: It is highly dangerous to inject Xanax®. It is also pointless, because Xanax®, like most benzodiazepines (including Valium®) are not water soluble. This means that they remain in the chalky residue at the bottom of your spoon when you inject it. Recently in the ACT and in the Northern Territory they did a campaign where they asked people who were using Xanax® IV to try bunting it (putting it up your bum) as this is the quickest and most efficient way to absorb Xanax®. People were sceptical at first, but after they gave it a try, the majority switched to bunting, stating that they felt it very quickly and that it was far stronger.

If you are injecting Xanax® and you are feeling it, we wage a bet that you are injecting the entire pill chalk and all. This chalk and other binders are then flowing around in your bloodstream and then lodging somewhere in your body. Probably your lungs (causing emphysema and a multitude of other health problems). It is only then that the Xanax® will start to be absorbed into your body. Please people, injecting Xanax® is one of the leading causes of death by IV use. They even have a name for it – Xanax® collapse. Just try bunting It or if you don't like that idea, crush the pills up and swallow or pop the tablets under your tongue – it isn't worth your life.

Q: How many pills can you put through a wheel filter before it blocks up or how do I know which wheel filter to use?

A: As with anything wheelfilters take a little getting used to. Basically, those NSPs that carry them, including NUAA, stock two types: a coarser filter to get rid of all of the chalk and a bacterial filter to get rid of all of the bacteria but not viruses (see p11). So the answer really depends on what pills you are using and how you have pre-filtered them before using the wheel filter.

Generally, always use a cotton wool ball as a pre-filter before using a wheel filter. Once you have your pre-mix in a barrel look at it. If it is very chalky or gluggy, always put it through the coarser filter (1.2 micron and the ones we stock are red) or the filter

alprazolam [SEC=No Protective Marking]

[redacted]

1 Attachment

Alprazolam submission May 2012.docx

To: Medicines and Poisons Scheduling Secretariat
Re: interim decision to reschedule alprazolam to S8

In order to emphasise our concerns about alprazolam and the need for this drug to be scheduled S8, we are re-submitting our original submission which states our concerns.
Hopefully the S8 scheduling will alert doctors to the issues and reduce prescribing.

Kind regards
Jennie Houseman

Jennie Houseman
Consultant Pharmacist
Community GP & Pharmacy Liaison
Northern Sydney Area Drug and Alcohol Services
Herbert St Clinic, RNS Community Health Centre
[redacted]

Northern Sydney D & A Service
Herbert St Clinic,
Building 8, RNS Hospital
St Leonards 2065

ph 9926-7775

3 May 2012.

Mr Bruce Battye, Chairperson
Mr Peter Gilfedder, Secretary
Poisons Advisory Committee
NSW Health
PO Box 103
Gladesville
NSW 1675

Dear Mr Battye and Mr Gilfedder,

Re: Strategies to Manage the Misuse of Alprazolam

We have written previously about our concerns in relation to the misuse of alprazolam, and the negative impact on many of our patients**.** We received a response in August 2011 indicating that the National Drugs and Poisons Scheduling Committee considered this matter at a meeting last year and concluded there was insufficient evidence to support a change in scheduling of alprazolam.

Our concerns continue to grow, and have been highlighted by the deaths of two of our patients on opioid substitution therapy. It appears these deaths are attributable to alprazolam overdose with other CNS depressants. Since our earlier correspondence, we have subsequently been able to access more recent information about the toxicity and misuse of alprazolam when compared with other benzodiazepines (attached).

Isbister GK et al 2004 conducted a review of benzodiazepine overdose admissions between January 1987 and October 2002 in the Hunter Area, Australia. Cases where patients had ingested two benzodiazepines were excluded (so that only single benzodiazepine overdoses were analysed), as were second and subsequent admissions. Data from 2003 single benzodiazepine overdose admissions were reviewed, which included:

- 131 alprazolam overdoses;
- 823 diazepam overdoses;
- 1109 other benzodiazepine overdoses (bromazepam, clobazam, flunitrazepam, lorazepam, nitrazepam, oxazepam, temazepam and triazolam).

Alprazolam was found to be significantly more toxic than other benzodiazepines in overdose, as follows:

- 22% of alprazolam overdoses were admitted to ICU, a rate 2.06

times more likely compared with other benzodiazepines after multivariate analysis adjusting for age, dose, gender, time to ingestion and co-ingested drugs;
- the median length of stay for alprazolam overdoses was 19 hours, which was 1.27 times longer than for other benzodiazepines;
- Flumazenil was administered to 14% of alprazolam patients and 16% were ventilated, significantly more than for other benzodiazepines (8% and 11% respectively);

The authors note that 85% of prescriptions for alprazolam are for panic disorder, anxiety, depression or mixed anxiety/depression states. They conclude that alprazolam is relatively more toxic than other benzodiazepines and this is due to the intrinsic toxicity of alprazolam. They also conclude that because suicide attempts are more prevalent in people with panic disorder than the general population, the use of alprazolam in this group needs to be reviewed and better controlled.

Jones K et al 2011 conducted 18 open-ended qualitative interviews with key experts from criminal justice, law enforcement, alcohol and drug treatment agencies and primary health care services. The interviews focused on the contribution of benzodiazepines to criminal activity. The concluded:

- most key experts were of the opinion that alprazolam was associated with more harm and criminal activity compared with other benzodiazepines;
- crimes committed during alprazolam intoxication were often described as "impulsive" and not well planned.

Nielsen S et al 2011 conducted a pilot study to look at the effects of alprazolam in combination with methadone, and alprazolam in combination with buprenorphine-naloxone. Of note are the findings in relation to methadone and alprazolam on memory. The methadone subjects had a mean age of 36.8 years, had been in current treatment for 9.1 months and were on a mean methadone dose of 61.3 mg. Subjects were given a memory test and the memory prose score recorded for immediate recall and delayed recall. Findings indicated:

- the methadone only subjects scored 7 for immediate recall. In contrast, the methadone + 2mg alprazolam subjects scored 4;
- the methadone only subjects scored 6 for delayed recall. In contrast, the methadone + 2mg alprazolam subjects scored 0 and recalled none of the information in the memory test.

Dore G et al 2012 in preparation: A study in our own service found that of 49 patients admitted for treatment of high dose benzodiazepine dependence, almost half of the group reported using more than 100mg diazepam equivalents daily. Of the total group, 84% reported misusing diazepam and 65% reported misusing alprazolam (Xanax in all cases). This is despite the limited indications for prescribing Xanax on an authority prescription, namely Panic disorder where other treatments have failed or are inappropriate. It's also of note given that diazepam is prescribed at 5 – 10 times the rate of alprazolam in Australia (Isbister et al 2004).

Alprazolam is currently a Schedule 4 Appendix D medication, and an authority prescription can be provided if the patient has Panic Disorder, where other treatments have failed or are inappropriate. This criterion has not stopped doctors writing private prescriptions for alprazolam, and has not deterred doctors in obtaining authority prescriptions for patients with substance use disorders. Our clinical experience also suggests that some doctors are writing authority prescriptions when there is no clear evidence of Panic Disorder.

Given the popularity of alprazolam as a drug of abuse, and the levels of morbidity and mortality as a consequence, we request a major change in the way alprazolam is currently prescribed.

Reclassification of alprazolam

We request that alprazolam be **reclassified as a Schedule 8 medication**, and that criteria for the prescribing of alprazolam be established along the lines of *"The Criteria for the Diagnosis and Management of ADHD in Adults"* established by NSW Health Pharmaceutical Services Branch (under The Poisons and Therapeutic Goods Act 1966).

Criteria for the Prescribing of Alprazolam could include the following:

1. That the prescribing of alprazolam is limited to patients with a diagnosis of **Panic Disorder where other treatments have failed or are inappropriate.**

2. That the assessment of the suitability of alprazolam as a treatment, and the initial prescribing of alprazolam be limited to **Psychiatrists who have been issued with an authority number** by Pharmaceutical Services Branch of the NSW Department of Health (similar to S28c for the prescription of psychostimulants for ADHD).

3. That an **application for an authority to prescribe** for an individual patient must be made where there is a history of **substance misuse or dependence.**

- Where this is a history of substance misuse or dependence, applications for authority to prescribe must be supported in writing by a detailed second opinion from an independent psychiatrist (e.g. from a different practice). The application or second opinion should be from **a psychiatrist experienced in drug and alcohol issues**.

- Applications may be referred to the Medical Committee, established under Section 30 of the Poisons and Therapeutic Goods Act, for its advice.

4. Applications may be accepted from the patient's General Practitioner or another treating practitioner after a minimum of 6 months with the treating Psychiatrist and with their approval. A letter from the Psychiatrist to this effect must accompany the application.

5. Applications from General Practitioners to increase the dose or change the drug must be accompanied by a report from the referring Psychiatrist supporting the change.

Many thanks for your consideration of these matters.

Yours faithfully,

Dr Glenys Dore, Clinical Director, Addiction Psychiatrist
Sue Banks, Manager Opioid Treatment Program
Dr Simon de Burgh, Senior Staff Specialist (Addiction Medicine)
Jennie Houseman, GP & Pharmacy Liaison Officer

References

Dore GM, Mawson K, Bezyan S. Clinical profile, doctor shopping and treatment in patients with high dose benzodiazepine dependence admitted for withdrawal management. Being prepared for submission to Medical Journal Australia.

Isbister GK, O'Regan L, Sibbritt D, Whyte IM. Alprazolam is relatively more toxic than other benzodiazepines in overdose. British Journal of Clinical Pharmacology 2004;58:88-95.

Jones K, Nielsen S, Bruno R, Lubman D. A Pinch in Every Bottle: Expert perspectives of alprazolam use in relation to offending. Poster at APSAD conference, Hobart, 2011.

Nielsen S et al. Pharmacodynamic interactions of alprazolam in buprenorphine-naloxone and methadone patients. Turning Point Alcohol & Drug Centre, 2011.

Coroners Court of Victoria
Level 11, 222 Exhibition Street Melbourne 3000
[redacted]
W www.coronerscourt.vic.gov.au

6 June 2013

The Secretary
Medicines and Poisons Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

RE: Delegate's interim decision on proposal to reschedule benzodiazepines

I write in response to the May 2013 notice of the delegate's interim decision and reasons for decision regarding the proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (the Poisons Standard).

As a person who made a valid submission in response to the initial public invitation for comment on the proposal, I wish to accept your invitation to make a further submission in response to the delegate's interim decision.

I welcome the indication that alprazolam will be rescheduled, but I maintain that all other benzodiazepines should also be rescheduled to (1) reduce the misuse, harms and deaths associated with these drugs, and (2) prevent the shifting of harms from alprazolam to other benzodiazepines. I adopt the reasoning of my colleague Coroner Audrey Jamieson, who is making a further submission under separate cover letter.

I will be pleased to consider any requests from you for further information or clarification regarding my submission. I can be contacted via my Executive Assistant Nola Los on (03) 8688 0720 or <nola.los@coronerscourt.vic.gov.au>.

Yours sincerely

[redacted]

Judge Ian Gray
State Coroner
Coroners Court of Victoria

Coroners Court of Victoria
Level 11, 222 Exhibition Street Melbourne 3000
[redacted]
W www.coronerscourt.vic.gov.au

6 June 2013

The Secretary
Medicines and Poisons Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

RE: Delegate's interim decision on proposal to reschedule benzodiazepines

I write in response to the May 2013 notice of the delegate's interim decision and reasons for decision regarding the proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (the Poisons Standard).

As the applicant whose recommendation in the death of David Trengrove was the basis for the original proposal, I wish to accept your invitation to make a further submission in response to the delegate's interim decision.

Please find my further submission and supporting material enclosed with this covering letter. The further submission represents my views as a coroner at the Coroners Court of Victoria, but not necessarily the views of Victoria's other coroners.

The essence of my further submission is that I welcome the indication that alprazolam will be rescheduled, but I maintain that all other benzodiazepines should also be rescheduled to (1) reduce the misuse, harms and deaths associated with these drugs, and (2) prevent the shifting of harms from alprazolam to other benzodiazepines. I note that the delegate's stated reasons in the interim decision for rescheduling alprazolam are equally applicable to other benzodiazepines including particularly diazepam.

I will be pleased to consider any requests from you for further information or clarification regarding my submission. I can be contacted via my Registry team on (03) 8688 0700 or <registryteam3@coronerscourt.vic.gov.au>.

Yours sincerely

[redacted]

Coroner Audrey Jamieson
Coroners Court of Victoria

Further submission

Preliminary matters

Delegate's interim decision

I note the delegate referred the rescheduling proposal to the Advisory Committee on Medicines Scheduling (ACMS). The delegate's interim decision was consistent with the ACMS advice and comprised the following elements:

1. That alprazolam be rescheduled from Schedule 4 to Schedule 8.
2. That the scheduling of the remaining benzodiazepines remains appropriate.
3. That benzodiazepines be included in Appendix D, paragraph 5 of the Poisons Standard.

I note the reasons for the interim decision comprised the following:

(a) Alprazolam has increased morbidity and mortality in overdose with possible increased toxicity. It does not appear to have any additional therapeutic benefits compared with any other substance in the class.

(b) There has also been a rapid increase in use of Alprazolam compared with other benzodiazepines and evidence of widespread misuse.

(c) Concerns of possible increased toxicity.

(d) Concern that current pack size is inappropriate for indications.

(e) There is evidence of abuse of the substance and misuse with opioids.

(f) Listing in Schedule 8 of Alprazolam does not restrict its short-term use for the approved indication.

Structure of the further submission

In this further submission I outline my responses to the three elements of the delegate's interim decision.

1. Response to interim decision on alprazolam

I support the delegate's interim decision to reschedule alprazolam from Schedule 4 to Schedule 8. Alprazolam is a contributing drug in many deaths reported to the Coroners Court of Victoria; a number of deaths have involved alprazolam obtained, through diversion, doctor shopping and/or inappropriate prescribing. The rescheduling will create opportunities to prevent these deaths as well as broader harms associated with alprazolam.

2. Response to interim decision on remaining benzodiazepines

On the evidence available to me I cannot support the delegate's interim decision that the scheduling of the remaining benzodiazepines remains appropriate. Rather I maintain my recommendation that all benzodiazepines must be rescheduled from Schedule 4 to Schedule 8. My reasons for pressing this recommendation are:

- Deaths reported to the Coroners Court of Victoria show that all benzodiazepines are targeted for misuse, diversion and doctor shopping, and that dependence, fatal and non-fatal overdose are issues across all benzodiazepines.
- The qualitatively similar pharmacological effects of all benzodiazepines mean that any initiative to limit access to one benzodiazepine will most likely shift harms to other benzodiazepines rather than reducing overall harms.

In particular, I cannot give support to the delegate's interim decision that diazepam should remain in Schedule 4. I received a copy of the Scheduling Evaluation Report dated 25 January 2013, in which the independent evaluator appointed by the ACMS considered my recommendation and concluded that:

> On pragmatic grounds [...] it is recommended that alprazolam and diazepam be rescheduled from S4 to S8 while the other benzodiazepines remain in S4.

I understand that the ACMS is not bound by the independent evaluator's conclusions. However as I indicated in my response to the Scheduling Evaluation Report (by letter dated 25 February 2013), the independent evaluator's report was balanced and thorough and the rescheduling of alprazolam and diazepam would create opportunities for death prevention while the Court monitored any signs of a shift in abuse and deaths to other benzodiazepines.

Finally, I note the delegate's stated reasons for the interim decision to reschedule alprazolam, if applied consistently, would support the rescheduling of at least diazepam and clonazepam in addition to alprazolam. The following is a point-by-point discussion of the stated reasons accompanied by empirical evidence to support my position.

(a) Alprazolam has increased morbidity and mortality in overdose

As described in my finding for the death of David Trengrove, the Court holds substantial data on Victorian deaths involving acute drug toxicity (drug 'overdose' deaths). Attachment A to this further submission contains a table of the most frequent individual contributing drugs in Victorian drug overdose deaths, for the years 2010-2012. It shows inter alia that:

- Diazepam was the most frequent individual contributing drug in Victorian drug overdose deaths for 2012. It contributed to a greater frequency of overdose deaths than heroin.
- Alprazolam was the sixth most frequent contributing drug.
- The other benzodiazepines among the most frequent contributing drugs were (in order) oxazepam, temazepam, nitrazepam and clonazepam.

This data suggests that a far greater mortality burden is associated with diazepam than alprazolam. This was explored further using the OD4 index, which is a standard index used to measure relative mortality burden in drug deaths.[1] The OD4 index for a drug is the annual frequency of overdose deaths associated with the drug per million defined daily doses of the drug dispensed in the year.[2] Attachment B explains and sets out the defined daily dose and OD4 calculations that were undertaken for diazepam, alprazolam, oxazepam, temazepam, nitrazepam and clonazepam. The overall results of the calculations are summarised in Table 1.

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1 See for example Pilgrim J, McDonough M, Drummer O, "A review of methadone deaths between 2001 and 2005 in Victoria, Australia", *Forensic Science International*, no 226, vol 1-3, 2013; Strang J, Hall W, Hickman M, Bird SM, "Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland", *British Medical Journal*, published online 16 September 2010, DOI 10.1136/bmj.c4851.

2 The defined daily dose is a standardised unit of measurement used by the World Health Organization and defined as: "[...] the assumed average maintenance dose per day for a drug used for its main indication in adults". See World Health Organization, "Defined daily dose: definition and general considerations", 17 December 2009, <http://www.whocc.no/ddd/definition_and_general_considera/>, accessed 31 May 2013.

Table 1. OD4 indices for alprazolam, clonazepam, diazepam, nitrazepam, oxazepam and temazepam, Victoria 2010-2012

Drug	OD4 2010	OD4 2011	OD4 2012	OD4 Average
Alprazolam	7.2	6	7.3	6.8
Clonazepam	67.2	109.5	130.7	102.5
Diazepam	9.5	11.4	10.8	10.6
Nitrazepam	5.5	4.3	9.1	6.3
Oxazepam	5.1	12.9	11.4	9.8
Temazepam	3.3	8	5.7	5.7

Table 1 clearly shows that alprazolam has the second-lowest OD4 index of the six benzodiazepines that most frequently contributed in Victorian overdose deaths, 2010-2012. Clonazepam had by far the largest OD4 index, followed by diazepam. This data indicates that alprazolam is not associated with increased mortality relative to other benzodiazepines.

(b) Rapid increase in alprazolam use and widespread misuse

I agree that there has been a rapid increase in alprazolam use, and that alprazolam is widely misused. However, I add that widespread misuse is not limited to alprazolam. In many overdose deaths involving other benzodiazepines reported to the Court, there is evidence of misuse and diversion.

(c) Alprazolam has possible increased toxicity

The OD4 data presented above does not support a claim that alprazolam is more toxic than other benzodiazepines. Clonazepam, diazepam and oxazepam were found to have higher OD4 indices than alprazolam.

(d) Concern that current pack size is inappropriate for indications

This could be addressed through reducing the pack size for alprazolam, and thus is a consideration of at best tangential relevance to rescheduling.

(e) Evidence of abuse of the substance and misuse with opioids

There is evidence across all benzodiazepines of abuse and misuse in combination with opioids. Diazepam is particularly concerning in this respect. Attachment C outlines recent Court research on the co-contribution of diazepam and opioids in Victorian overdose deaths, 2000-2012. The key findings were:

- Of 1284 Victorian overdose deaths involving diazepam between 2000 and 2012, pharmaceutical opioids were found to have co-contributed in 826 deaths (64.3%). Illegal drugs - the predominant drug being the illegal opioid heroin - co-contributed in 584 deaths (45.5%).
- Pooling all opioids (pharmaceutical and illegal), it was found that one or more opioids contributed in 1080 (84.1%) of the 1284 Victorian overdose deaths involving diazepam between 2000 and 2012.
- The relative co-contributions of different opioids varied over time. For example, heroin co-contributed to nearly 75% of the deaths in 2000, but by 2012 pharmaceutical opioids were the dominant co-contributors.

If evidence of abuse and misuse in combination with opioids is an important consideration, this evidence strongly indicates that at the very least diazepam should be rescheduled in addition to alprazolam.

(f) Listing in Schedule 8 of Alprazolam does not restrict its short-term use

This would be equally true of any other benzodiazepine and is therefore not a factor that recommends rescheduling of alprazolam over any other benzodiazepine.

3. Response to interim decision on remaining benzodiazepines

I support the delegate's interim decision that benzodiazepines be included in Appendix D, paragraph 5 of the Poisons Standard. I note the effect of this inclusion is that possession of benzodiazepines without authority (ie other than in accordance with a legal prescription) is illegal.

Attachment A

Table A1. *Annual frequency of deaths involving acute drug toxicity by drug involvement (single versus multiple drugs), Victoria 2010-2012*

Drug involvement	2010	2011	2012
Single drug toxicity	123 (36.4%)	129 (36.2%)	116 (31.6%)
Multiple drug toxicity	215 (63.6%)	227 (63.8%)	251 (68.4%)
All deaths	338 (100.0%)	356 (100.0%)	367 (100.0%)

Table A2. *Annual frequency of deaths involving acute drug toxicity by main contributing drugs, Victoria 2010-2012 (individual drugs were included that contributed in at least 12 deaths in any one year).*

Contributing drug	2010	2011	2012
Diazepam	108 (32.0%)	123 (34.6%)	131 (35.7%)
Heroin	139 (41.1%)	129 (36.2%)	109 (29.7%)
Codeine	55 (16.3%)	66 (18.5%)	89 (24.3%)
Alcohol	82 (24.3%)	85 (23.9%)	80 (21.8%)
Methadone	53 (15.7%)	72 (20.2%)	74 (20.2%)
Alprazolam	56 (16.6%)	43 (12.1%)	55 (15.0%)
Paracetamol	20 (5.9%)	24 (6.7%)	48 (13.1%)
Oxycodone	38 (11.2%)	46 (12.9%)	46 (12.5%)
Oxazepam	19 (5.6%)	44 (12.4%)	41 (11.2%)
Quetiapine	37 (10.9%)	33 (9.3%)	40 (10.9%)
Temazepam	21 (6.2%)	48 (13.5%)	36 (9.8%)
Methamphetamine	14 (4.1%)	29 (8.1%)	34 (9.3%)
Amitriptyline	25 (7.4%)	21 (5.9%)	33 (9.0%)
Mirtazapine	20 (5.9%)	23 (6.5%)	26 (7.1%)
Citalopram	21 (6.2%)	21 (5.9%)	25 (6.8%)
Nitrazepam	16 (4.7%)	11 (3.1%)	24 (6.5%)
Olanzapine	18 (5.3%)	17 (4.8%)	22 (6.0%)
Doxylamine	16 (4.7%)	11 (3.1%)	20 (5.4%)
Clonazepam	9 (2.7%)	14 (3.9%)	18 (4.9%)
Fentanyl	1 (0.3%)	5 (1.4%)	17 (4.6%)
Tramadol	8 (2.4%)	15 (4.2%)	17 (4.6%)
Venlafaxine	11 (3.3%)	16 (4.5%)	15 (4.1%)
Duloxetine	5 (1.5%)	7 (2.0%)	14 (3.8%)
Fluoxetine	9 (2.7%)	8 (2.2%)	14 (3.8%)
Metoclopramide	8 (2.4%)	8 (2.2%)	14 (3.8%)
Pharma. morphine	10 (3.0%)	10 (2.8%)	13 (3.5%)
Zopiclone	3 (0.9%)	6 (1.7%)	13 (3.5%)
Sertraline	6 (1.8%)	4 (1.1%)	12 (3.3%)
Amphetamine	10 (3.0%)	19 (5.3%)	11 (3.0%)
Buprenorphine	4 (1.2%)	14 (3.9%)	4 (1.1%)

Attachment B

The first step in calculating the OD4 indices for alprazolam, clonazepam, diazepam, nitrazepam, oxazepam and temazepam was to identify all Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) item codes for each drug. This was done using the PBS Schedule Search.[3] The amount of the drug contained in each item code was calculated as follows:

Dose strength of drug in item code × quantity of drug in the item code.

For example, item code 2723H was 25 tablets of 5mg nitrazepam, so the quantity of nitrazepam in item code 2723H was 125mg (5mg tablet strength × 25 tablets). Item code 2131E was 50 tablets of 0.5mg alprazolam, so the quantity of alprazolam in item code 2723H was 25mg (0.5mg tablet strength × 50 tablets).

The second step was to obtain the defined daily doses for the six drugs from the World Health Organization.[4] The defined daily doses are:

- Alprazolam 1mg
- Clonazepam 8mg
- Diazepam 10mg
- Nitrazepam 5mg
- Temazepam 20mg
- Oxazepam 50mg

With this information, the number of defined daily doses contained in each item code could be calculated as follows:

Amount of drug in item code ÷ defined daily dose of drug

For example, item code 2723 contained 125mg of nitrazepam, which was 25 defined daily doses (125mg ÷ 5mg defined daily dose). Item code 2131E contained 25mg alprazolam, which was 25 defined daily doses of alprazolam (25mg ÷ 1mg defined daily dose).

Finally, Medicare data cubes were used to extract the annual number of prescriptions dispensed on the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) in Victoria, 2010-2012, for each item code.[5] The annual number of dispensed scripts for each item code was multiplied by the number of defined daily doses contained in that item code, to derive the annual number of dispensed defined daily doses under that item code. The annual number of dispensed defined daily doses was summed across all item codes for each drug, to determine the total number of defined daily doses of clonazepam, diazepam, nitrazepam, oxazepam and temazepam that were dispensed on the PBS/RPBS in Victoria for each year 2010-2012 (see table B1).

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3 Accessed at Department of Health and Ageing, "Pharmaceutical Benefits Scheme (PBS)", <http://www.pbs.gov.au/pbs/home>.

4 Defined daily doses were obtained via World Health Organization, "ATC/DDD Index 2013", <http://www.whocc.no/atc_ddd_index/>.

5 Data cubes for PBS items by state and calendar year can be generated and downloaded at Commonwealth Department of Human Services, "Pharmaceutical Benefits Schedule Item Reports", <https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml>.

Table B1. Annual number of defined daily doses dispensed on the PBS/RPBS for alprazolam, clonazepam, diazepam, nitrazepam, oxazepam and temazepam, Victoria 2010-2012

Drug	2010 DDDs	2011 DDDs	2012 DDDs
Alprazolam	7,759,138	7,181,913	7,578,813
Clonazepam	133,974	127,858	137,674
Diazepam	11,324,100.0	10,907,605.0	12,100,145.0
Nitrazepam	2,900,025	2,570,725	2,645,575
Oxazepam	3,723,548	3,414,983	3,609,945
Temazepam	6,435,013	5,993,338	6,366,388

The OD4 index for a drug is the annual frequency of overdose deaths in which that drug is involved, divided by the annual number of defined daily doses dispensed for that drug, multiplied by 1,000,000. The OD4 indices for clonazepam, diazepam, nitrazepam, oxazepam and temazepam were calculated using this formula, and the results are shown in the tables below.

Table B2(a). Annual OD4 index for alprazolam, 2010-2012

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	7,759,138	56	7.2
2011	7,181,913	43	6.0
2012	7,578,813	55	7.3

Table B2(b). Annual OD4 index for clonazepam, 2010-2012

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	133,974	9	67.2
2011	127,858	14	109.5
2012	137,674	18	130.7

Table B2(c). Annual OD4 index for diazepam, 2010-2012

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	11,324,100	108	9.5
2011	10,907,605	124	11.4
2012	12,100,145	131	10.8

Table B2(d). Annual OD4 index for nitrazepam, 2010-2012

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	2,900,025	16	5.5
2011	2,570,725	11	4.3
2012	2,645,575	24	9.1

Table B2(e). Annual OD4 index for oxazepam, 2010-2012

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	3,723,548	19	5.1
2011	3,414,983	44	12.9
2012	3,609,945	41	11.4

Table B2(b). *Annual OD4 index for temazepam, 2010-2012*

Year	Annual DDDs dispensed	Annual deaths	OD4
2010	6,435,013	21	3.3
2011	5,993,338	48	8.0
2012	6,366,388	36	5.7

Attachment C

The Coroners Prevention Unit (CPU) maintains a database of deaths involving acute drug toxicity (overdose deaths) reported to the Coroners Court of Victoria. The following overview describes the subset of overdose deaths contained in the database for which diazepam was a contributing drug, and explores the co-contributory role of opioids in these deaths.

C1. Annual frequency

Using the overdose deaths database, the CPU identified 1284 Victorian deaths reported to the Court between 2000 and 2012 for which diazepam played a causal or contributory role.

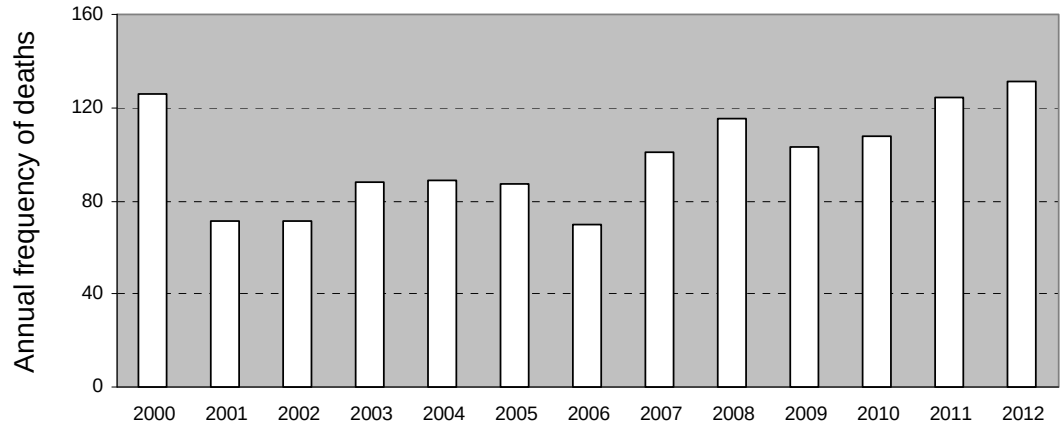

Figure C1: Annual frequency of overdose deaths involving diazepam, Victoria 2000-2012.

Figure C1 shows the annual frequency of overdose deaths involving diazepam fluctuated over time. In 2000 the frequency was 125 deaths; this dropped to between 70 and 90 deaths annually between 2001 and 2006, before lifting to over 100 deaths per year and reaching 131 deaths in 2012.

C2. Co-contributing drugs

Table 1 shows the frequency of overdose deaths involving diazepam, Victoria 2000-2012, by drug involvement (diazepam alone versus diazepam in combination with at least one other drug).

Table C1: Deaths involving diazepam classified by drug involvement, Victoria 2000-2012

Contributing drugs	n	%
Diazepam alone	2	0.2%
Multiple drugs including diazepam	1282	99.8%
Total	1284	100.0%

Deaths from multiple acute drug toxicity comprised the clear majority of overdose deaths involving diazepam (n = 1282, 99.8%).

To explore further the types of drugs that co-contributed with diazepam, the CPU classified each drug that co-contributed in each death using a modified version of the Drug Abuse Warning Network (DAWN) Drug Vocabulary level two groupings. The major CPU departure from DAWN practice, was that the CPU split the DAWN 'anxiolytics, sedatives, and hypnotics' category into a 'benzodiazepines' category' and a 'non-benzodiazepine anxiolytics, sedatives, and hypnotics' category, so that benzodiazepine contribution to deaths was clear.

Table C2 shows the most frequent co-contributing drug groups to Victorian overdose deaths involving diazepam, 2000-2012. Opioid analgesics were the top contributing drug group (n = 826, 64.3%), followed by antidepressants (n = 604, 47.0%) then illegal drugs (n = 584, 45.5%).

Table C2: Deaths involving diazepam classified by drug involvement, Victoria 2000-2012

Co-contributing drug types	n (N = 1284)	%
Opioid analgesics	826	64.3%
Antidepressants	604	47.0%
Illegal drugs	584	45.5%
Benzodiazepines	481	37.5%
Alcohol	403	31.4%
Antipsychotics	287	22.4%
Non-opioid analgesics	182	14.2%

C3. Diazepam and opioids

Pooling all opioids (including pharmaceutical opioids and the illegal drug heroin), the CPU found that one or more opioids contributed in 1080 (84.1%) of the 1284 overdose deaths involving diazepam.

To explore the nature of opioid co-contribution to overdose deaths involving diazepam over time, the CPU divided the annual frequency of deaths involving diazepam into four mutually exclusive groups:

- deaths to which heroin co-contributed but prescription opioids did not co-contribute;
- deaths to which both heroin and prescription opioids co-contributed;
- deaths to which prescription opioids co-contributed but heroin did not co-contribute; and
- deaths to which neither heroin nor prescription opioids contributed.

Figure C2 shows the annual frequency of deaths involving diazepam within each of these four groups.

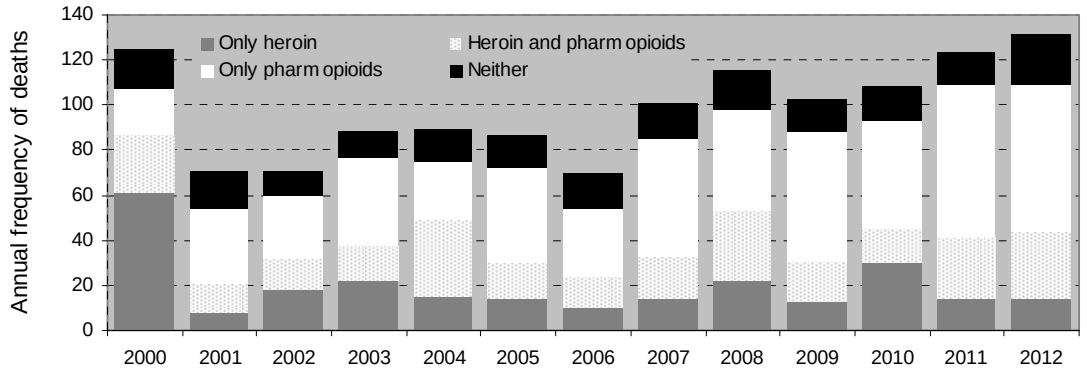

Figure C2: Annual frequency of overdose deaths involving diazepam by heroin and pharmaceutical opioid co-contribution, Victoria 2000-2012.

Figure C2 shows that over time, opioids contributed to a relatively steady proportion of annual overdose deaths involving diazepam. However, there were some notable shifts in the types of opioids that co-contributed. For example, in 2000 (at the height of the Victorian heroin 'glut') heroin co-contributed in around two-thirds of all

overdose deaths involving diazepam. This dropped to less than half in subsequent years, and by 2012 pharmaceutical opioids were the dominant co-contributors.