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16 January 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

RE: Proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8

I write in response to your notice inviting public submissions regarding a proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons (the Poisons Standard).

Victoria's coroners do not ordinarily engage in public submissions processes, as our findings into individual deaths are the primary vehicle through which we highlight public health issues and make recommendations aimed at preventing further deaths. However given the potential for the rescheduling proposal to reduce significantly drug related harms and deaths in the State of Victoria, I have determined it is appropriate for me to respond to your invitation.

Please find my submission and supporting material enclosed with this covering letter. The submission represents my views as the State Coroner of Victoria, but not necessarily the views of Victoria's other coroners.

The essence of my submission is that all benzodiazepines currently classified within Schedule 4 of the Poisons Standard should be reclassified to Schedule 8 of the Poisons Standard. Benzodiazepines are among the most frequent contributing drugs in Victorian deaths involving acute drug toxicity; rescheduling them will create opportunities to prevent the inappropriate prescribing, abuse and illicit diversion that underpin so many of these deaths.

I will be pleased to consider any requests from you for further information or clarification regarding my submission. I can be contacted via my Associate Lisa Nicholas on (03) 8688 0723 or <lisa.nicholas@justice.vic.gov.au>.

Yours sincerely

Judge Ian Gray
State Coroner
Coroners Court of Victoria

Submission

Preliminary matters

Structure of the submission

Under subsection 52D(2) of the *Therapeutic Goods Act 1989* (Cwth) ('the Act'), the Secretary of the Department of Health and Ageing may amend the current Poisons Standard. In exercising this power, the Secretary must take the following matters into account where relevant under subsection 52E(2) of the Act:

(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;

(f) any other matters that the Secretary considers necessary to protect public health.

Consistent with this framework, I have structured my submission in six parts, each of which addresses one of the subsection 52E(2) matters the Secretary must take into account when considering the proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 of the Poisons Standard.

Scope of the submission

In this submission I address the rescheduling proposal from a Victorian perspective, and do not consider the implications of the proposal for other states and territories of Australia.

Terminology

For convenience, throughout my submission I refer to the need to reschedule all benzodiazepines from Schedule 4 to Schedule 8 of the Poisons Standard. I am aware that flunitrazepam has already been moved to Schedule 8. In addition, while I refer to all benzodiazepines, my primary concern is with diazepam, alprazolam, oxazepam, temazepam and nitrazepam, which are the benzodiazepines most frequently involved in Victorian deaths.

1. Risks and benefits of benzodiazepines

I accept that benzodiazepines have therapeutic benefits for certain patients when prescribed and used appropriately. However I am deeply concerned that in Victoria benzodiazepines contribute to a substantial number of deaths from acute drug toxicity; many of these deaths occur outside the context of appropriate use and feature benzodiazepine dependence, diversion, prescription shopping,[1] inappropriate prescribing and multiple substance use.

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1 I have adopted the definition of prescription shopping set out in Parliament of Victoria Drugs and Crime Prevention Committee, *Inquiry into the Misuse/Abuse of Benzodiazepines and Other Forms of Pharmaceutical Drugs in Victoria: Final Report*, December 2007, p.108. The definition is: "[Prescription shopping] involves patients attending several doctors in order to obtain several prescriptions for controlled drugs so as to get a quantity of drugs greater than their therapeutic needs, which are then used for personal consumption or sold on the street market".

In this section I set out the empirical evidence regarding benzodiazepine involvement in Victorian deaths from acute drug toxicity. I then discuss the recurring themes that underpin these deaths. Finally, I present my reasons why the risks that benzodiazepines present can be better managed through shifting them from Schedule 4 to Schedule 8.

1.1 Benzodiazepine contribution to Victorian deaths from acute drug toxicity

In preparing this submission I directed the Coroners Prevention Unit (CPU)[2] to compile relevant information on the role of benzodiazepines in Victorian deaths from acute drug toxicity; the CPU provided two reports that I have attached to this submission.

By way of introduction, I note that the information the CPU provided pertains only to Victorian deaths from acute drug toxicity in which the expert death investigator (the investigating coroner and/or forensic pathologist) determined that the acute toxic effects of one or more benzodiazepines played a causal or contributory role. This is a very conservative measure of benzodiazepine contribution to Victorian deaths, as it excludes deaths associated with chronic use and deaths where the behavioural effects of benzodiazepines may have contributed.[3]

The first CPU report (see Attachment A) comprised an overview of deaths from acute drug toxicity reported to the Coroners Court of Victoria in 2010 and 2011, focusing particularly on the contribution of benzodiazepines to these deaths. Pertinent findings included:

- In 2010, 338 deaths from acute drug toxicity were investigated by the Coroners Court of Victoria. Benzodiazepines were the most frequent contributing drug group in these deaths (n = 165, 48.8%), followed by illegal drugs (n = 149. 44.1%) and opioid analgesics (n = 140, 41.4%).
- In 2011, 356 deaths from acute drug toxicity were investigated by the Coroners Court of Victoria. Benzodiazepines were the second most frequent contributing drug group in these deaths (n = 179, 50.3%), closely following opioid analgesics (n = 183, 51.4%).
- In both 2010 and 2011, the benzodiazepine diazepam was the second most frequent individual contributing drug after heroin to the Victorian deaths from acute drug toxicity (for diazepam n = 108 in 2010, n = 123 in 2011; for heroin n = 139 in 2010, n = 129 in 2011).
- Among the 344 deaths (165 in 2010, 179 in 2011) from acute drug toxicity where benzodiazepines contributed, the most frequent contributing benzodiazepines were diazepam (n = 231), alprazolam (n = 99), temazepam (n = 69) and oxazepam (n = 63). The overwhelming majority of the deaths (n = 335, 97.4%) involved other drugs co-contributing with benzodiazepines. The most frequent co-contributing drugs were the illegal drug heroin (n = 134), the opioid analgesics codeine (n = 99), methadone (n = 83) and oxycodone (n = 56), the antipsychotic quetiapine (n = 53), and alcohol (n = 86).

The CPU data shows that benzodiazepines play a central role in Victorian deaths from acute drug toxicity. Expert death investigators (coroners and forensic

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2 The Coroners Prevention Unit is a specialist service for Victoria's coroners created to strengthen their prevention role and provide them with assistance on issues pertaining to public heath and safety.

3 Examples of the latter category would be a motor vehicle crashes where the driver's performance was affected by benzodiazepines, and a drowning where the deceased was sedated by benzodiazepines.

pathologists) found that one or more benzodiazepines contributed in approximately 50% of Victorian acute drug toxicity deaths in 2010 and 2011: a greater proportion than either opioid analgesics or illegal drugs.

The CPU data further shows that while acute benzodiazepine toxicity alone is rarely the cause of deaths, benzodiazepines are ubiquitous in deaths from multiple drug toxicity. Fatal outcomes are particularly associated with combinations of benzodiazepines and heroin, opioid analgesics, alcohol and/or antidepressants. This finding is consistent with the extensive literature demonstrating that benzodiazepines produce strong additive or synergistic depressive effects on the central nervous system when combined with a broad range of other central nervous system depressants.[4]

The high risk of fatally toxic outcomes when benzodiazepines are combined with other central nervous system depressants is clearly illustrated in the second CPU report (see Attachment B), which describes the co-contributory role benzodiazepines played in Victorian deaths from acute drug toxicity involving the Schedule 8 opioid analgesics methadone and oxycodone. Pertinent findings included:

- Among 462 deaths from acute drug toxicity including methadone that were investigated by the Coroners Court of Victoria between 1 January 2000 and 31 December 2011, 389 (84.2%) were multiple drug deaths. Benzodiazepines were the most frequent co-contributing drugs with methadone; they played a co-contributory role in 278 (71.5%) of the 389 multiple drug deaths. Diazepam was the largest individual co-contributing drug, playing a role in 228 (58.6%) of the 389 multiple drug deaths.
- Among 265 deaths from acute drug toxicity including oxycodone that were investigated by the Coroners Court of Victoria between 1 January 2000 and 31 December 2011, 233 (87.9%) were multiple drug deaths. Benzodiazepines were the most frequent co-contributing drugs with oxycodone; they played a co-contributory role in 175 (75.1%) of the 233 multiple drug deaths. Diazepam was the largest individual co-contributing drug, playing a role in 128 (54.96%) of the 233 multiple drug deaths.

Again, these findings are consistent with the well-documented depressive effects produced by the combination of benzodiazepines and opioids. They are also consistent with the literature on benzodiazepine misuse, which shows that many people misuse benzodiazepines to enhance the effects of opioids, usually for recreational and/or quasi-therapeutic purposes.[5]

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4 See for example El-Guebaly N, Sareen J, Stein MB, "Are there guidelines for the responsible prescription of benzodiazepines?", *Canadian Journal of Psychiatry*, vol 55, no 11, November 2010, p.709; Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M, "A systematic review of research examining benzodiazepine-related mortality", *Pharmacoepidemiology and Drug Safety*, vol 18, no 2, February 2009, p.94; Ashton H, "Toxicity and adverse consequences of benzodiazepine use", *Psychiatric Annals*, vol 25, no 3, March 1995, p.158.

5 See for example Rowlett JK, Duke AN, Platt DM, "Abuse and dependence liability of GABA-A receptor modulators", in *The Receptors: The GABA Receptors*, edited by Enna SJ and Möhler H, 3rd edition, Totowa, New Jersey: Humana Press, 2007, pp.152-153; Griffiths RR, Weerts EM, "Benzodiazepine self-administration in humans and laboratory animals: implications for problems of long-term use and abuse", *Psychopharmacology*, vol 134, no 1, 1997, p.2; Reed K, Bond A, Witton J, Cornish R, Hickman M, Strang J, "The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England", *The National Addiction Centre*, Kings College London, 2011, p.15; Trafton JA, Ramani A, "Methadone: a new old drug with promises and pitfalls", *Current Pain and Headache Reports*, vol 13, no 1, February 2009, p.28.

1.2 Recurring themes in the deaths

The CPU reports included in Attachments A and B provide a valuable overview of benzodiazepine involvement in Victorian deaths from acute drug toxicity, however they do not provide detailed insight into the context and circumstances of the deaths, including the types of risky behaviours associated with benzodiazepine use and misuse that contributed to the deaths.

Therefore I asked CPU members who assist Victoria's coroners with investigations into a range of drug-related deaths for their observations on recurring themes in the deaths from acute drug toxicity including benzodiazepines. The following were the major themes identified:

- Many deceased obtained benzodiazepines through prescription shopping - that is, from multiple prescribers who were not aware of one another.
- Whereas prescribers usually exercised great caution with respect to Schedule 8 opioids, they often did not exercise the same caution with benzodiazepines. In a significant number of deaths, multiple doctors supplied benzodiazepines to the deceased upon request and without question.
- In many cases, the deceased had been prescribed benzodiazepines continually for several months if not years leading up to the death. On occasion the original purpose of the benzodiazepine prescribing had been entirely forgotten.
- Deaths from multiple drug toxicity including both benzodiazepines and opioids (illegal and/or prescription) occurred frequently among people with an established history of substance abuse. Of the 334 Victorian deaths from acute drug toxicity in 2010 and 2011 where benzodiazepines contributed, 139 deceased (41.6%) had an established history of substance abuse and died from the combined toxic effects of benzodiazepines and opioids.

These themes are reflected in recent findings published on the Coroners Court of Victoria website,[6] such as Coroner John Olle's finding in the death of James (surname redacted, court reference 20095181), Coroner Audrey Jamieson's finding in the death of David Trengrove (court reference 20084042), and Deputy State Coroner Iain West's finding in the death of Rory Denman (court reference 20104232).

1.3 Managing benzodiazepine risks through rescheduling

In 2010 and 2011, benzodiazepines contributed to more Victorian deaths from acute drug toxicity than any other drug group including opioid analgesics and illegal drugs. In nearly all cases benzodiazepines combined with other drugs, particularly central nervous system depressants, to produce the fatally toxic outcome.

The prevalence of benzodiazepine contribution in Victorian deaths from acute drug toxicity strongly indicates that they are inappropriately classified as Schedule 4 poisons, which are:

> Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.

Rather, they more closely fit the Schedule 8 description:

> Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

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6 Go to <http://www.coronerscourt.vic.gov.au/home/case+findings/>, where the public can search for findings by deceased name and/or court reference number.

Rescheduling benzodiazepines from Schedule 4 to Schedule 8 of the Poisons Standard will create new opportunities to prevent Victorian deaths from acute drug toxicity, thus ensuring that the public can receive the therapeutic benefits of these drugs while managing associated risks.

A central prevention opportunity created by rescheduling is that benzodiazepine prescribing would need to meet the Victorian Department of Health's permit requirements for prescribing of Schedule 8 poisons, which include:

> In order to ensure that Schedule 8 poisons are available to patients with genuine therapeutic needs whilst minimising the potential for concurrent prescribing and successful drug-seeking activities, medical practitioners must obtain a permit (section 34A(1)) from DPRG [the Drugs and Poisons Regulation Group]:
>
> - Before treating a drug-dependent person with any Schedule 8 poison. Permits to prescribe pharmacotherapy to treat opioid-dependence may be issued to medical practitioners who have been specifically approved by the DPRG.
> - To treat a person, who is not drug-dependent, with any Schedule 8 poison for a period greater than 8 weeks [...].[7]

With the permit requirements in place, prospective benzodiazepine prescribers would be required to reflect on the appropriateness of long-term prescribing and the dangers of prescribing to drug-dependent persons. In addition the Department of Health would be alerted when a doctor intended to prescribe to a person who was already receiving benzodiazepines and/or Schedule 8 opioids, and would be able to intervene with alerts and safety information. Prescription shopping for benzodiazepines would become much more difficult, thus reducing misuse and diversion of the drugs and associated deaths.

Further to this last point, another important prevention opportunity that would be facilitated through rescheduling benzodiazepines to Schedule 8 of the Poisons Standard, pertains to the real-time prescription monitoring system that is being developed and implemented throughout Australia to prevent prescription shopping and associated harms and deaths associated with prescription drug diversion and misuse.

The Australian Government has committed to introducing a real-time prescription monitoring system called the Electronic Recording and Reporting of Controlled Drugs initiative, or ERRCD. The ERRCD will collect information on all dispensing of Controlled Drugs (defined as Schedule 8 poisons), and make this data available to prescribers and dispensers:

> During a clinical interaction, authorised prescribers and pharmacists may access data on a consumer via a secure web portal that may help to inform their clinical decision-making. The ability of prescribers and pharmacists to view the history of Controlled Drugs that have been dispensed to a consumed will be a key feature of the system.[8]

If benzodiazepines are rescheduled to Schedule 8 of the Poisons Standard, all prescribing and dispensing will be recorded under the ERRCD initiative and the

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7 Victorian Department of Health, "Schedule 8 permit requirements plus notification requirements: information for medical practitioners", September 2010.

8 Australian Government Department of Health and Ageing, "Electronic Recording and Reporting of Controlled Drugs: Fifth Community Pharmacy Agreement Other Initiatives Factsheet", April 2012.

information made available to all prescribers and dispensers. This will further curtail opportunities for prescription shopping. Prescribers will know when a patient is receiving central nervous system depressants - particularly Schedule 8 opioids such as methadone and oxycodone - so they will be able to assess the appropriateness of the benzodiazepine prescribing put in place safety measures if necessary. The overall result, it is hoped, would be a reduction in harms and particularly deaths caused by multiple drug toxicity including benzodiazepines.

A third benefit is that the restrictions and requirements for prescribing Schedule 8 poisons in Victoria, closely match current clinical guidelines for prescribing benzodiazepines.

At present the benzodiazepines that contribute most frequently to Victorian deaths from acute drug toxicity are diazepam, alprazolam, oxazepam, temazepam and nitrazepam. The main approved clinical indications[9] for these benzodiazepines are to treat anxiety, panic disorder, insomnia and (for diazepam) symptoms of alcohol withdrawal.

I note that a broad range of recent clinical guidelines published both in Australia and internationally emphasise that, except in certain circumstances, benzodiazepines should only be prescribed on a short-term basis to treat the above conditions. For example:

- Recent guidelines for treatment of generalised anxiety disorder indicate that benzodiazepines can be used at any time to treat short-term (four to six weeks), acute, severe exacerbations of generalised anxiety disorder. In addition they are an appropriate short-term second-line treatment for generalised anxiety if first-line treatments such as psychological therapies and treatment with certain antidepressants fails.[10]
- Recent guidelines for treatment of panic disorder vary in their advice regarding benzodiazepines. The range of advice includes that benzodiazepines should never be prescribed for panic disorder, that benzodiazepines should only be used for short-term treatment of severe panic disorder, and that benzodiazepines can be used as a final resort when the patient cannot tolerate other recommended drugs.[11]

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9 As approved by the Therapeutic Goods Administration and listed on the Australian Register of Therapeutic Goods (ARTG). See Therapeutic Goods Administration, "eBS Australian Register of Therapeutic Goods and Devices", <https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuDevices?OpenView>, accessed 5 March 2012.

10 Therapeutic Guidelines, <http://online.tg.org.au/ip/>, *eTG Complete*, accessed 2 March 2012; Canadian Psychiatric Association, "Clinical Practice Guidelines: Management of Anxiety Disorders", *Canadian Journal of Psychiatry*, vol 51, supplement 2, July 2006; National Institute for Health and Clinical Excellence, "Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care," *NICE Clinical Guideline 113*, January 2011; Western Australian Psychotropic Drugs Committee, "Anxiety Disorders: Drug Treatment Guidelines", August 2008.

11 Therapeutic Guidelines, <http://online.tg.org.au/ip/>, *eTG Complete*, accessed 2 March 2012; Canadian Psychiatric Association, "Clinical Practice Guidelines: Management of Anxiety Disorders", *Canadian Journal of Psychiatry*, vol 51, supplement 2, July 2006; National Institute for Health and Clinical Excellence, "Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care," *NICE Clinical Guideline 113*, January 2011; Western Australian Psychotropic Drugs Committee, "Anxiety Disorders: Drug Treatment Guidelines", August 2008.

- Recent guidelines for treatment of insomnia indicate that a benzodiazepine is an appropriate treatment for acute insomnia expected to resolve within four weeks. Otherwise, a benzodiazepine might be an appropriate second-line treatment for chronic insomnia.[12]
- Recent guidelines for treatment of alcohol withdrawal symptoms identify diazepam as the gold standard first-line treatment. The recommended fixed dosing schedule for this purpose extends no longer than six days.[13]
- Throughout all the clinical guidelines, there are repeated warnings regarding the risk that patients will develop tolerance to and dependence on benzodiazepines if prescribed for a prolonged period (greater than four to six weeks).

The Victorian Department of Health requirement that a medical practitioner should obtain a permit to prescribe a Schedule 8 poison (a) for a period greater than eight weeks, or (b) to a drug-dependent person, closely aligns with the principles enunciated in the above clinical guidelines.

1.4 Concluding comment

In Chapter 3 of the *Scheduling Policy Framework for Medicines and Chemicals* dated 1 July 2010, the National Coordinating Committee on Therapeutic Goods set out its principles for poison scheduling and the standardised set of factors to be considered when making a scheduling decision. Three specific factors were listed for Schedule 8 controlled drugs:

1. The substance is included in Schedule I or II of the United Nations Single Convention on Narcotic Drugs 1961 or in Schedule II or III of the United Nations Convention on Psychotropic Substances 1971.
2. The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use.
3. The substance has an established therapeutic value but by reason of its novelty or properties carries a substantially increased risk of producing dependency, misuse, abuse or illicit use.[14]

I acknowledge that benzodiazepines have an established therapeutic value. However I submit that this therapeutic value must be balanced against the large number of Victorian deaths from acute drug toxicity involving benzodiazepines, and the misuse and abuse, prescription shopping and illicit diversion that underpins many of these deaths. These factors make Schedule 8 a more appropriate classification than Schedule 4 for benzodiazepines, with regard to the *Scheduling Policy Framework*.

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12 National Prescribing Service, "Addressing hypnotic medicines use in primary care", *NPS Newsletter*, no 67, February 2010; British Association for Psychopharmacology, "Consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders", *Journal of Psychopharmacology*, vol 24, no 11, November 2010; American Academy of Sleep Medicine, "Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults", Journal of Clinical Sleep Medicine, vol 4, no 5, 15 October 2008; Therapeutic Guidelines, <http://online.tg.org.au/ip/>, *eTG Complete*, accessed 2 March 2012.

13 Haber P, Lintzeris N, Proude E, Lopatko O, *Guidelines for the Treatment of Alcohol Problems*, Australian Government Department of Health and Ageing, June 2009; Amato L, Minozzi S, Vecchi S, Davoli M, "Benzodiazepines for alcohol withdrawal (Review)", *The Cochrane Library*, issue 3, 2010.

14 National Coordinating Committee on Therapeutic Goods, *Scheduling Policy Framework for Medicines and Chemicals*, 1 July 2010, p.25.

2. The purpose and extent of benzodiazepine use

I do not make any submission regarding the purpose and extent of benzodiazepine use.

3. The toxicity of benzodiazepines

The data provided by the CPU clearly demonstrates that although benzodiazepines alone are rarely the cause of Victorian deaths from acute drug toxicity, they frequently contribute to deaths in combination with other drugs, particularly central nervous system depressants such as heroin, pharmaceutical opioids, alcohol, antidepressants and certain antipsychotics. In assessing the toxicity of benzodiazepines, it is essential to consider the ubiquity of benzodiazepines in deaths from combined drug toxicity.

4. Dosage, formulation, labelling, packaging and presentation

I do not make any submission regarding the dosage, formulation, labelling, packaging and/or presentation of benzodiazepines.

5. The potential for benzodiazepine abuse

There is an extensive literature on benzodiazepine abuse and associated phenomena such as the reinforcing effect of benzodiazepines and the development of tolerance, dependence and withdrawal symptoms among users.[15] As already discussed, substance abuse - including abuse of benzodiazepines - features frequently among Victorian deaths from acute drug toxicity.

6. Any other matters

My colleague Coroner Audrey Jamieson made the following recommendation to the Commonwealth Department of Health and Ageing in her finding dated 18 May 2012 for the death of David Trengrove (court reference 20084042):

> Recommendation 3. To reduce the harms and death associated with benzodiazepine use in Victoria, within 12 months the Therapeutic Goods Administration of the Australian Government Department of Health and Ageing should move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons.

In the Therapeutic Goods Administration response to this recommendation dated 6 November 2012, National Manager Dr John Skerritt listed 11 factors that he considered in evaluating Coroner Jamieson's recommendation. These factors are reproduced verbatim here:

- The finding that Mr Trengrove died from the toxic effects of morphine in a setting of benzodiazepine dependency.

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15 See for example Tan KR, Rudolph U, Luscher C, "Hooked on benzodiazepines: GABA-A receptor subtypes and addiction", *Trends in Neurosciences*, vol 34, no 4, April 2011; Lalive AL, Rudolph U, Luscher C, Tan KR, "Is there a way to curb benzodiazepine addiction?", *Swiss Medical Weekly*, vol 141, 19 October 2011; Sievewright NA, Dougal W, "Benzodiazepine misuse", *Current Opinion in Psychiatry*, vol 5, no 3, June 1992; Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M, "A systematic review of research examining benzodiazepine-related mortality", *Pharmacoepidemiology and Drug Safety*, vol 18, no 2, February 2009; Rowlett JK, Duke AN, Platt DM, "Abuse and dependence liability of GABA-A receptor modulators", in *The Receptors: The GABA Receptors*, edited by Enna SJ and Möhler H, 3rd edition, Totowa, New Jersey: Humana Press, 2007; Licata SC, Rowlett JK, "Abuse and dependence liability of benzodiazepine-type drugs: GABA-A receptor modulation and beyond", *Pharmacology Biochemistry and Behavior*, vol 90, no 1, July 2008.

- The uncertainty about the role that benzodiazepines played in Mr Trengrove's death.
- Mr Trengrove's medical history (including his "significant history of mental ill health including schizophrenia, depression and psychosis" and his "history of use of ecstasy, protein supplements, alcohol and injecting testosterone and other steroids").
- The multiple medications he was using at the time of his death.
- The prescribing and use of prescription-only benzodiazepines in a manner contrary to the medicine's published Product Information, including Mr Trengrove's abuse of these prescription medications.
- Mr Trengrove's practice of "Doctor / Prescription Shopping".
- The admissions of Dr Thai Chin Lim "that his prescribing of benzodiazepines to Mr Trengrove was excessive and not correct".
- The lack of evidence that inclusion of benzodiazepines in Schedule 8 would have prevented Mr Trengrove's death, noting that general practitioners are still able to prescribe Schedule 8 medicines (albeit under a stricter regulatory framework).
- The further cost to Australian taxpayers of governments regulating benzodiazepines as Schedule 8 medicines.
- The additional regulatory impact upon the pharmaceutical industry of regulating benzodiazepines as Schedule 8 medicines.
- That benzodiazepines continue to be supplied as prescription-only medicines in countries such as the United Kingdom and USA.

Dr Skerritt concluded that, having considered these factors:

> [...] on balance, the TGA does not agree with the coroner's recommendation that all benzodiazepines should be moved into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons.

I note that this public consultation process was announced only three weeks after the TGA rejected Coroner Jamieson's recommendation. It is my respectful submission that the Therapeutic Goods Administration use the public consultation process as an opportunity to reconsider its position, as benzodiazepines contribute to a large number of Victorian deaths every year and moving them to Schedule 8 will create new opportunities to prevent these deaths.

Attachment A

Victorian deaths from acute drug toxicity, 2010-2011

The Coroners Prevention Unit (CPU) maintains a database of deaths from acute drug toxicity investigated by the Coroners Court of Victoria. The CPU used this database to prepare Attachment A, which describes deaths from acute drug toxicity reported to the Court in the years 2010 and 2011, and focuses on the contribution of benzodiazepines to these deaths.

A1. Acute drug deaths database

The following is a basic description of the CPU's acute drug deaths database, and the cases and data it contains.

A1.1 Definitions

Where a death is currently under investigation by a coroner, it is described as an 'open case'; likewise, where a coroner has completed his or her investigation into a death it is described as a 'closed case'.

The CPU definition of the term 'drug' is largely consistent with the Australian Bureau of Statistics (ABS) definition, encompassing substances that "may be used for medicinal or therapeutic purposes, or to produce a psychoactive effect".[16] Like the ABS, the CPU excludes tobacco and volatile solvents such as petrol and toluene from its definition of a drug. However, the CPU considers alcohol to be a drug, whereas it is excluded under the ABS definition.

A death from acute drug toxicity is a death for which the acute toxic effects of one or more drugs played a causal or contributory role. More specifically, a death from single drug toxicity is a death for which the acute toxic effect of a single drug contributed; a death from multiple drug toxicity is a death for which the acute toxic effects of two or more drugs contributed.

A1.2 Inclusion criteria

To be coded as a death from acute drug toxicity, the death must meet one of the following two criteria:

- the coroner's death investigation was complete and the coroner found that acute drug toxicity played a causal or contributory role in the death; or
- the coroner's death investigation was still under way and the forensic pathologist determined that acute drug toxicity played a causal or contributory role in the medical cause of death.

Deaths from causes other than acute drug toxicity where consumption of drugs by the deceased or another person may have contributed to the death (such as motor vehicle crashes and drownings) are excluded.

A1.3 Case identification

The CPU identifies potentially relevant deaths through searches (including keyword searches and coded field searches) of the CPU surveillance database, the National Coroners Information System (NCIS), and other coronial data repositories. The CPU uploads all potentially relevant deaths into the acute drug deaths database and reviews them to determine whether they meet the inclusion criteria.

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16 Australian Bureau of Statistics, "Drug-induced deaths: a guide to ABS causes of death data", 8 August 2002, p.2.

A1.4 Data collection

For each death meeting the inclusion criteria, the CPU records the following information: the deceased's age and sex; cause of death; and the suburb and local government area where the fatal drug consumption occurred. Additionally the CPU records every drug that the expert death investigator (coroner for closed cases, forensic pathologist for open cases) found to have made an acute toxic contribution to the cause of death. The coding rules for contributing drugs are:

- If the finding or forensic pathology report explicitly nominates the specific contributing drugs (for example "1(a) combined toxic effects of morphine and diazepam"), each nominated drug is coded as contributory.
- If the finding or forensic pathology report does not explicitly nominate the specific contributing drugs (for example "1(a) combined drug toxicity"), all drugs present in post-mortem toxicology are coded as contributory.

Further enhanced data is recorded where needed for specific projects; for example the deceased's history of drug use and abuse is recorded in many deaths, as is any evidence of prescription shopping behaviour.

A1.5 Limitations

The database only contains confirmed deaths from acute drug toxicity reported to the Court. Where (for example) a cause of death is not ascertained, or the contribution of acute drug toxicity is not clearly indicated, or contributing drugs cannot be established, the death is not included in the database, which may lead to an under-estimation of Victorian deaths from acute drug toxicity.

A2. Victorian deaths involving acute drug toxicity, 2010-2011

The CPU used the database to identify all deaths from acute drug toxicity that were reported to the Coroners Court of Victoria in the period 1 January 2010 to 31 December 2011.

A2.1 Annual frequency of deaths from acute drug toxicity

Table A1 shows the annual frequency of Victorian deaths from acute drug toxicity by drug involvement (single drug toxicity versus multiple drug toxicity) for 2010 and 2011. There was a slight increase between 2010 and 2011, which in the absence of broader trends data is probably not notable. Just over a third of deaths from acute drug toxicity each year involved a single drug, with the remainder involving two or more drugs.

Table A1: Annual frequency of deaths from acute drug toxicity by drug involvement, Victoria 2010-2011.

Drug involvement	2010	2011
Single drug toxicity	123 (36.4%)	129 (36.2%)
Multiple drug toxicity	215 (63.6%)	227 (63.8%)
Total	338 (100.0%)	356 (100.0%)

A2.2 Drug contribution by group to death

To explore further the drugs involved in these deaths, the CPU classified each drug that 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 A2 shows the most frequent contributing drug groups to Victorian deaths from acute drug toxicity in 2010 and 2011.[17] Benzodiazepines were the top contributing drug group in 2010 (n = 165, 48.8%), following by illegal drugs (n = 149, 44.1%) then opioid analgesics (n = 140, 41.4%). In 2011 opioid analgesics moved to be the top contributing drug group (n = 183, 51.45), followed closely by benzodiazepines (n - 179, 50.3%) then illegal drugs (n = 153, 43.0%).

Table A2: Annual frequency of drug group contribution in deaths from acute drug toxicity, Victoria 2010-2011.

Drug group	2010 (n = 338)	2011 (n = 356)
Benzodiazepines	165 (48.8%)	179 (50.3%)
Illegal drugs	149 (44.1%)	153 (43.0%)
Opioid analgesics	140 (41.4%)	183 (51.4%)
Antidepressants	102 (30.2%)	99 (27.8%)
Alcohol	82 (24.3%)	85 (23.9%)
Antipsychotics	64 (18.9%)	64 (18.0%)

A2.3 Individual contributing drugs

Table A3 shows the most frequent contributing individual drugs in Victorian deaths from acute drug toxicity for 2010 and 2011.[18] The illegal drug heroin was the most frequent individual contributor in both years, followed by the benzodiazepine diazepam. Other benzodiazepines included on the list were alprazolam, temazepam and oxazepam.

Table A3: Annual frequency of individual drug contribution in deaths from acute drug toxicity, Victoria 2010-2011.

Drug	Drug group	2010	2011
Heroin	Illegal	139 (41.1%)	129 (36.2%)
Diazepam	Benzodiazepine	108 (32.0%)	123 (34.6%)
Alcohol	Alcohol	82 (24.3%)	85 (23.9%)
Alprazolam	Benzodiazepine	56 (16.6%)	43 (12.1%)
Codeine	Opioid analgesic	55 (16.3%)	66 (18.5%)
Methadone	Opioid analgesic	53 (15.7%)	72 (20.2%)
Oxycodone	Opioid analgesic	38 (11.2%)	46 (12.9%)
Quetiapine	Antipsychotic	37 (10.9%)	33 (9.3%)
Amitriptyline	Antidepressant	25 (7.4%)	21 (5.9%)
Citalopram	Antidepressant	21 (6.2%)	21 (5.9%)
Temazepam	Benzodiazepine	21 (6.2%)	48 (13.5%)
Mirtazapine	Antidepressant	20 (5.9%)	23 (6.5%)
Paracetamol	Non-opioid analgesic	20 (5.9%)	24 (6.7%)
Oxazepam	Benzodiazepine	19 (5.6%)	44 (12.4%)
Methamphetamine	Illegal	14 (4.1%)	29 (8.1%)

17 Table A2 includes drug groups that contributed in at least 10% of Victorian deaths from acute drug toxicity in 2010 or 2011.

18 Table A3 includes individual drugs that contributed in at least 20 Victorian deaths from acute drug toxicity in 2010 or 2011.

A2.4 Deaths involving acute benzodiazepine toxicity

To determine the role of benzodiazepines in Victorian deaths from acute drug toxicity, the CPU pooled for further analysis the 344 Victorian deaths (165 in 2010, 179 in 2011) in which one or more benzodiazepines contributed.

Table A4 shows, in decreasing order of frequency, the individual benzodiazepines that contributed in each of the 344 deaths.[19] The most frequent contributing benzodiazepine was diazepam (n = 231, 67.2%) followed by alprazolam (n = 99, 28.8%) then temazepam (n = 69, 20.1%).

Table A4: Frequency of individual benzodiazepine contribution in the 344 deaths from acute drug toxicity, Victoria 2010-2011.

Benzodiazepine	n	%
Diazepam	231	67.2%
Alprazolam	99	28.8%
Temazepam	69	20.1%
Oxazepam	63	18.3%
Nitrazepam	27	7.8%
Clonazepam	23	6.7%
Midazolam	4	1.2%
Flunitrazepam	3	0.9%
Lorazepam	3	0.9%

Table A5 shows the 334 deaths from acute drug toxicity involving benzodiazepines, tabulated by the number of contributing benzodiazepines (one versus two or more), and by the number of non-benzodiazepine drugs that contributed (none versus one or more). Nine deaths (2.6%) involved acute toxic effects of benzodiazepines alone, whereas the remaining deaths (n = 335, 97.4%) involved benzodiazepines in combination with other drugs.

Table A5: Frequency of deaths from acute drug toxicity including benzodiazepines, by number of contributing benzodiazepines and number of co-contributing non-benzodiazepine drugs, Victoria 2010-2011.

Number of contributing benzodiazepines	Number of other (non-benzodiazepine) co-contributing drugs		
	None	One or more	*Total*
One	8 (2.3%)	206 (59.9%)	*214 (62.2%)*
More than one	1 (0.3%)	129 (37.5%)	*130 (27.8%)*
Total	*9 (2.6%)*	*335 (97.4%)*	*344 (100%)*

Table A6 shows the most frequent co-contributing drug groups in the 334 deaths from acute drug toxicity involving benzodiazepines.[20] Opioid analgesics are the top co-contributors (n = 225, 65.4%) followed by illegal drugs (n = 150, 43.6%) and antidepressants (n = 145, 42.2%).

19 Benzodiazepines that do not appear in the table (such as bromazepam, clobazam and triazolam) did not contribute in any deaths from acute drug toxicity during the period.

20 Table A5 includes drug groups that co-contributed in at least 10% of Victorian deaths from acute drug toxicity involving benzodiazepines in 2010-2011.

Table A6: Frequency of non-benzodiazepine drug group co-contribution to the 334 deaths from acute drug toxicity including benzodiazepines, Victoria 2010-2011.

Drug group	n	%
Opioid analgesics	225	65.4%
Illegal drugs	150	43.6%
Antidepressants	145	42.2%
Antipsychotics	98	28.5%
Alcohol	86	25.0%

Table A7 shows the individual drugs that most frequently co-contributed in the 334 deaths from acute drug toxicity involving benzodiazepines.[21] With the exception of alcohol, the top five most frequent co-contributing individual drugs were all opioids: heroin, codeine, methadone and oxycodone.

Table A7: Frequency of individual drug contribution in deaths from acute drug toxicity, Victoria 2010-2011.

Drug	Drug group	n	%
Heroin	Illegal	134	39.0%
Codeine	Opioid analgesic	99	28.8%
Alcohol	Alcohol	86	25.0%
Methadone	Opioid analgesic	83	24.1%
Oxycodone	Opioid analgesic	56	16.3%
Quetiapine	Antipsychotic	53	15.4%
Citalopram	Antidepressant	34	9.9%
Mirtazapine	Antidepressant	32	9.3%
Amitriptyline	Antidepressant	29	8.4%
Paracetamol	Non-opioid analgesic	29	8.4%
Olanzapine	Antipsychotic	26	7.6%
Methamphetamine	Illegal	24	7.0%
Doxylamine	Antihistamine	21	6.1%
Tramadol	Opioid analgesic	21	6.1%
Venlafaxine	Antidepressant	20	5.8%

21 Table A6 includes individual drugs that co-contributed in at least 20 Victorian deaths from acute drug toxicity involving benzodiazepines in 2010-2011.

Attachment B

Methadone, oxycodone and benzodiazepines

The database of deaths from acute drug toxicity investigated by the Coroners Court of Victoria, was described in detail in Attachment A to this submission. The CPU used this database to prepare Attachment B, which describes the subsets of deaths from acute drug toxicity including methadone and oxycodone reported to the Court in the years 2000 to 2011, and highlights the co-contributory role of benzodiazepines in these deaths.

B1. Victorian acute drug deaths involving methadone, 2000-2011

The CPU used the database to identify all deaths from acute drug toxicity including methadone that were investigated by the Coroners Court of Victoria in the period 1 January 2000 to 31 December 2011.

B1.1 Annual frequency of deaths

The CPU identified 462 Victorian deaths from acute drug toxicity including methadone reported to the Court between 2000 and 2011.

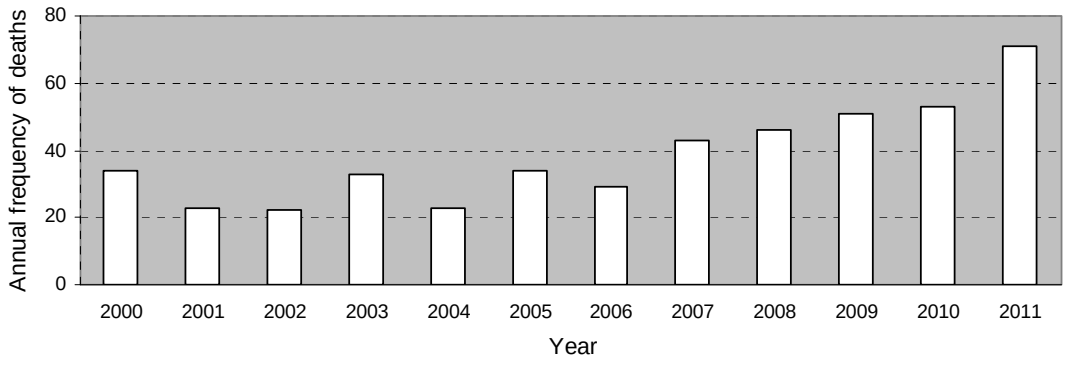

Figure B1: Annual frequency of deaths from acute drug toxicity including methadone, Victoria 2000-2011.

Figure B1 shows the annual frequency of deaths fluctuated between 2000 and 2005, before settling into a pattern of consistent year-on-year increases between 2006 and 2011. Notably, the annual frequency jumped from 53 deaths to 71 deaths between 2010 and 2011 - an increase of 34%.

B1.2 Co-contributing drugs

Table B1 shows the frequency of deaths from acute drug toxicity including methadone, by drug involvement (methadone alone versus methadone in combination with at least one other drug). The majority of deaths (n = 389, 84.2%) were from multiple drug toxicity.

Table B1: Deaths from acute drug toxicity including methadone classified by drug involvement, Victoria 2000-2011.

Drug involvement	n	%
Multiple drugs including methadone	389	84.2%
Methadone alone	73	15.8%
Total	*462*	*100%*

Using the same drug group classifications that were described in Attachment A, the CPU examined the drug groups that most frequently co-contributed with methadone

in the 389 multiple drug deaths. Table B2 shows that benzodiazepines were the most frequent co-contributors; they played a role in 278 multiple drug deaths involving methadone (71.5%). The next two most frequent contributing groups were illegal drugs (n = 157, 40.4%) and antidepressants (n = 148, 38.0%).[22]

Table B2: Frequency of drug group co-contribution to multiple drug deaths including methadone, Victoria 2000-2011.

Drug group	n	% of multiple drug deaths (n = 389)	% of all deaths (n = 462)
Benzodiazepines	278	71.5%	60.2%
Illegal drugs	157	40.4%	34.0%
Antidepressants	148	38.0%	32.0%
Opioid analgesics	125	32.1%	27.1%
Antipsychotics	76	19.5%	16.5%
Alcohol	68	17.5%	14.7%

Table B3 shows the most frequent individual drugs that co-contributed to the 389 deaths from multiple drug toxicity including methadone.[23]

Table B3: Most frequent individual co-contributing drugs to multiple drug deaths including methadone, Victoria 2000-2011. (%M is percentage of multiple drug deaths involving methadone; %A is percentage of all deaths involving methadone).

Drug	Drug group	n	%M	%A
Diazepam	Benzodiazepine	228	58.6%	49.4%
Heroin	Illegal	122	31.4%	26.4%
Codeine	Opioid analgesic	78	20.1%	16.9%
Alcohol	Alcohol	68	17.5%	14.7%
Alprazolam	Benzodiazepine	57	14.7%	12.3%
Oxazepam	Benzodiazepine	48	12.3%	10.4%
Methamphetamine	Illegal	45	11.6%	9.7%
Temazepam	Benzodiazepine	39	10.0%	8.4%
Olanzapine	Antipsychotic	32	8.2%	6.9%
Amitriptyline	Antidepressant	29	7.5%	6.3%
Nitrazepam	Benzodiazepine	29	7.5%	6.3%
Mirtazapine	Antidepressant	28	7.2%	6.1%
Oxycodone	Opioid analgesic	24	6.2%	5.2%
Paracetamol	Non-opioid analgesic	24	6.2%	5.2%
Quetiapine	Antipsychotic	24	6.2%	5.2%
Citalopram	Antidepressant	21	5.4%	4.5%
Venlafaxine	Antidepressant	19	5.0%	4.1%

The two most frequent co-contributing drugs in deaths from multiple drug toxicity including methadone were the benzodiazepine diazepam (n = 228, 49.4% of all deaths) and the illegal drug heroin (n = 122, 26.4%). Together with diazepam, four

22 Table B2 shows the drug groups that co-contributed in at least 10% of deaths from acute drug toxicity including methadone.

23 Table B3 shows the individual drugs that co-contributed in at least 5% of the 389 deaths from multiple drug toxicity including methadone.

other benzodiazepines were found to be frequent contributors: alprazolam, oxazepam, temazepam and nitrazepam.

B2. Victorian acute drug deaths involving oxycodone, 2000-2011

The CPU used the database to identify all deaths from acute drug toxicity including oxycodone that were reported to the Coroners Court of Victoria in the period 1 January 2000 to 31 December 2011.

B2.1 Annual frequency of deaths

The CPU identified 265 Victorian deaths involving acute oxycodone toxicity reported to the Court between 2000 and 2011. Figure B2 shows the annual frequency of deaths for the period 2000-2011. There was a steady increase in the annual frequency over time, from three deaths in 2000 to 46 deaths in 2011.

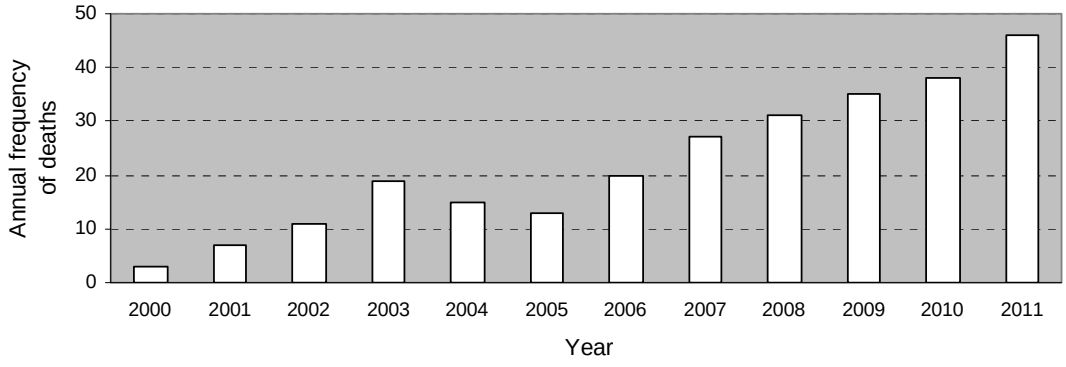

Figure B2: Annual frequency of deaths from acute drug toxicity including oxycodone, Victoria 2000-2011.

B2.2 Co-contributing drugs

Table B4 shows the frequency of deaths from acute drug toxicity including oxycodone, by drug involvement (oxycodone alone versus oxycodone in combination with at least one other drug). The majority of deaths (n = 233, 87.9%) were from multiple drug toxicity.

Table B4: Deaths from acute drug toxicity including oxycodone, classified by drug involvement, Victoria 2000-2011.

Drug involvement	n	%
Multiple drugs including oxycodone	233	87.9%
Oxycodone alone	32	12.1%
Total	265	100.0%

Table B5 shows that the drug groups that most frequently co-contributed with oxycodone to the 233 deaths from multiple drug toxicity.[24] Benzodiazepines were the most frequent co-contributors (n = 175, 71.5%), followed by antidepressants (n = 118, 50.6%) and opioid analgesics (n = 114, 48.9%).

Table B6 shows the individual drugs that most frequently co-contributed to the 233 deaths from multiple drug toxicity including oxycodone.[25]

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24 Table B5 shows the drug groups that co-contributed in at least 10% of deaths from acute drug toxicity including oxycodone.

25 Table B6 shows the individual drugs that co-contributed in at least 5% of the 265 deaths from multiple drug toxicity including oxycodone.

Table B5: Frequency of drug group co-contribution to multiple drug deaths involving methadone, Victoria 2000-2011.

Drug group	n	% of multiple drug deaths (n = 389)	% of all deaths (N = 462)
Benzodiazepines	175	75.1%	66.0%
Antidepressants	118	50.6%	44.5%
Opioid analgesics	114	48.9%	43.0%
Alcohol	68	29.2%	25.7%
Illegal drugs	43	18.5%	16.2%
Non-opioid analgesics	40	17.2%	15.1%
Antipsychotics	39	16.7%	14.7%
Non-benzodiazepine anxyolitics, sedatives, hypnotics	28	12.0%	10.6%

Table B6: Most frequent individual co-contributing drugs to multiple drug deaths including oxycodone, Victoria 2000-2011. (%M is percentage of multiple drug deaths involving oxycodone; %A is percentage of all deaths involving oxycodone).

Drug	Drug group	n	%M	%A
Diazepam	Benzodiazepine	128	54.9%	48.3%
Alcohol	Alcohol	68	29.2%	25.7%
Codeine	Opioid analgesic	64	27.5%	24.2%
Alprazolam	Benzodiazepine	41	17.6%	15.5%
Paracetamol	Non-opioid analgesic	36	15.5%	13.6%
Citalopram	Antidepressant	31	13.3%	11.7%
Amitriptyline	Antidepressant	30	12.9%	11.3%
Oxazepam	Benzodiazepine	30	12.9%	11.3%
Heroin	Illegal	28	12.0%	10.6%
Temazepam	Benzodiazepine	26	11.2%	9.8%
Methadone	Opioid analgesic	24	10.3%	9.1%
Tramadol	Opioid analgesic	24	10.3%	9.1%
Quetiapine	Antipsychotic	21	9.0%	7.9%
Doxylamine	Non-benzo anxiolytic	17	7.3%	6.4%
Mirtazapine	Antidepressant	17	7.3%	6.4%
Venlafaxine	Antidepressant	16	6.9%	6.0%
Fluoxetine	Antidepressant	15	6.4%	5.7%
Clonazepam	Benzodiazepine	13	5.6%	4.9%
Methamphetamine	Illegal	13	5.6%	4.9%
Morphine	Opioid analgesic	13	5.6%	4.9%

The benzodiazepine diazepam was the most frequent co-contributing drug (n = 128, 54.9%). Other frequent contributing benzodiazepines included alprazolam, oxazepam, temazepam and clonazepam.