Austin Health

Evidence to inform the inclusion of Schedule 4 prescription medications on a real-time prescription monitoring system

Department of Clinical Pharmacology and Therapeutics and Pharmacy Department

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List of tables

Commonly used abbreviations

ABS	Australian Bureau of Statistics
AIHW	Australian Institute for Health and Welfare
AOD	Alcohol and Other Drugs
ASM	Australian Statistics on Medications
CCOV	Coroners Court of Victoria
CPU	Coroners Prevention Unit
DDD	Defined daily dose
DHHS	Department of Health & Human Services
DUID	Driving under the influence of drugs
DUSC	Drug Utilisation Sub-Committee
ED	Emergency Department
FDA	US Food and Drug Administration
GABA	Gamma-Amino butyric acid
ICD	International Statistical Classification of Diseases and Related Health Problems-10th Revision
MDMA	methylenedioxymethamphetamine
NCIS	National Coronial Information System
NDARC	National Drug and Alcohol Research Centre
NOMAD	National Opioid Medications Abuse Deterrence
OPPIDUM	Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse
ORT	Opioid replacement therapy
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PDMP	Prescription Drug monitoring Program
PIC	Poisons Information Centre
RPBS	Repatriation Pharmaceutical Benefits Scheme
RTPM	Real time prescription monitoring
S4	Schedule 4 (Australian)
SAMHSA	Substance Abuse and Mental Health Services Administration
SNRI	serotonin noradrenalin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TCA	Tricyclic antidepressant
TGA	Therapeutic Goods Administration
TTAC	PDMP Training and Technical Assistance Center
VAED	Victorian Emergency Minimum Dataset
VPIC	Victorian Poisons Information Centre
WHO	World Health Organisation
Z-drug	Zolpidem or zopiclone

Executive Summary

Any Schedule 4 medications monitored by the real-time prescription monitoring (RTPM) system must be carefully chosen to sufficiently mitigate harm without adding to the regulatory burden of end users or diluting the impact of the RTPM on Schedule 8 medications. This report addresses many challenges surrounding collecting and interpreting information that might aid a truly informed decision as to which Schedule 4 medications should be monitored on a RTPM system to reduce medication-related morbidity and mortality. Overdose deaths, poisons information centre data, ambulance callout data as well as trends of use, misuse and abuse have been derived from the peer-reviewed literature and multiple local databases, delineating where possible the harm from individual medications. This has helped build an understanding of the evolution of harm from individual prescription medications so that current and future harms might be appreciated. Endpoints have been corrected for supply per prescription in order to estimate the true burden of harm for each drug and its potential for prescription monitoring.

Multiple confounders might influence these assessments, including forensic misattribution, misattribution in reporting, misestimates of supply and toxicity of combination compounds. Death due to a specific medication may represent not just direct pharmacological dangers and the cultural pattern of use, but also the type of consumer that is using it and their risk profile. The previous experience in Australia and the US has demonstrated two unintended systemic consequences of regulation: the chilling effect, where prescribers might make suboptimal changes in prescribing to avoid increased regulations, and the substitution effect, or ‘squeezed balloon’ effect, where harm is displaced to related medications if regulation is not coordinated across these medications.

Benzodiazepines were subject to the substitution effect with the rescheduling of alprazolam and there is no pharmacological or practical reason to think this would not occur again in the future. Clonazepam, alprazolam and diazepam are associated with high metrics of harm but all benzodiazepines seem harmful and, in any case, the evidence would strongly support a co-ordinated approach to monitoring all in this class to avoid the substitution effect. The z-drugs have similarly been associated with high metrics of harm and would also be susceptible to the substitution effect from benzodiazepines if not similarly monitored. Quetiapine has higher metrics of harm than other antipsychotics and many other medications, and has been strongly associated with trends of abuse. Its harm appears largely independent of heroin or methamphetamine. Schedule 4 codeine is associated with high total levels of harm but less so when considered in the context of supply, however multiple confounders make this interpretation difficult. Tramadol, pregabalin and gabapentin demonstrate a stable and low burden of harm proportionate to supply.

In summary, benzodiazepines and z-drugs confer a significant burden of harm and require a co-ordinated response across the class to reduce systemic harm. Quetiapine appears to represent a true and sustained source of harm markedly in excess of other antipsychotics and antidepressants. The harm from Schedule 4 codeine in the current regulatory environment appears mitigated although its estimation is subject to confounders. Other prescription medications examined did not demonstrate a large current direct correlation to prescription medication-related harm. Precedents suggest that, with effective implementation, a RTPM system could reduce the harm that carefully selected Australian Schedule 4 medications pose and, while not sufficient to control overdose deaths by itself, is likely to be an important innovation if supported by a suite of related measures.

Chapter 1. Introduction and rationale of research question

1.1. Why is a RTPM system required?

A real time prescription monitoring (RTPM) system is intended to monitor the prescribing and dispensing of prescription medications in a given jurisdiction, with information ideally accessible to prescribers, pharmacists and government regulators. It represents the most recent generation of prescription drug monitoring programs, and is intended to reduce inappropriate multiple prescribing events, reduce fraudulent prescribing and improve quality of care by facilitating a patient-centred approach in addressing prescription drug misuse(1). It also could be used to collect important data regarding trends of use of monitored drugs which are not currently collected in Australia and which could be used to direct other public health interventions. These benefits need to be weighed against concerns regarding increased regulatory burden for health practitioners having to check the system, prescription of suboptimal therapeutic options, wrongful categorisation and the potential for breaches of patient privacy through inappropriate use of the system. In the case of Victoria, these factors are under constant consideration from the Real Time Prescription Monitoring Taskforce in each aspect of implementation. It is in this context that this report has been commissioned by the Taskforce.

It should be noted that this report was commissioned in the context of an existing plan to implement a RTPM system in Victoria in 2018 and thus is not intended to address the overall validity of such plans. The authors strongly support the implementation of RTPM, but acknowledge the significant challenges in ensuring that implementation best serves the needs of all end users and the patients they serve.

1.2. Why might Schedule 4 medications be monitored?

Determination of which drugs should be entered as Controlled Drugs on Schedule 8 of the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons) is closely regulated. The Therapeutic Goods Administration (TGA) manages the scheduling of pharmaceutical drugs under the 'cascading' guidelines detailed in the Australian Health Ministers' Advisory Council's Scheduling Policy Framework(2). For a medication to be entered onto Schedule 8, the following factors must be met:

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.

Medications may still lead to significant harm as a consequence of misuse, abuse or illicit use and yet may not satisfy the above factors. Despite a process of constant reassessment (which has led to 'upscheduling' of a number of drugs in the context of changing patterns of use) the Poisons Standard and its associated regulatory mechanisms may be insufficient to optimally address risk of harm for all medications. The RTPM system might be able to detect and prevent emerging misuse (including therapeutic misadventure) and abuse in individual patients, as well as broader trends which might suggest changes in use or risk of diversion for individual medications.

Anecdotally there have been significant concerns regarding the harm that some Schedule 4 medications might cause, both locally and internationally. Diazepam has been considered by a number of key stakeholders as a potential source of significant harm from trends in their own data and personal experience, and was considered for 'upscheduling' at the same time as alprazolam in 2013, but was considered not to sufficiently meet the above factors. It may be the case that harm from such medications could be mitigated by the RTPM system without the burden of Schedule 8.

Limitations to monitoring Schedule 4 medications to a RTPM system

It is important to recognise that the RTPM system may be insufficient alone to optimally protect consumers from prescription drug-related harm, but that it may be part of an overall multifaceted solution. A number of organisations already exist to manage different aspects of this approach and monitoring of Schedule 4 medications should not be expected to remove the need for these organisations, nor does it necessarily reduce the benefit that might be derived from other interventions.

It is important that any RTPM system should be sufficiently inclusive as to adequately perform its purpose in mitigating harm without unreasonably adding to the significant regulatory burden that prescribers and pharmacists already face, or diluting the impact of the RTPM on the actions of prescribers and pharmacists related to Schedule 8 medications. Any decision to monitor a medication on the RTPM system must take this into account. It should be noted that there are no plans or precedents in Australia for inclusion of Schedule 4 medications in any other jurisdiction, although alprazolam was a Schedule 4 medication at the time of its inclusion in the Tasmanian RTPM system.

1.3. How should this report be interpreted, and what are its limitations?

This report was commissioned by the Victorian Department of Health and Human Services' Real Time Prescription Monitoring Taskforce to derive, in a limited timeframe, the existing evidence which would aid the decision to include or exclude Schedule 4 medications on the RTPM system. Due to restraints on cost and time, the depth of analysis of this report has been restricted to readily accessible data sources and may exclude other data. To this end, while previously unpublished data has been extracted and analysed from several different databases, the intention of this report is strictly only to support the stated aim rather than other academic interests. Use of this report for other purposes is therefore limited as the style and complexity of analysis has been performed with relevance to the research question in mind.

Use and replication of this report

Chapter 2. Scope of this report

The challenge faced in deciding on the inclusion of Schedule 4 medications on the RTPM system is that no organisation or researcher has previously addressed this specific situation. In addition, given that each intervention should be interpreted in the context of the environment surrounding it, there are few, if any, directly applicable precedents.

2.1. How can we understand the need for a drug to be included on the RTPM system?

There are three areas which might contribute to our understanding of a drug's suitability for inclusion for monitoring on a RTPM system:

- An estimation of the current harm that it confers in a local context with consideration to the amount and manner that it is used,
- An understanding of the trends in its misuse and abuse seen globally, to help us predict emerging threats of harm, and
- A survey of the precedents for monitoring the drug and subsequent changes to the burden of harm.

The combination of these three factors combined can be used to assess the current and future need for a drug to be increasingly monitored.

Not all three factors are equal. A burden of drug misuse or abuse rarely develops overnight; it progressively emerges over years. Some earlier indicators, such as observations of misuse, diversion and ambulance presentations, become evident earlier than other 'harder' endpoints such as drug-related overdose deaths. Given the process for adding new drugs is the future is yet to be confirmed, this window of opportunity must be utilised to ensure those drugs with current emerging trends are included. To this end, noting trends in overseas use may not carry the significance for current need that overdose deaths might, but it may be one of the better tools to fulfil the difficult task of predicting future need.

It should also be noted that it is crucial that data not be overextrapolated or considered without its broader context. Public health interventions do not exist in the context of a vacuum and inclusion of a drug by other jurisdictions does not mean it is appropriate, nor does apparent failure mean that the intervention is unsuccessful. The escalation over the last decade of prescription medication abuse in North America means that the trend itself is an escalating one, and effective programs have rarely achieved their goals without a co-ordinated multi-faceted response. Precedents may speak to the effectiveness of a similar intervention in Australia but only if viewed through the correct lens.

This report will address these factors in turn, and seek to interpret their significance to an Australian RTPM system, but no evidence will be able to guarantee the appropriateness or otherwise of including a drug.

Chapter 3. Approach to the research question

3.1 What data are important when considering evidence of harm from prescription drugs?

Harm can come about from prescription drugs in many different domains, and consequently there are many organisations that are responsible for monitoring these different domains. The diversity of organisation involved is further accentuated by a spread of governance for different domains of harm in Australia between federal and state government organisations as well as non-governmental organisations. A direct consequence of this decentralised data collection is that, while a large pool of data exists, it is highly heterogenous in nature as each organisation aims to collect data which serves the purposes relevant to that particular organisation.

This presents a significant challenge to answering this research question as no organisation has specifically sought to determine the harm from Schedule 4 prescription drugs, and thus such information has not been previously compiled. In considering Schedule 4 prescription drugs specifically, it is important to determine what information is useful.

Granularity of individual drug contribution to harm

The scheduling of drugs in Australia is determined on risk of harm from individual drugs rather than of overall drug classes(1). A consequence of this is that currently many important drug classes contain individual drugs in different schedules. Critically, tramadol, dextropropoxyphene and codeine (in combination formulations ≤30mg) are different to other prescription opioids in that they will all be regulated by Schedule 4 in 2018 (when codeine in combination formulations <30mg are due to be 'upscheduled' from Schedule 3 to Schedule 4), and alprazolam and flunitrazepam are the only benzodiazepines not regulated by Schedule 4.

Data collection which includes Schedule 4 medications seldom makes a distinction between medications based on schedule, and often measures of harm from medications are grouped by overall drug class. The Victorian Government itself, in collecting drug usage statistics, moved to collecting drug statistics aggregated by drug class from 2012 onward. This means that, to quantify total harm from schedule 4 drugs, one must study each potentially harmful drug individually within a data set rather than simple extraction by schedule. In the absence of accessible individual drug data, aggregated drug class data may help to suggest overall trends in harm when interpreted in combination with other data.

Combinations of individual drugs contributing to harm in an individual

One factor affecting the attribution of causality to individual drugs can be the combination in which they are taken, and whether that combination has the plausible capacity for additive toxicity. A benzodiazepine may be taken in a non-toxic, therapeutic range cumulative dose, but if taken in combination with other benzodiazepines similarly dosed can lead to harm. Similar harm may occur from the combination of drugs leading to pharmacodynamic drug

interactions such as between related drugs (such as gabapentin and pregabalin) and drugs with similar toxicities (such as drugs with high serotonergic potential). These combinations may be prescribed by a single prescriber, but may also be prescribed by different prescribers oblivious to the prescribing intentions of others.

The presence of such a drug combination helps to suggest that harm has been directly derived from the administration of drugs constituting the combination, and it would seem plausible that a RTPM system would help to identify this potential for harm at either a prescriber or pharmacist level. This is particularly the case where estimations of causality have been made more conservatively. Potentially harmful combinations are therefore of interest to this report where it is possible to examine them.

Intent associated with drug-associated harm

Prescription medications may be easily accessible and can be used by individuals to enact intentional self- harm or overdose from supratherapeutic use. The majority of pharmaceutical drug-related harm in Victoria, however, comes about from unintentional harm associated with therapeutic misadventure (Dwyer 2016). Many data sets have come to document perceived intent as this may be important in targeting preventative interventions. Given that a RTPM system might assist the prevention of intentional and unintentional harm, this information is considered not essential to the assessment. It should be noted, however, that understanding intent may be relevant in specific circumstances to allow for interpretation of future risk from the introduction of a RTPM system.

Demographic data associated with drug-associated harm

Location, age, sex and indigenous status are all frequently recorded in some data sets as they may be used to target certain interventions for at-risk groups. A RTPM system, by its nature, should be applied universally without discrimination and is designed to capture both self-use and diversion. For these reasons, demographic data have not been a focus of this assessment.

Examining diversion

Harm can come about as a direct or indirect consequence of diversion. Direct harm (eg crime associated with the theft of prescription medications) is unlikely to be affected by a RTPM system. An RTPM system will be likely to affect indirect harm from diversion (eg overdose from illicitly traded prescription drugs, if not modified to non-prescription drugs) in the same way as harm not arising from diversion, and similar overall metrics will capture indirect harm and harm not arising from diversion (eg overdose-related deaths). In addition, this report was asked to only consider the potential for misuse of prescription medications rather than modification of prescription medications to illicit drug substances (such as pseudoephedrine to amphetamines) or monitoring of such drug trends. For these reasons, diversion has not been specifically examined in this assessment.

3.2 How can we interpret data related to harm from prescription drugs in the context of changing usage and supply?

For a prescription drug to warrant increased monitoring it is more important to consider the harm that might arise proportional to usage or from an individual prescription rather than the overall burden of harm to the community. Drugs which are frequently used would be expected to inflict greater total harm to the community compared with less frequently used drugs and therefore total harm may not accurately reflect the risk posed by an individual prescription drug. Furthermore, increased usage of a drug over time may better explain an increase in total harm rather than other temporal trends in abuse or misuse. This distinction is not absolute as increased usage itself may reflect a temporal trend in abuse or misuse, particularly if this increased usage is not able to be otherwise readily explained.

Factors that may contribute to increased usage and supply

It is important to recognise that factors outside of trends in abuse or misuse may explain changes in overall use.

Changes in funding arrangements may alter rates of use, even if these seemingly appear to be subtle. Pharmaceutical Benefits Scheme (PBS) funding arrangements for pregabalin were changed in 2013 from a routine authority prescription limited to the Repatriation Pharmaceutical Benefits Scheme (RPBS) (which required the prescriber to make a phone call to an authority hotline) to a streamline authority prescription (which requires the prescriber to write a short alphanumeric code on the prescription). The subsequent increase in per capita consumption of pregabalin between 2011 (the last applicable year for data from the last Pharmacy Guild survey of private prescription dispensing) and 2016 could be conservatively estimated at thirteen-fold, from 233,059 prescriptions to 3,226,555 prescriptions (see Appendix 1). Furthermore on the RPBS, where access criteria were identical but the method of obtaining that approval changed, use itself changed markedly after this change in funding approval (Fig. 3.2.1).

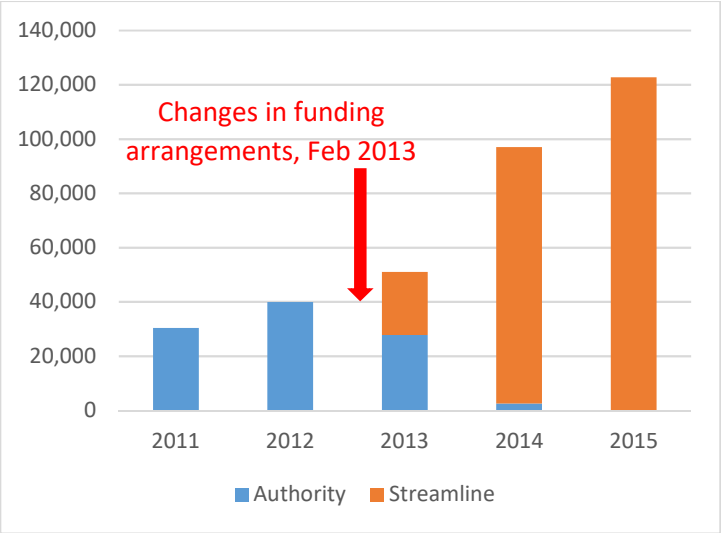


Figure 3.2.1. RPBS prescriptions in Australia for pregabalin for neuropathic pain, 2011-2015

Changes in regulation may also alter rates of use. The Therapeutic Goods Administration (TGA) scheduling delegate rescheduled alprazolam from Schedule 4 to Schedule 8, with implementation in February 2014. Poisons information calls(2) and other metrics consequently reduced in absolute quantity; this change however does not necessarily reflect a reduction in harm proportional to usage (i.e. harm on average from an individual prescription of alprazolam). Usage per capita through the PBS halved between 2012 and 2015 (see Appendix 1), complicating the harm proportional to usage. In addition, it should be noted that this can change rates of use and harm for related drugs whose regulation has not been co-ordinated, displacing use and harm to these drugs (known as the substitution or 'squeezed balloon' effect', see Figure 4.1.1.)

Any such statistics must therefore be interpreted in their overall funding and regulatory context.

Estimating harm per prescription

The estimation of harm proportional to usage is complicated by the difficulty in estimating usage in any given jurisdiction.

First, prescriptions for schedule 4 medications in Australia can be issued through parallel funding mechanisms without community-wide universal monitoring of use. Prescriptions can, depending on eligibility, be issued as eligible for PBS or Repatriation Pharmaceutical Benefits Scheme (RPBS) funding, but are subject to the restrictions on formulation, indication and quantity as specified in the PBS Schedule. Prescriptions can also be issued privately and schedule 4 medications prescribed in this manner are only recorded by the prescriber (or their organisation) and the dispensing pharmacy.

This usage has been of ongoing interest to the Pharmaceutical Benefits Advisory Committee (PBAC), and in particular, the Drug Utilisation Sub-Committee (DUSC) who make relevant data publicly accessible and for which there is significant precedent as a research tool(3). In the periods 1989-1999 and 2001-2011, DUSC commissioned the Pharmacy Guild of Australia to conduct an annual survey of sentinel pharmacies belonging to Guild members to estimate non-PBS prescription volumes. This included private prescriptions as well as PBS prescriptions priced under the general payment co-payment. At the time of data from the last survey in 2011, 370 dispensing pharmacies contributed data, and previously in 2002 the Australian Bureau of Statistics (ABS) had validated the representative nature of these pharmacies. As this survey was representative rather than comprehensive, the way in which these data were subsequently published by the DUSC in their annual Australian Statistics on Medications (ASM) report was as a defined daily dose per 1000 people per day (DDD) alongside equivalent data from the PBS. Using this proportion, it is therefore possible to estimate the private prescription usage in Australia up until 2011. A further estimate can be made using regression of the existing data to project private prescription DDD and thus total prescriptions from 2012 onward. This process and its details are illustrated in chapter 4.2. This estimation of supply can be used (as it has done by other investigators(4, 5)) to calculate a normalised rate of deaths or incidents per prescription, known as a fatal toxicity

index(6) or incident toxicity index. This has been expressed in this report as deaths or incidents per million prescriptions. The indices are expressed per prescription, as opposed to by per number of defined daily dose (DDD). While this does facilitate comparison at the state level more easily (where DDD data is not published), more importantly is this more relevant for a prescription monitoring system where any points of systematic control occur a set number of times per prescription (at prescribing, dispensing etc). This might argue to bias against drugs which provide smaller numbers of DDDs per prescription, but the more valid comparison for this report is the relative evidence of harm in the current context, including the current regulatory environment, which includes limited supply per script.

This approach is limited by a number of factors, importantly including the presumption that trends in use are progressive and are not subject to significant external variables which might invoke sudden changes in the patterns of use such as the changes in funding arrangements and regulation as detailed above. The possible effect of these factors, especially on alprazolam and pregabalin, is noted in commentary throughout the relevant parts of this report.

Secondly, it should be noted that diversion might complicate estimations of use. These data will capture diversion from individual prescriptions filled in Australia but may not capture data from non-prescription diversion or access from overseas sources. Importation of Schedule 4 prescription drugs for personal use is allowed under TGA regulations however is unlikely to be a significant factor for the prescription drugs examined given their affordability under the PBS and the absence of regulation. Future assessments following the implementation of a RTPM system should consider the role of importation if possible as increased monitoring may lead to a preference for access through this method.

Thirdly, it should be noted that standard prescriptions are for variable numbers of defined daily doses and thus comparisons of the total number of prescriptions may not represent the total burden of medication consumed. It might be considered that the total number of prescriptions is a better consideration for the risk of overdose that might be improved by a RTPM system. It should nevertheless be considered that prescriptions for medications such as clonazepam may allow for over six months' supply of normal use and may therefore underestimate use and overestimate harm proportional to usage.

It is nevertheless of greater utility to consider the impact of prescription drugs in the context of harm per prescription using the methods above than to consider total harm in isolation. This report therefore publishes, where appropriate, both absolute harm and harm proportional to prescription usage.

Chapter 4. Evidence of harm in Australia from Schedule 4 medications

The first factor considered in understanding the suitability of drugs for inclusion for monitoring on a RTPM system is an estimation of the current harm that it confers in a local context with consideration to the amount and manner that it is used.

To this end, this report has assessed data relating to different elements of harm in Australia. Two broad categories of data sources exist: that available in the indexed peer-reviewed literature, and that available from local databases, whether published in reports (commonly referred to as 'grey literature') or raw data (either collated statistics or raw data sets).

4.1. Indexed peer-reviewed literature and selected other reports

The methodology for this review of the peer-reviewed literature is articulated in Appendix 2, and is described in a narrative form given the gross heterogeneity of the data sources. It should be noted that data published in the peer-reviewed literature often reflects aggregated summaries obtained from local databases. This report will describe the peer-reviewed literature as it is published but will suggest where further information can be found in following sub-chapters. It is crucial that the peer-reviewed literature and the other reports discussed in this section are not considered a comprehensive assessment of local evidence for harm as significantly more detail is often available in data from local databases.

One Australian source of peer-reviewed literature of note is that derived from the Hunter Area Toxicology Service based in Newcastle, New South Wales (NSW). Since its establishment in January 1987, this service has provided a full toxicology treatment service and, since 1992, has comprehensively captured structured prospective data on every adult (age ≥14 years) toxicology presentation to any hospital in the area in its catchment of approximately 500,000 people through its referral service(1). A number of peer-reviewed articles have been derived from this database, and it provides a valuable local cross-sectional insight into typical usage habits and overdose.

Opioid medications (codeine, tramadol, dextropropoxyphene)

It is well documented that there has been increasing usage of prescription opioids in Australia, and overall unaggregated harm has mirrored this rise. This is described in a published overview of publicly available data from Australian Institute for Health and Welfare (AIHW) sources(2). This study first examined opioid-related hospitalisations recorded in the National Hospital Morbidity Database excluding those from heroin, methadone and other narcotics, and showed an increase from 605 to 1464 cases from 1998 to 2009. The death rate cumulatively due to accidental poisonings from illicit and prescription opioids recorded in the Australian Bureau of Statistics (ABS) Causes of Death increased from 0.78 to 1.19 deaths per 100,000 people between 2002 and 2011. More recent data from the same sources but specific to Victoria demonstrated a similar phenomenon(3). Data from either

study cannot be delineated further due to the methods of collection and more recent data are presented in chapter 4.8 using the same data sources.

More specifically, the rise in codeine-related deaths in Australia has been well documented and has heavily contributed to a decision to reschedule over-the-counter codeine in December 2016. Data from the National Coronial Information System (NCIS) showed an increase in the rate of codeine-related deaths from 3.5 per million in 2000 to 8.7 per million in 2009, equivalent to approximately half of the burden of deaths from Schedule 8 opioids(4). Most of these deaths were due to multiple drug toxicity and were accidental rather than intentional overdoses. In a cohort of unexpected deaths where alprazolam was detected, codeine was the second most commonly detected individual drug after diazepam(5). It should be noted that this is on the background of a significant base of codeine abuse. In the National Opioid Medications Abuse Deterrence (NOMAD) study, which included a survey of patients who inject, snort, chew or smoke prescription opioids, 43-61% had used codeine recently, although few experienced overdose(6, 7). Codeine was also the equal most common presenting problem drug in a survey of clients of Australian drug treatment services who had graduated from prescription drug misuse(8), and the number of people being treated for primarily for codeine dependence more than tripled in the eight years between 2002-3 and 2010-11(9) . Codeine has therefore led to a large burden of mortality in the context of an even broader base of possible abuse.

In contrast, few data from the peer-reviewed literature exist about tramadol-associated morbidity and mortality, and those which do largely focus on tramadol's serotonergic properties and the potential for serotonin syndrome when combined with other drugs of high serotonergic potential. An observational case series examined all 71 tramadol overdoses captured by the Newcastle toxicology service prospective cohort between 2000 and 2013, and while seizures occurred in 8 patients and respiratory depression in 13 patients, no patients developed serotonin syndrome despite many of them also ingesting other serotonergic medications(10). A qualitative description of serotonergic risk in patients using methylenedioxymethamphetamine (MDMA) also suggested that the risk of serotonin syndrome with co-ingested tramadol was low. A coronial series looking at deaths over seven years involving serotonergic drugs found tramadol was detected in 11 of 28 cases with possible serotonin toxicity, but only in 1 of 5 cases where the pathologist reported serotonin toxicity, and in this case tramadol was combined with citalopram(11). Apart from this and another case report of a single tramadol overdose patient experiencing serotonin syndrome (12), there are few other data to suggest this clinical situation is common and while other cases may not have been reported as they may not have been considered sufficiently novel, on the basis of the representative cohort the risk of serotonin syndrome from tramadol overdose appears a lesser concern.

It should be noted that, in the NOMAD cohort, tramadol was infrequently used by those manipulating prescription opioids despite the corresponding high rates of tramadol prescribed at the time of the survey(6, 7), very few unexpected deaths where alprazolam was detected also had tramadol detected(5), only one person was abusing tramadol in a survey of 75 prescription opioid abusing clients of Australian drug treatment services(8) and amongst patients who had received buprenorphine or methadone and had needle syringe

programmes, very few reported tramadol use(13). It therefore seems less likely that tramadol is commonly abused.

Following electrophysiological cardiac concerns(14) and the identification of a ten-times increased risk of mortality with dextropropoxyphene-paracetamol compared to codeine-containing compounds(15), dextropropoxyphene was planned to be withdrawn in Australia in line with actions in other countries(16, 17). A series of appeals made to the Administrative Appeals Tribunal in 2013(18), however, subsequently led to two products remaining available in Australia subject to mandated prescribing regulations aimed at improving prescribing and reducing prescription shopping(19). As a consequence, few peer-reviewed data have subsequently been recorded about dextropropoxyphene. It should be noted that no deaths due to dextropropoxyphene were recorded between 1991-2010 in the Newcastle toxicology service(1).

Benzodiazepines

There has been an increasing burden of harm noted in Australia from benzodiazepines. As a drug group, benzodiazepines have been recorded as causing the highest attendance rates for ambulances in Melbourne(20, 21), the highest number of presentations for medication-related overdose to an inner-city Melbourne emergency department(22), causing the highest number of presentations for deliberate self-poisoning to a different large health network in Melbourne(23), being the most commonly detected prescription drug class in injured Victorian drivers following motor vehicle accidents(24), and the largest cause of admissions to the comprehensively captured Newcastle toxicology service prospective cohort(1). It was also the most common prescription medicine recently taken by drug and alcohol service clients in a survey in Sydney(25). Local and global trends in misuse and abuse are further described in greater detail in chapter 5.1 of this report but what is clear is that regular benzodiazepine use is associated with a significantly increased rate of benzodiazepine-related mortality, particularly in non-elderly populations(26), and while the proportion of poisonings in older people attributable to benzodiazepines is decreasing, it still remains the greatest contributor by drug class(27).

Benzodiazepines appear to be particularly hazardous in combination with opioids, an escalating trend globally which has been associated with escalating harm in large cohorts(28), and is also addressed in chapter 5.1 in the section ‘Combination with other drugs’. Beyond the additive risk of respiratory depression conferred by both drugs, the reason for the increased risk from this combination is unclear(29). In Australia, heroin users are more likely to clinically overdose if they have recently used benzodiazepines(30), and methadone users even more so(31). It is also notable that the majority of deaths associated with alprazolam were accidental multidrug overdoses(5) and there is no clear reason why this would be unlikely to extend to other benzodiazepines. This is all particularly concerning as this is not an infrequent combination, with 19% of people in the NOMAD cohort of opioids abusers having benzodiazepine dependence(7).

It is nevertheless difficult to separate the possibility of confounding from benzodiazepines, as a frequently used drug, acting as ‘bystander’ drugs. It is particularly commonly used in high-

risk individuals, having been shown in different Australian cohorts to be the most commonly combined drug with prescription opioids(32), buprenorphine opioid replacement(13) and alcohol(21). It has also been shown that pre-incarceration benzodiazepine use is associated with non-fatal overdose in injecting drug users recently released from prison in Queensland(33). It is correspondingly hard to interpret, from the peer-reviewed literature, to what extent benzodiazepines are culpable for harm or to what extent they are 'bystander' drugs who may even have putative effects in attenuating drug-induced manic violence and the corresponding harm to users and others.

Another limitation of the peer-reviewed literature for evidence of harm from benzodiazepines in Australia is that it is almost all unaggregated between different benzodiazepines in the period prior to rescheduling of alprazolam. Prior to rescheduling, alprazolam had been the fastest growing drug in class for emergency department presentations(34) and, in the twelve months following rescheduling, prescribing, dispensing, and poisons information centre calls all reduced(35). This means that harm arising from alprazolam may have subsequently reduced and concordantly reduced the overall harm associated with the drug class. It should be noted that, with an unco-ordinated response across all benzodiazepines, patients might preference the less regulated Schedule 4 benzodiazepines and derive more harm from these(36) (harm from the restricted benzodiazepine causing displacement of harm to other benzodiazepines, known as the substitution effect or 'squeezed balloon' effect).

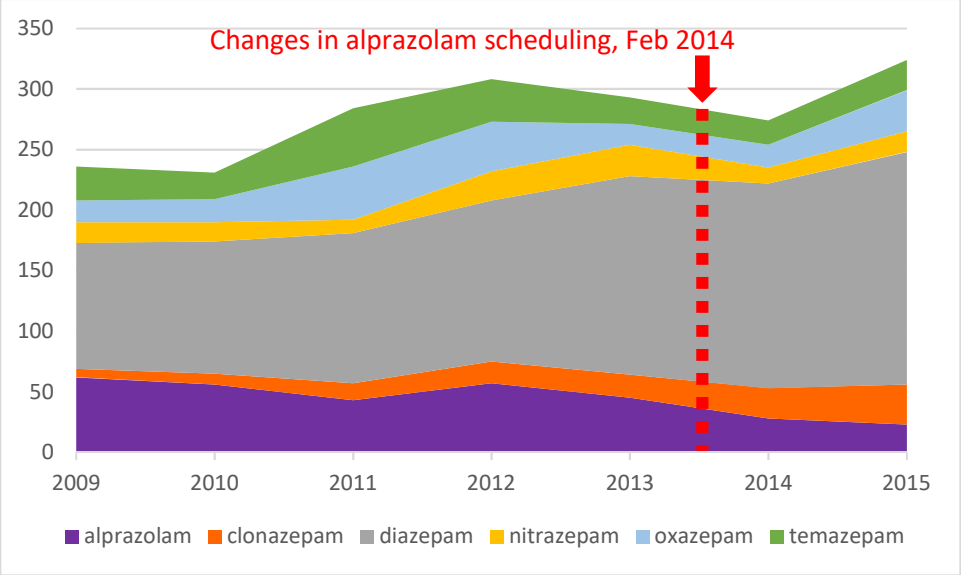


Figure 4.1.1. Coroners Court of Victoria overdose deaths register (Coronial Prevention Unit), benzodiazepine related deaths by year. Area relates to frequency; multiple specific benzodiazepines may have contributed to a single death so overall area overrepresents total deaths. Note as alprazolam related deaths (represented by the purple segment) decrease, diazepam (grey segment) and clonazepam (orange segment) related deaths increase. This constitutes the substitution effect (or 'squeezed balloon' effect), where an uncoordinated response leads to the restricted drug being displaced by others in class. Constructed from data published by Lloyd et al.(36)

In summary, in the peer-reviewed literature benzodiazepines do seem to represent an increasing source of harm in Australia, particularly in combination with other drugs, but the peer-reviewed literature alone is insufficient to appreciate the impact of Schedule 4 benzodiazepines or the potential effect of mitigating confounders such as 'bystander' status and changes after the rescheduling of alprazolam.

Other sedatives ('z-drugs', barbiturates, baclofen, doxylamine, clonidine)

The 'z-drugs', of which only zolpidem and zopiclone are registered by the TGA for human use in Australia, were initially intended to be improvements on benzodiazepines by more selectively targeting the same GABA-A receptors, and were intended to not impair memory and cognition as greatly as benzodiazepines but still lead to sedation and coma in overdose(37) and have been associated with amnesia and compulsive behaviour in Australia(38). In NSW, a cohort looking at Department of Forensic Medicine cases between 2001-2010 where zolpidem was detected showed toxicity in one-third, but also showed death as a consequence of compulsive behaviour in two other cases, although in the context of usage at that time the authors felt the number of cases was "relatively small"(39). More current data are found later this chapter.

Phenobarbital is one of only two barbiturates registered by the TGA for human use in Australia and has increasingly infrequently used with the introduction of newer anti-epileptics; consequently, few data describe its associated harm in Australia. It should be noted that in the Newcastle toxicology service prospective cohort that prescribing steadily declined over the time of the study period to become almost negligible, and that from 1993 onward overdoses were only occasional. No data were captured for primidone.

Baclofen, a GABA-B receptor agonist, has been used for spasticity and increasingly off-label for alcohol abuse. It lacks the affinity for the GHB receptor that gamma-hydroxybutyric acid has, and has not been associated with euphoria and the consequent abuse potential. Its withdrawal syndrome, in contrast, can present with a marked withdrawal delirium. In addition, baclofen does have some GABA-A effect which can lead to sedation and anxiolysis and cases of abuse in Australia with and without suicidal intent have been reported(40). In a ten year experience from the Newcastle toxicology service prospective cohort, 23 overdoses were seen with no associated deaths(41).

Doxylamine, a first generation antihistamine, had a mild sedative effect and is frequently sold in combination with analgesics or pseudoephedrine in order to aid sleep. Few Australian data have explored harm that might arise from it independent of other drugs in combination.

Clonidine, a centrally acting alpha-2 adrenergic agonist and imidazoline receptor agonist, was initially used as an anti-hypertensive, but in the last thirty years has come to be used for opioid and alcohol dependence, sedation and attention deficit hyperactivity disorder. Despite being prescribed to potentially high risk patients, few data describe overdose in Australia. Between 1988-2015 in the Newcastle toxicology service prospective cohort there were only 133 admissions for clonidine poisoning, and none of died or had other severe toxicity(42).

Anti-psychotics

As a class, there has been increased visibility from the overall burden of antipsychotic-related harm in Australia. In the Newcastle toxicology service prospective cohort, there was a large increase in atypical antipsychotic-related overdoses from 2002 to 2012 as a proportion of total overdoses(1). A further subgroup analysis in this cohort showed that this increase was accompanied by a proportionate decrease in typical antipsychotic-related overdoses, and that while the absolute number of total antipsychotic overdoses increased by 1.8 times over 26 years, total antipsychotic prescribing increased by 2.3 times over the same period(43).

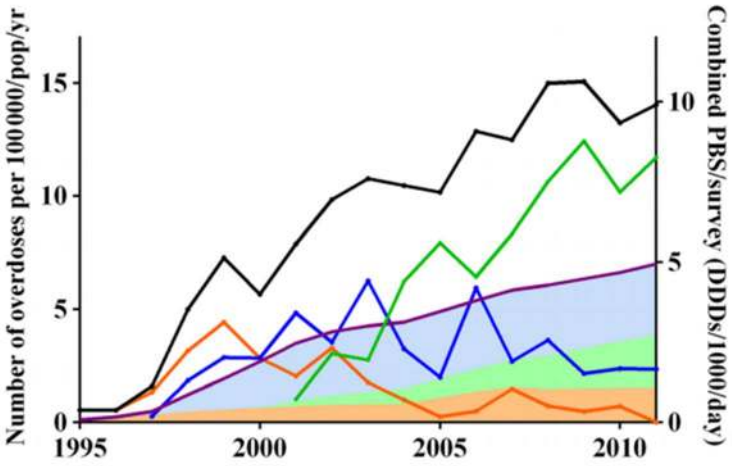


Figure 2
Changes in prescription rates of quetiapine, olanzapine and risperidone. Shaded areas reflect prescription rates and lines reflect overdose presentations. Black line represents total overdose data for quetiapine, olanzapine and risperidone, blue olanzapine, orange risperidone and green quetiapine. (DDDs/1000/day = defined daily doses/1000 people/day). (—) Total OD data for quetiapine, risperidone and olanzapine, (—) Olanzapine OD, (—) Risperidone, (—) Quetiapine OD, (—) Total all 3 prescription data

Figure 4.1.2. Changes in prescription rates and overdoses related to atypical antipsychotics in the Newcastle toxicology service prospective cohort. Quetiapine-related overdoses (green line) increase dramatically over time in comparison to other drugs and prescribing (shaded green segment) and constitute a large segment of total atypical antipsychotic overdoses (black line). Replicated from Berling et al.(43)

Quetiapine has possibly demonstrated the most concerning trend of all the antipsychotics in recent years, underpinned by an earlier progressive increase in off-label prescribing(44, 45). This has been particularly prominent given its notable toxidrome(46-48). In the Newcastle toxicology service prospective cohort, as time progressed, quetiapine-related overdoses increased out of proportion to increases in prescribing and in relation to olanzapine and risperidone overdoses and prescribing (Fig. 4.1.2.). This has corresponded with concerns from post-marketing surveillance of misuse and diversion(49) and data from several different sources suggesting increasing evidence of harm in Australia in different domains, more than other atypical antipsychotics(50). It is of note that initial data surrounding quetiapine toxicity from coronial sources did not suggest a disproportionate burden of misuse(49) but subsequent analyses of an injecting drug user cohort(51) and ambulance data(45) have

suggested increasing misuse and harm. This trend is especially notable in the context of declining olanzapine and risperidone-related harm despite increases in prescribing(45), and few other recent Australian data describe concerns from atypical antipsychotic overdoses. This suggests that concern regarding quetiapine in particular has become progressively more evident over time.

Anticonvulsants

Despite often being prescribed to at-risk patients, particularly when used off-label for a number of psychiatric disorders, few Australian data detail evidence of harm from anticonvulsants, with only infrequent prescribing in cases from the Sydney Mental Health Client Mortality Audit(52) and only case reports of overdoses recorded otherwise.

There is increasing concern globally regarding gabapentinoid drugs (pregabalin and gabapentin)(53), the use of which has escalated rapidly. In Australia, this change was particularly precipitated by changes in PBS approval mechanisms (see Chapter 3.2). While systematic reviews have captured its abuse potential and growing evidence of harm globally(54), this has not yet been captured in the Australian peer-reviewed literature.

Anti-depressants

In considering the evidence of harm from antidepressants, it should be noted that patients being treated with antidepressants often suffer from depressive disease which predisposes to suicidality. This can make data regarding detection rather than causality difficult – for example, in NSW between 2001 and 2010 the vast majority of occasions when citalopram was detected on forensic investigation it was incidental rather than contributory(55). There has also previously been concern that antidepressants themselves (particularly the newer generation agents) might increase the risk of suicidal ideation in young people, culminating in the US Food and Drug Administration (FDA) issuing a black-box warning in 2004 on the basis of a series of meta-analyses. This warning did appear, despite a modification in 2007, to reduce prescribing rates of antidepressants in Australia(56), and while the evidence is challenging for Australian prescribers to interpret(57) it does seem probable that the risk of suicidality from antidepressants is outweighed on an ongoing basis by the benefit from therapy(58). This discussion is contextual to evidence of harm from antidepressants but a full discussion of this sits outside the scope of the report and is fully addressed in other publications(59).

It should be noted that the introduction of newer generation antidepressants has coincided with a significant reduction in toxicity in Australia. In examining the Victorian Emergency Minimum Dataset (VAED), from 1998 to 2007 there was a progressive decline in overdoses proportional to supply in all classes, with the older tricyclic antidepressants (TCAs) and the newer serotonin selective reuptake inhibitors (SSRIs) demonstrating similar rates throughout(60). Similar data have been seen in the Newcastle toxicology service prospective cohort with TCAs and SSRIs in more contemporary data since 1998, and with serotonin noradrenaline reuptake inhibitors (SNRIs) since 2004 since their use became more common and more practiced(1). In the same cohort between 1991 and 2010, the time during which

newer generation antidepressants have been introduced in Australia, antidepressant prescribing has increased sixfold but the overall proportion of poisonings has only increased by 1.34 times(1). This mirrors a trend that antidepressants as a class seem broadly safe, and their burden of harm has lessened over time.

It is generally considered that TCAs are the most dangerous of the antidepressants in overdose(61), and in medication-related ambulance callouts between 1998 and 2002 in Melbourne they had the highest rate of altered conscious state of any drug type(21). Having said this, while over the course of the Newcastle study TCAs led to the highest number of overdose deaths of drugs considered to be 'usually prescribed', this was not only overshadowed by opioid-related deaths over the same period, but also TCA-related poisonings as a proportion of the total have declined since 1995, as have TCA-related poisonings proportional to supply. This change may relate to better prescribed usage of TCAs, prescribing of TCAs to lower-risk patients (particularly as off-label usage has increased), measures which reduce abuse potential (particularly as off-label usage tends to be in lower doses using lower dosage tablets), or a combination of all of these factors.

In the context of frequent prescribing, SSRI overdose is relatively common. It represented the third most common cause of deliberate self-poisoning in adolescents to a Victorian paediatric emergency department(62) and the third most common cause of medication-related ambulance attendances in Melbourne(21), yet as seen in these cohorts the sequelae of overdose are often less severe. The risk of serotonin syndrome is often considered with SSRIs, particularly in combination with MDMA(63); it is notable however, that while a coronial series of deaths involving serotonergic drugs over seven years showed 9 of 28 cases with SSRIs detected who has possible serotonin toxicity, SSRIs were evident in only 1 of 5 had serotonin toxicity reported by the pathologist, and this was in combination with tramadol(11). Severe toxicity with SSRIs is less commonly reported; of 79 consecutive escitalopram poisoning presentations to the Newcastle toxicology service prospective cohort over a similar period, none had life-threatening serotonin toxicity and neurological toxicity was rare(64).

It should be noted that any favourable effect of SSRIs compared to other serotonergic antidepressants in contemporary series may be partially attributable to its current status as first-line therapy; patients deliberately self-poisoning with venlafaxine were more likely to have suicidal intent that those deliberately self-poisoning with SSRIs(65). Despite this, the suggestion from larger cohorts in the peer-reviewed Australian data is that the patterns of harm from SNRIs are similar to that of SSRIs. In the Newcastle toxicology service prospective cohort, SNRIs represent the second most common cause of overdose by antidepressant class, but also the second most frequently prescribed, and currently have stable rates of overdose at levels similar to SSRIs and TCAs(1). While similar questions are often raised about serotonin syndrome about SNRIs as with SSRIs, duloxetine does not appear to overrepresent in reported sudden deaths when taken alone, although it has significant serotonergic potential in combination(66) (and particularly in combination with CYP2D6 inhibitors such as paroxetine), and toxidromes associated with desvenlafaxine similarly tend to be relatively mild(67).

There are limited Australian data on other antidepressants, but these are also largely reassuring. Mirtazapine overdoses appear to be stable and similar to other antidepressants when compared proportional to supply. It was also shown to be relatively benign in overdose by the Newcastle toxicology service prospective cohort(68) and even its serotonergic potential, which is part of its therapeutic justification, has been questioned(69). Lithium poisoning has a low mortality rate, and the majority of the morbidity arises from chronic rather than acute lithium poisoning(70). Moclobemide, despite its serotonergic and QT interval prolonging potential, has yet to produce concerning Australian data regarding its overdose; a series of 75 patients with moclobemide deliberate self-poisoning failed to demonstrate any cardiac arrhythmias(71). In short, none of the antidepressants appear, from the Australian peer-reviewed literature, to show significant evidence of harm, particularly compared to the other drug classes considered by this report.

4.2. Approach to understanding evidence from local databases

A significant body of evidence describing current patterns of harm deriving from prescription medications can be found outside the peer reviewed literature, in the multiple local databases which are essential for monitoring different aspects of prescription drug harm. While peer reviewed literature often draws on these databases, often what is published is limited by the scope of the question, which inevitably looks at a specific problem which rarely approaches mirroring that which this report addresses. In addition, the delay in the peer review process confers a delay in appreciating emerging drug trends.

It is impractical to assess every Schedule 4 prescription drug in every database, especially given that many of the data that comprise this section of the report were given *pro bono* out of the goodwill of the administrators of the relevant databases. Drugs have been selected to assist with answering the research question underpinning the report. Drugs to be analysed have been selected on the risk profile conferred to them on the basis of the peer-reviewed literature of harm which help to highlight drugs of concern (chapter 4.1) and global trends in misuse and abuse which might predict emerging local threats (chapter 5). In addition, the top-ranking drugs from the Coronial Prevention Unit reports have been the focus of our investigations. In this respect, this is not designed to be a comprehensive survey of the local databases for all drugs but to focus on the drugs likely to be problematic.

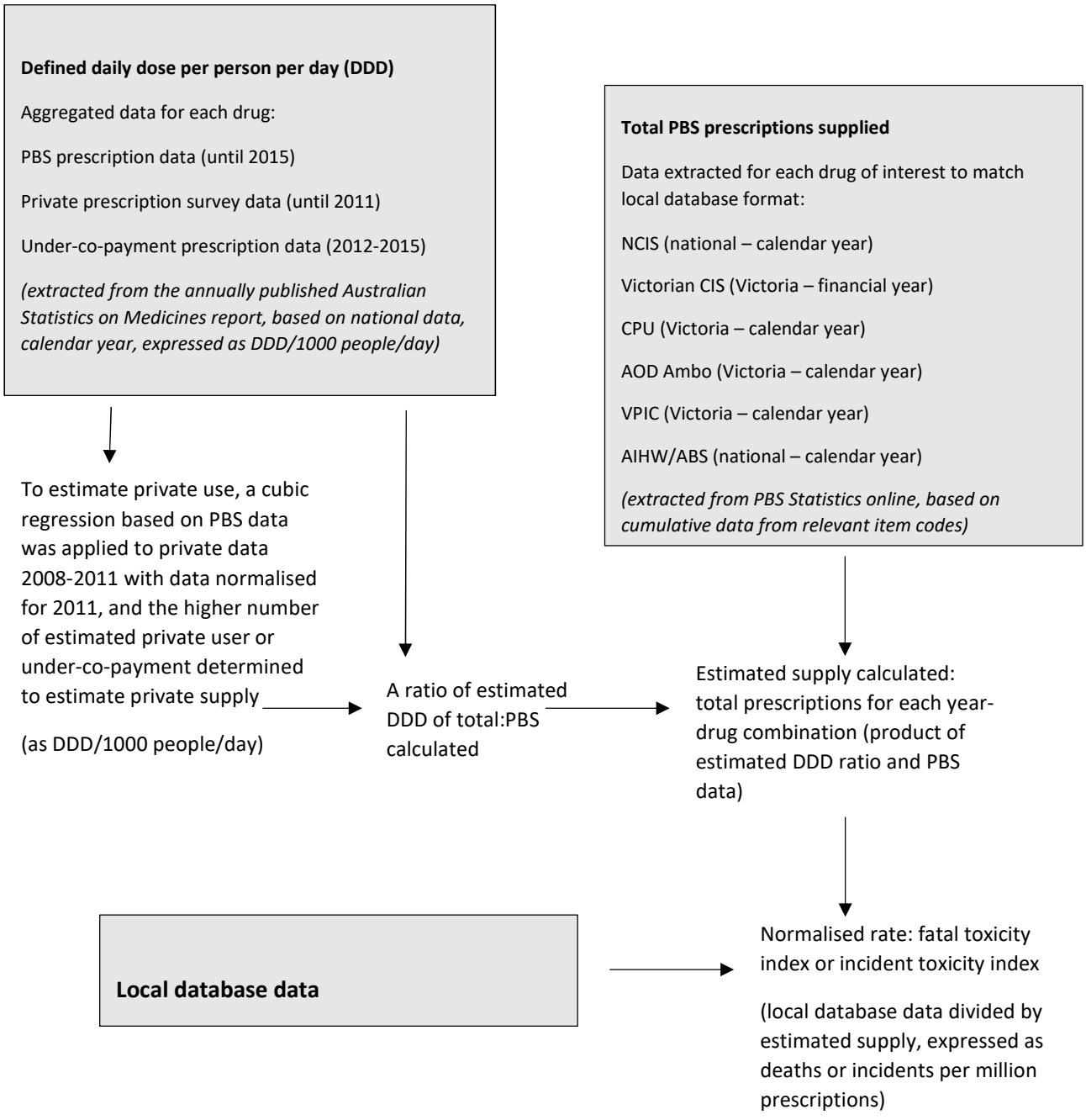
Appreciating concordant use and fatal toxicity/incident toxicity indices

One weakness of data derived directly from local databases of interest is that the endpoint is the total number of deaths or other incidents observed in their cohort (coronial databases, patients accessing their service etc.). This fails to address the disparity that more frequently supplied medications will be more greatly represented then medications of similar harm which are less frequently supplied medications. The reasons behind this, the principles behind the method used, and the in-principle limitations of this process are further outlined in chapter 3.2.

For this report, a ratio of PBS supply to total supply was calculated using DDD data (defined daily dose/1000 people/day), as illustrated in Appendix 1. In extrapolating forward data from 2012, a cubic regression was calculated for PBS supply (quoted in DDD) from 2008-2015, and applied to Pharmacy Guild private prescription survey data to estimate values from 2012-2015. During this time, under-co-payment values were published (also quoted as DDD), and in the case that this exceeded the estimate, the under-co-payment value was used. From these data, for all drugs, a ratio of total estimated supply (PBS + private) to PBS supply was calculated, in order that it could be applied to PBS total prescriptions to calculate overall estimated total prescriptions. These data are summarised in Table 4.2.3, with occasions where the under-co-payment value was used noted. The Australian Statistics on Medicines (ASM) data for 2016 had not been released at the time of publication of this report and hence the 2015 DDD ratio was used as the last recorded value being extrapolated forward. In order to estimate supply in financial years (as required for the Victorian contribution to the NCIS), DDD data for the latter calendar year was used (i.e. 2008 ratios for 2007-08).

Pregabalin's dramatic change in PBS supply corresponding with changes to qualifying criteria (leading to PBS and private supply inverting due to displacement rather than being concordant) and the likely lower subsequent rate of private supply, the under-co-payment value was used rather than extrapolating response. This would, if anything, overestimate the proportionate harm from pregabalin. The exception to this was for 2012 (before this change in supply but after private data became available); similar to the 2016 data, the last recorded value (2011) was extrapolated forward as the DDD ratio for pregabalin in 2012.

Figure 4.2.1: Methodology used to calculate fatal toxicity indices (deaths normalised for supply), incident toxicity indices (incidents normalised for supply)



Challenges in estimating the impact from codeine, and all medications

Codeine supply is difficult to estimate using the above method, especially as the ASM has published DDD values for aggregates for combination and plain codeine, rather on the basis of Poisons Standard scheduling. Almost all of the codeine accessed through the PBS is for prescription-only formulations which are on Schedule 4 (see Table 4.2.2 for PBS supply prior to private estimation calculations), however it is likely that the majority of non-PBS utilisation (including under-co-payment utilisation) will be non-Schedule 4 medication, especially as Schedule 3 medications do not require a prescription (and are only on the PBS for RPBS indications). This disparity is most readily appreciated when looking at the ratio of under-co-payment prescriptions to PBS prescriptions. There is a large difference between that for combination formulation codeine (Schedule 3 and 4) compared with plain formula codeine (Schedule 8), suggesting the flaws in these data. PBS-based estimations in this report only represent a small portion of all codeine use (but the majority of schedule 4 use), and therefore underestimate codeine supply. This is reflected in a study performed by the National Drug and Alcohol Research Centre (NDARC), where a pharmaceutical wholesale firm which supplies the vast majority of Australia's codeine supplied sale data for codeine, which showed consumption of codeine 30mg/paracetamol 500mg at 6.2 times that reflected in our estimates(72).

It therefore stands that normalised codeine harm (fatal toxicity indices and incident toxicity indices) might be overestimated in this report. A number of other factors might affect the interpretation of our normalised rates for toxicity with codeine (see Table 4.2.1), and can be applied to other medications.

One of the factors with greatest magnitude which might lead to underestimated toxicity (i.e. codeine more dangerous than this report's data suggest) is the expression of normalised rates by prescription instead of defined daily dose (a WHO standard designed to normalise for normal dose/day) (see table 4.2.4). The amount per prescription can vary quite dramatically in Australia – for example, zopiclone, similar to many medications, allows for 30 DDD/prescription, but codeine 30mg/paracetamol 500mg averages at 3.9 DDD/prescription based on 2015 PBS data (1.425 million at 20 tablets/script, 0.855 million at 60 tablets/script, and a DDD of nine tablets). This disparity would mean that codeine toxicity should potentially be corrected, compared to zopiclone, by 7.5x if the normalisation is for DDD rather than prescription. This distinction should, however, be balanced against a number of different factors.

- It may be more appropriate, when looking at endpoints directly related to codeine toxicity, to look at the DDD for codeine itself (which is 100mg instead of 270mg ie 2.7x less);
- Ignoring that, underestimates of supply as detailed above would underestimate normalised rates of toxicity (12.15 million prescriptions versus 2.16 million prescriptions is 5.6x less);
- Even then, such an estimate does not account for population growth, as DDD is usually corrected for population, although population growth was not large in this period;

- Most importantly, toxicity per DDD is the less relevant metric for the purposes of this report, particularly given any points of systematic control occur a set number of times per prescription (at prescribing, dispensing etc) rather than per dose (see chapter 3.2).

These factors should be considered in interpreting codeine data, but this report will present codeine data without further correction given the unclear value of all of these considerations.

Table 4.2.1. Potential confounders for estimating codeine's toxicity; also applicable to all medications

Factors which might underestimate toxicity i.e. why codeine is more dangerous than estimated in this report	***Factors which might overestimate toxicity i.e. why codeine is less dangerous than estimated in this report***
Factors which would decrease estimates of normalised rates (fatal toxicity index or incident toxicity index) for codeine-related incidents/million scripts: Forensic misattribution: codeine-related deaths may be attributed to morphine due to the absence of specific metabolites, thus underestimating the number of codeine-related deaths Coding misattribution: deaths from combination products may be misattributed to paracetamol rather than codeine Smaller pack sizes: S4 codeine (both combination and plain) is more commonly sold with fewer DDD than other drugs, thus leading to more prescriptions and a lower rate normalised per prescription, although the implications for this report can be debated	*Factors which would increase estimates of normalised rates (fatal toxicity index or incident toxicity index) for codeine-related incidents/million scripts* Underestimated private use: a NDARC study(72) using wholesale data estimated S4 codeine at 5.6x more than this report's estimates, most likely attributable to underestimated private use, thus underestimating supply and overestimating toxicity per prescription
Factors which might mean codeine is more dangerous than its normalised rates would suggest: Combination compound toxicity: if current paracetamol/codeine combinations are ingested, paracetamol is likely to be toxic before codeine is Masking by dilution with low-risk subgroups: Lower risk individuals might be more likely to take codeine products given (a) often a first line opioid therapy, so more general patients are on it, of which most are lower-risk i.e. protected by 'adverse selection' (b) larger overall supply This might mask toxicity in higher risk patients, who make up a smaller proportion of use Future displacement (i.e. substitution theory): If other opioids are more strictly regulated, and codeine's regulation is not co-ordinated with it, other opioids might be substituted with codeine, displacing the risk and, given it is usually a therapeutically inferior option, potentially encouraging misuse and abuse	*Factors which might mean codeine is more dangerous than its normalised rates would suggest:* Data contaminated with current non-Schedule 4 formulations: While every attempt has been made to exclude 2016 non-Schedule 4 codeine formulations, datasets which use aggregated toxicity data for codeine are likely to include contribution from 2016 Schedule 2 and Schedule 3 codeine, which have not yet reflected the effects of rescheduling

Table 4.2.2. PBS/RPBS supply data for codeine combination and plain products, 2008-2015 (extracted from PBS Online Statistics, http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp)

Product	Item	Formulation	2008	2009	2010	2011	2012	2013	2014	2015
CODEINE with PARACETAMOL	01215Y	Tablet 30mg-500mg 20	1,643,549	1,648,464	1,464,999	1,372,701	1,503,580	1,269,985	1,537,084	1,546,165
CODEINE with PARACETAMOL	03316M	Tablet 30mg-500mg 20	47,480	52,674	55,929	55,194	61,630	46,645	58,405	58,711
CODEINE with ASPIRIN	04061R	Tablet soluble 8mg-300mg 50	427	300	336	308	233			
CODEINE with PARACETAMOL	04170L	Tablet 15mg-500mg 20	2,145	1,934	1,825	1,576	1,596	1,630	1,169	585
CODEINE with PARACETAMOL	04171M	Tablet 8mg-500mg	21,483	18,180	14,919	12,045	7,814	2,907	2,833	1,997
CODEINE with PARACETAMOL	08785J	Tablet 30mg-500mg 60	655,267	668,328	792,003	821,266	912,503	796,564	947,067	974,009
ASPIRIN with CODEINE	04286N	Tablet 300mg 8mg 40					130	287	284	366
PARACETAMOL with CODEINE	04275B	Tablet 500mg 8mg 40					2,878	4,166	4,345	3,619
CODEINE with PARACETAMOL	10186D	Tablet containing codeine phosphate 15 mg with paracetamol 500 mg 20								107
Total codeine - combination			*2,370,351*	*2,389,880*	*2,330,011*	*2,263,090*	*2,490,364*	*2,122,184*	*2,551,187*	*2,585,559*
CODEINE	01214X	Tablet 30mg	50,734	52,416	51,864	50,628	56,202	49,505	61,901	63,545
CODEINE	05063L	Tablet 30mg	69	51	76	51	37	37	55	90
CODEINE	07530H	Codeine linct 100mL	130,441	128,670	119,357	118,475	123,763	85,706	123,777	124,105
Total codeine - plain			*181,244*	*181,137*	*171,297*	*169,154*	*180,002*	*135,248*	*185,733*	*187,740*
Total codeine - 2016 S4			*2,346,296*	*2,369,466*	*2,312,931*	*2,249,161*	*2,477,713*	*2,113,194*	*2,542,556*	*2,578,885*
Total codeine			2,551,595	2,571,017	2,501,308	2,432,244	2,670,366	2,257,432	2,736,920	2,773,299
% S4 codeine			*92.0%*	*92.2%*	*92.5%*	*92.5%*	*92.8%*	*93.6%*	*92.9%*	*93.0%*

Table 4.2.3 DDD ratio estimates: Estimated total prescriptions (including private prescriptions) as a proportion of recorded PBS prescriptions. Note that larger percentages will result in lower estimations of fatal toxicity indices or incident toxicity indices.

Darker shading indicates estimates based on Pharmacy Guild survey data. Lighter shading with italic characters indicates extrapolated data. Red shading indicates values extrapolated forward from last estimated variable. Asterix indicates under-co-payment published DDD exceeds the projections for private data and has been preferentially applied, and are thus more likely to represent underestimates (consequently resulting in possible minor overestimate of risk; to which the degree depends on how large the proportion of the 2008-2011 private surveys represented private prescriptions rather than under-co-payment prescriptions). It also stands that to calculate indices normalised for PBS supply only (rather than accounting for private supply), the fatal toxicity indices and incident toxicity indices in this report should be multiplied by these ratios.

	quetiapine	olanzapine	risperidone	diazepam	alprazolam	temazepam	oxazepam	clonazepam	nitrazepam	bromazepam
2008	108.6%	102.3%	101.2%	132.3%	157.6%	131.2%	121.4%	242.7%	117.8%	2600.0%
2009	106.9%	102.2%	101.2%	131.5%	159.3%	131.9%	121.8%	267.4%	118.5%	2780.0%
2010	105.0%	101.4%	101.4%	133.1%	160.0%	131.7%	122.1%	276.6%	119.9%	3100.0%
2011	104.6%	101.1%	101.5%	134.7%	165.4%	133.8%	123.0%	271.7%	120.8%	3300.0%
2012	*113.4%*	*102.5%*	*100.7%**	*134.4%*	*159.9%*	*130.6%*	*118.5%*	*277.0%*	*113.8%*	*3778.3%*
2013	*118.8%*	*103.2%*	*101.5%**	*134.2%*	*153.3%*	*130.1%**	*114.1%*	*283.1%*	*111.4%**	*4179.6%*
2014	*121.9%*	*102.5%*	*102.8%**	*133.2%*	*152.9%*	*131.5%**	*114.3%**	*282.9%*	*111.5%**	*4946.6%*
2015	*121.8%*	*105.0%**	*104.8%**	*133.1%*	*122.4%**	*132.6%**	*114.9%**	*279.4%*	*111.6%**	*5613.7%*
2016	*121.8%*	*105.0%**	*104.8%**	*133.1%*	*122.4%**	*132.6%**	*114.9%**	*279.4%*	*111.6%**	*5613.7%*

	codeine - combination	codeine - plain	tramadol	fentanyl	mirtazapine	amitriptyline	citalopram	zopiclone	pregabalin	gabapentin
2008	138.09%	131.50%	120.7%	101.0%	108.3%	131.9%	137.4%	423.8%	1002.9%	155.4%
2009	141.26%	127.78%	121.8%	100.8%	117.3%	131.0%	134.2%	479.0%	771.7%	161.8%
2010	135.39%	126.98%	121.9%	100.8%	114.9%	129.3%	130.5%	519.6%	752.0%	164.0%
2011	135.79%	130.95%	122.6%	100.7%	113.6%	129.4%	138.7%	640.0%	766.7%	170.9%
2012	*135.86%*	*132.94%*	*123.1%**	*105.6%*	*118.7%**	*132.4%**	*155.6%**	*655.0%*	*766.7%*	*169.1%*
2013	*136.12%*	*136.24%*	*127.5%**	*106.8%*	*127.3%**	*136.9%**	*168.9%**	*670.3%*	*100.7%*	*167.1%*
2014	*135.17%*	*140.13%*	*129.4%**	*104.9%*	*129.4%**	*137.8%**	*171.4%**	*683.8%*	*100.9%*	*167.8%*
2015	*132.39%*	*145.39%*	*129.6%**	*101.4%**	*130.8%**	*138.6%**	*172.5%**	*687.2%*	*101.0%*	*158.7%*
2016	*132.4%*	*145.4%*	*129.6%**	*101.4%**	*130.8%**	*138.6%**	*172.5%**	*687.2%*	*101.0%*	*158.7%*

Table 4.2.4. WHO defined daily doses per prescription, PBS average in 2015.
Supply data derived from PBS Online Statistics.

DDD values from the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index (https://www.whocc.no/atc_ddd_index/), slash indicates different formulations (e.g. plain, depot). For 2015 data, each PBS item number had number of units and dose per unit calculated, and then the total number of defined daily doses for that item number calculated using PBS data for individual item number supply. DDD/script represent mean values for whole of drug supply, although note that this only applies to PBS supply and that private supply may not use individual items in proportion.

	DDD (mg)	Number of scripts (national)	Total DDD (national)	DDD/script
codeine - combination- 2016 S4	270	2,578,885	10,059,784	3.90
tramadol	300	2,171,449	13,305,621	6.13
quetiapine	400	1,039,535	24,699,833	23.76
olanzapine	10	1,067,665	25,174,556	23.58
risperidone	5/2.7	678,735	11,552,163	17.02
diazepam	10	1,963,086	45,549,577	23.20
alprazolam	1	231,538	12,728,875	54.98
temazepam	20	1,785,676	22,361,375	12.52
oxazepam	50	1,003,041	12,677,393	12.64
clonazepam	8	53,919	1,121,512	20.80
mirtazapine	30	1,782,281	52,688,175	29.56
amitriptyline	75	1,633,741	29,284,253	17.92
citalopram	20	1,129,445	34,633,844	30.66
zopiclone	7.5	24,454	733,620	30.00
pregabalin	300	3,196,187	62,688,402	19.61
gabapentin	1800	115,091	2,224,950	19.33

4.3. National Coronial Information Service

The National Coronial Information Service (NCIS) is a national database of coronial information that combines data accumulated across Australia and New Zealand. The database was initiated in 1997 by researchers from Monash University and continues to be administered by the Victorian Department of Justice from the offices of the Victorian Institute of Forensic Medicine. The purpose of the database is to collate the national experience of deaths reported to a coroner, to replace the *ad hoc* system of informal communication between jurisdictions which preceded it, and make them available for further health policy research. Findings, autopsy reports, toxicology reports and police narratives are also collected where possible.

The determination of whether a drug is contributory to a death is not standardised among jurisdictions. This determination is based on the individual professional opinions of the forensic pathologist conducting the autopsy and any other information an investigating coroner may deem relevant. Contributions across jurisdictions may therefore be inconsistent for certain drugs often present at moderate therapeutic concentrations. This means that national and comparative data may be less likely to be representative as the reporting of specific drugs may differ by jurisdiction.

Data from this database was provided to the authors as collated data under an agreement between the Taskforce and the NCIS in aggregated form only, as a data readout, and not for disclosure to the public domain. We gratefully acknowledge the contributions of Thomas Burgess, Katherine Dartnell and Caitlin Ring in making these data available, and the advice of Dr Jennifer Pilgrim.

Determination of drug-related causality of death

Each case included in the NCIS is classified on the basis of both ICD-10 coding and a customised NCIS code. The ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) is a broad, internationally used tool which is used to classify medical cases broadly. Its coding does not provide significant granularity in terms of specific drugs or the nature of their involvement and thus is a lesser (but better known) tool. The NCIS coding system is a customised system developed in-house in order to serve the research goals of the NCIS, and confers greater detail than ICD-10 coding. Further information on the NCIS coding system is available on the NCIS website.

Codes for both systems are allocated by informatics staff in each state on the basis of the finding and final reports as they become available. Unlike the Victorian Overdose Death Register, the findings are strictly interpreted as the only validated source of information and no data is extrapolated. This results in a less sensitive but more specific dataset. It should be noted that there might be variability between different reporting coroners and different jurisdictions. The description of the contribution of drugs in reports may be variable due to stylistic differences between coroners, and toxicology report interpretation may also be variable due the difficulty in interpreting post-mortem drug concentrations, which still do not

have established reference ranges. This may mean that non-contributory drugs may still be included or contributory drugs missed.

While these limitations of the data should be noted, closed cases are routinely quality assessed to ensure that coding is appropriate. Amongst these assessments, unpublished data from internal validation studies by doctoral students suggest that NCIS coding accurately reflects causes of death.

Regarding determination of causality, the NCIS data report states:

> *"A substance was considered to have primarily contributed to a death where:*
> - *Drug toxicity was noted within the cause of death (1a) in the NCIS codeset, or*
> - *Aspiration of gastric contents was noted in the cause of death AND drug toxicity was noted anywhere in the cause of death*
>
> *A substance was considered to have had a secondary contribution to a fatality where:*
> - *The primary object/substance causing injury was not a pharmaceutical substance for human use, and*
> - *The secondary object coding fields included a pharmaceutical substance for human use.*
>
> *Additionally, if the death was noted as being contributed to by a combination of multiple coded drugs (such as 'mixed drug toxicity' or 'multiple drug overdose'), the drugs that were part of the 'multiple drug' combination were recorded (e.g.: oxycodone and methadone toxicity)."*

The data referred to in chapter 4.3 refer to data from the entirety of the NCIS unless directly referencing contributions from individual jurisdictions. Victorian contributions to the NCIS are further analysed in chapter 4.4.

Overdose deaths by individual contributing drugs

The NCIS data request detected 6335 deaths as a result of external causes associated with specified Schedule 4 or 8 drugs over the six years between 2009 and 2014 inclusive. This has been providing a progressively increasing contribution to the total number of deaths over this period.

Table 4.3.1. Schedule 4 and 8 medication-related deaths notified to the NCIS, as a proportion of overall deaths notified to the NCIS.

Year of notification	Number of deaths	Percentage of total deaths
2009	943	14.9%
2010	946	14.9%
2011	925	14.6%
2012	1146	18.1%
2013	1130	17.8%
2014	1245	19.7%

The vast majority, at 87.6%, were primary contributors to death. Unintentional deaths made up 60.9% of these deaths, compared to intentional self-harm at 27.9%. Complications of medical or surgical care made up only 0.3% of cases. No further granularity regarding this

was provided. Absolute numbers of fatalities in this dataset attributable to selected drugs have been included in Table 4.3.2 part A, and rates normalised for estimated supply (i.e. fatal toxicity index) in part B. These medications are schedule 4 except for alprazolam and fentanyl, which have been included for comparison. These data are expressed graphically in Figure 4.3.1, and without the highest rating drugs (clonazepam and alprazolam) for graphical clarity in Figure 4.3.2.

It should be noted that diazepam, when normalised, has been progressively more dangerous over time, increasing from 127 deaths/million prescriptions in 2009 to 189 deaths/million prescriptions in 2014, implying increasingly dangerous patterns of use. This pattern is mirrored by all the other benzodiazepines examined in this dataset, with the exception being a decrease from 2013 to 2014 with alprazolam in line with rescheduling from Schedule 4 to Schedule 8 in February 2014. Zopiclone also mirrors this escalation. Zolpidem had greater numbers of death in this dataset and, given that there is no reason to think that its supply in Australia is less than that of zopiclone, is likely to confer at least a similar risk.

Quetiapine, while not showing an increasing trend of use, conferred a proportional rate of death over this time comparable to the most recent values for fentanyl and zopiclone. This would suggest that it is a current threat rather than an emerging one. Conversely, olanzapine had a stable proportional rate of death over the examined time period, a pattern similar in trajectory and value as that of the anti-depressants examined. Risperidone had a very low proportional rate of death in comparison. Codeine displayed a slowly increasing rate over this time, at a slightly higher rate in the most recent year than the anti-depressants and olanzapine. Tramadol has a notably lower rate than all of these drugs. Gabapentin showed a marked escalation in its proportional rates of death in 2013 and 2014, although the overall numbers were small. Pregabalin values were only recorded for 2013 and 2014 and demonstrated proportional rates lower than any drug examined.

Data comparing deaths contributed to the NCIS database by different jurisdictions show Victoria overrepresenting in a number of different sections, although this may well merely represent more diligent reporting by Victoria (see Table 4.3.3). Pregabalin, zopiclone and risperidone seem to have accentuated mortality in Victoria compared to the remainder of the country, and this may mean they represent relatively large problems to Victoria than other jurisdictions.

In summary, in the NCIS dataset the benzodiazepines and z-drugs have been shown to be causing notable rates of danger proportional to use, increasingly so over time. Quetiapine, while not an increasing threat, continues to cause deaths at a similar rate. Codeine has been slowly increasing in danger proportional to use but has a rate not notably higher than anti-depressants and olanzapine, and tramadol has a very low rate. Finally, gabapentin is emerging and may pose a future threat but proportional rates of death in this cohort do not exceed those of anti-depressants, whereas pregabalin did not appear to pose risk based on the data from this cohort.

Table 4.3.2. NCIS prescription drug-related fatalities

A. Drug-related fatalities in Australia notified to the NCIS for selected prescription drugs, by year of notification and drug identified.
B. Fatal toxicity index on NCIS data, for selected prescription drugs (deaths/million prescriptions).

Note that zolpidem has not been on the PBS and thus supply data is not recorded in PBAC DUSC's ASM, although slightly more deaths are attributable to it compared to zopiclone.
Pregabalin was only recorded routinely post-mortem from 2013 onwards but the most recent data is available.
Note deaths will total to greater than the number of total deaths as more than one of the drugs may have been identified.

A	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	B	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*
diazepam	286	342	283	385	408	489	**diazepam**	127.48	155.08	131.34	162.53	198.31	189.23
alprazolam	112	147	112	149	162	105	**alprazolam**	170.01	227.89	174.76	224.62	326.28	235.82
temazepam	107	130	129	177	131	158	**temazepam**	39.63	51.41	53.60	71.90	64.85	65.31
oxazepam	75	110	94	133	97	117	**oxazepam**	55.78	86.98	79.58	111.66	100.49	102.30
clonazepam	24	23	28	42	40	47	**clonazepam**	195.01	182.71	230.37	311.95	345.43	320.50
codeine	212	197	194	235	235	263	**codeine**	58.77	58.42	58.89	64.87	76.47	70.92
tramadol	79	62	52	85	99	100	**tramadol**	38.08	30.35	25.75	38.13	48.03	37.21
fentanyl	16	33	57	79	90	108	**fentanyl**	35.78	61.17	97.77	113.05	142.47	147.57
mirtazapine	49	61	78	92	91	121	**mirtazapine**	40.45	47.52	57.81	57.06	59.16	58.24
amitriptyline	100	104	100	146	119	138	**amitriptyline**	69.21	70.32	65.75	81.11	70.77	65.10
citalopram	78	90	71	82	94	96	**citalopram**	48.40	58.95	46.51	47.76	60.60	50.57
quetiapine	85	120	105	132	139	184	**quetiapine**	158.17	184.15	138.27	128.82	134.77	143.57
olanzapine	63	45	52	59	62	70	**olanzapine**	66.09	47.77	55.81	56.70	67.95	62.43
risperidone	9	8	12	21	14	14	**risperidone**	14.08	12.41	18.53	30.65	24.30	20.26
zopiclone	7	5	13	20	21	19	**zopiclone**	59.87	41.14	90.64	127.76	150.13	117.48
zolpidem	24	23	16	18	26	22	**zolpidem**	-	-	-	-	-	-
pregabalin	-	-	-	-	14	37	**pregabalin**	-	-	-	-	19.69	16.63
gabapentin	2	2	3	1	4	12	**gabapentin**	12.94	12.72	18.11	5.29	23.57	61.13

Figure 4.3.1. Fatal toxicity index by NCIS notified data for selected prescription drugs 2009-2014, deaths per million prescriptions
Note that alprazolam, a Schedule 8 medication, has had a lower fatal toxicity index in recent years than clonazepam.

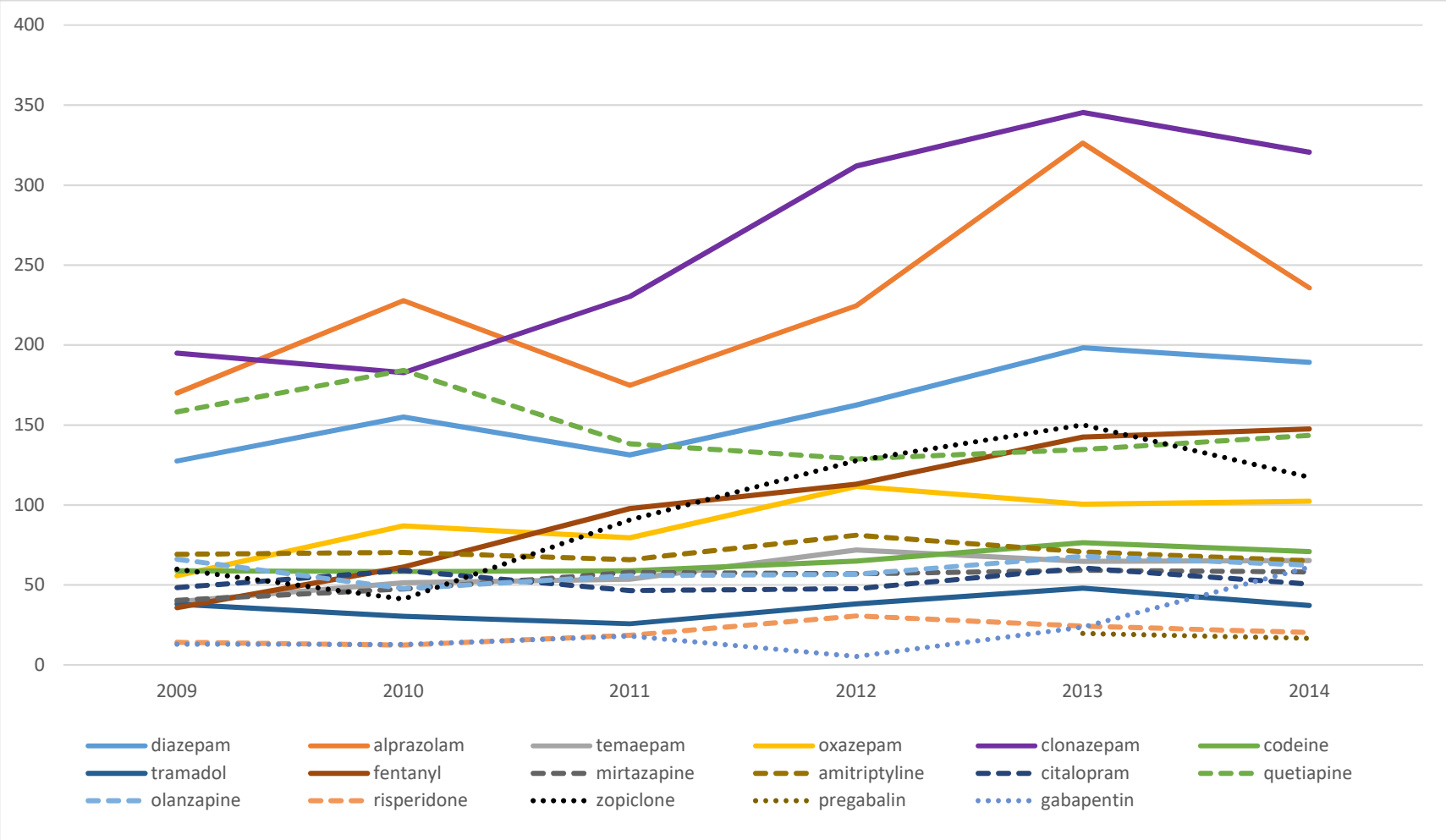


Figure 4.3.2. Fatal toxicity index by NCIS notified data for selected drugs, 2009-2014, deaths per million prescriptions.
Selected drugs are as per Figure 4.3.1. highest ranked drugs alprazolam and clonazepam excluded for graphical clarity.
Note that diazepam has exceeded other drugs in recent years, and that quetiapine and zopiclone approximate levels demonstrated by fentanyl.
The majority of other drugs, apart from oxazepam, have similar trajectories although tramadol, pregabalin and risperidone have lower indices than other drugs.

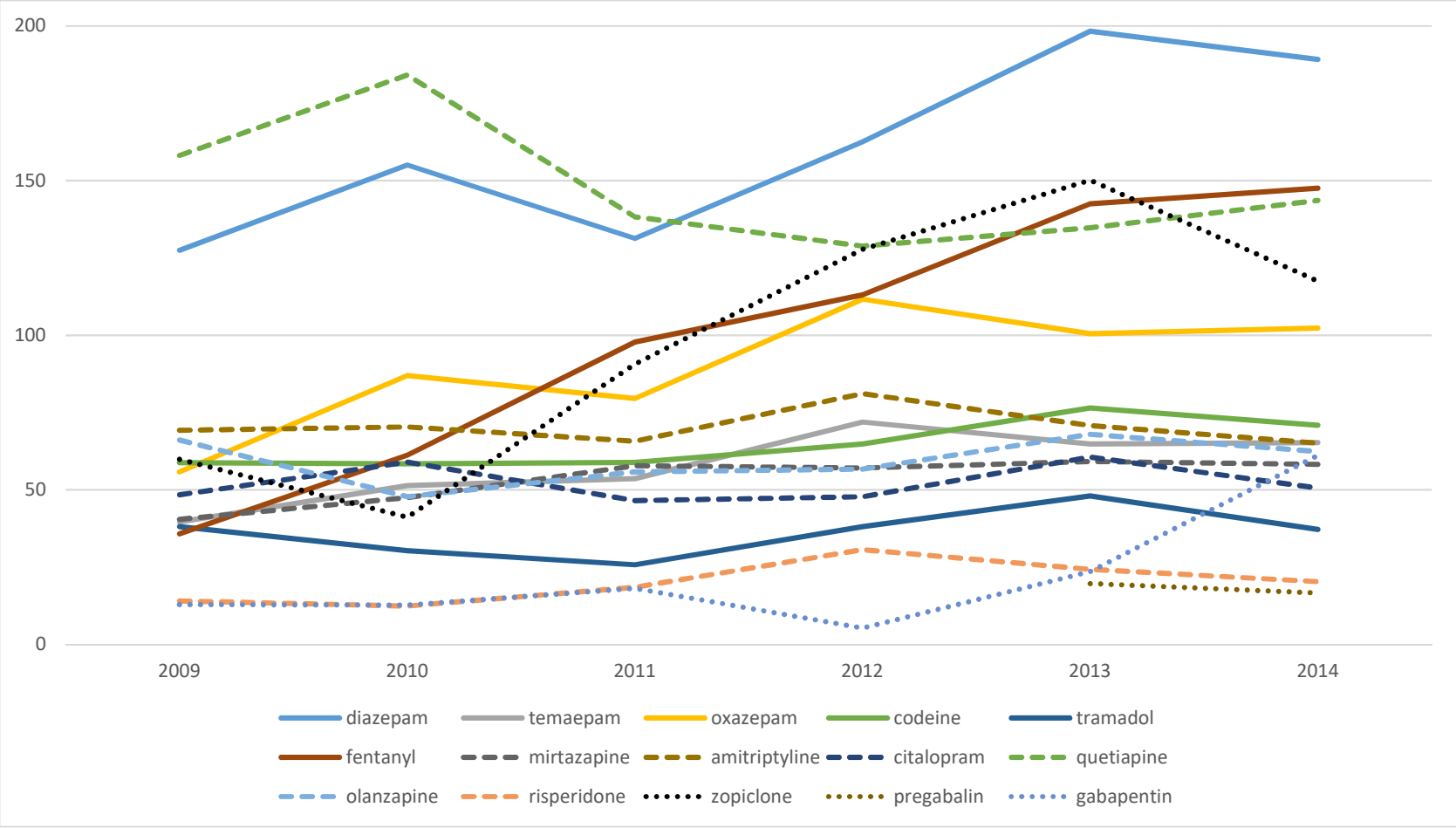


Table 4.3.3 NCIS prescription drug-related fatalities by drug and state over 2009-2014, with percentage over/underrepresentation based on proportion of harm associated with that drug over proportion of the overall population. Red highlighted drugs are those in which Victoria is >50% overrepresented. Population based on ABS population statistics from June 2014. Total population of Australia includes other states and territories. Data is limited by non-universal contribution from each jurisdiction and different coding and coroners practices in each jurisdiction.

	NSW	%over/ under	Victoria	%over/ under	Qld	%over/ under	SA	%over/ under	WA	%over/ under	Tasmania	%over/ under	NT	%over/ under	ACT	%over/ under	Australia
State population, June 2014	7,518,500	32.0%	5,841,700	24.9%	4,722,400	20.1%	1,685,700	7.2%	2,573,400	11.0%	514,800	2.2%	245,100	1.0%	386,000	1.6%	23,490,700
morphine	370	-23.9%	328	-13.2%	374	22.4%	92	-15.7%	265	59.1%	49	47.1%	18	13.5%	24	-3.9%	1,520
oxycodone	317	-15.9%	294	0.4%	294	24.1%	67	-20.7%	143	10.8%	33	27.8%	7	-43.0%	23	18.8%	1,178
fentanyl	118	-3.7%	49	-48.6%	136	76.6%	29	5.5%	47	12.0%	1	-88.1%	1	-75.0%	2	-68.2%	383
tramadol	83	-45.6%	119	0.3%	89	-7.2%	43	25.6%	114	118.2%	22	110.5%	5	0.5%	2	-74.5%	477
codeine	342	-20.0%	388	16.8%	266	-1.0%	57	-40.5%	217	48.3%	38	29.8%	10	-28.3%	18	-18.0%	1,336
alprazolam	197	-21.8%	**305**	**55.8%**	137	-13.4%	37	-34.5%	79	-8.4%	27	56.5%	3	-63.5%	2	-84.5%	787
diazepam	417	-40.6%	805	47.6%	452	2.5%	49	-68.9%	345	43.6%	96	99.8%	9	-60.7%	20	-44.5%	2,193
clonazepam	42	-35.7%	**100**	**97.1%**	35	-14.7%	8	-45.4%	15	-32.9%	4	-10.5%	0	-100.0%	0	-100.0%	204
oxazepam	183	-8.7%	169	8.6%	143	13.6%	19	-57.7%	92	34.2%	14	2.0%	2	-69.4%	4	-61.1%	626
lorazepam	1	-90.8%	**19**	**124.7%**	4	-41.5%	2	-18.0%	6	61.1%	0	-100.0%	1	181.9%	1	79.0%	34
temazepam	220	-17.4%	208	0.5%	171	2.2%	22	-63.2%	179	96.4%	23	26.1%	3	-65.4%	6	-56.1%	832
zopiclone	3	-89.0%	**62**	**193.3%**	11	-35.6%	0	-100.0%	5	-46.3%	2	7.4%	1	12.8%	1	-28.4%	85
zolpidem	28	-32.2%	48	49.6%	24	-7.5%	5	-46.0%	17	20.3%	6	112.2%	0	-100.0%	1	-52.8%	129
quetiapine	175	-28.5%	256	34.6%	159	3.4%	36	-34.4%	106	26.5%	21	25.3%	1	-87.5%	11	-12.5%	765
olanzapine	65	-42.1%	127	45.5%	73	3.5%	18	-28.5%	38	-1.2%	25	225.0%	1	-72.7%	4	-30.6%	351
risperidone	0	-100.0%	**56**	**188.7%**	12	-23.5%	4	-28.5%	6	-29.8%	0	-100.0%	0	-100.0%	0	-100.0%	78
anitriptyline	145	-35.9%	159	-9.6%	184	29.5%	42	-17.2%	127	64.0%	37	138.8%	2	-72.9%	11	-5.3%	707
citalopram	88	-46.2%	166	30.6%	120	16.8%	21	-42.7%	92	64.3%	19	69.7%	1	-81.2%	4	-52.4%	511
mirtazapine	96	-39.0%	156	27.5%	113	14.2%	15	-57.5%	87	61.4%	22	104.0%	2	-61.0%	1	-87.6%	492
pregabalin	0	-100.0%	**38**	**199.6%**	11	7.3%	2	-45.4%	0	-100.0%	0	-100.0%	0	-100.0%	0	-100.0%	51
gabapentin	0	-100.0%	7	17.3%	16	231.6%	0	-100.0%	0	-100.0%	1	90.1%	0	-100.0%	0	-100.0%	24

4.4. Victorian data contributed to the National Coronial Information System

The Mental Health & Drugs Information, Analysis & Reporting Unit of the DHHS capture Victorian data which is subsequently contributed to the NCIS – notification is routine in Victoria. As part of an agreement with the Department of Justice, which operates the Victorian Institute of Forensic Medicine which administers the NCIS, an agreement for access is in place for drug-related projects amongst other things. These data were made accessible to this report, and this allowed for data sets to be further analysed for dangerous combinations.

Overdose deaths by individual contributing drugs

The contributed data for all prescription drugs deaths is examined is published on Table 4.4.1, and a number of comparator Schedule 8 drugs are also included. The data is delineated by primary, secondary and tertiary causality, although given the vast majority are primary they have been considered as a whole. Heroin and methamphetamine-contributed prescription drug deaths were included in this dataset not for direct comparison but to facilitate assessment of the toxicity of combinations. They are incidentally included in this table. In addition, it should be noted that 2014-15 data is incomplete and therefore is not included in comparison to previous years, but is also included to enable totals to include the most recent data.

This data set includes propoxyphene and it is notable that since its increased regulation in 2013, only one person has died in Victoria as a consequence of its toxicity. Supply is unable to be estimated for propoxyphene and thus no further analysis has been made. Apart from clobazam (the use of which is anecdotally insufficiently common), other benzodiazepines not examined later in this report (such as lorazepam, and flunitrazepam) were well represented.

Fatal toxicity indices are published in Table 4.4.2. Notably, zopiclone's toxicity increased dramatically over the course of the study period, increasing five-fold. Clonazepam's toxicity increased twenty-fold over the study period, and these two drugs led to the highest fatal toxicity index in 2012-13. Alprazolam, diazepam and quetiapine also produced fatal toxicity indices above other drugs. There was little to separate amitriptyline, mirtazapine and citalopram. Tramadol had lower rates of toxicity compared to other drugs.

Table 4.4.1: Victorian NCIS contributed data; attributable total prescription drug-related deaths for reviewed S4 and S8 drugs over time, with data for associated illegal opioids (2007-08 to 2013-14) (note 2014-2015 data is incomplete)

year	degree	codeine	tramadol	propoxyphene	quetiapine	olanzapine	risperidone	diazepam	alprazolam	temazepam	oxazepam	clonazepam	benzodiazepines	mirtazapine	amitriptyline	citalopram	zolpidem	zopiclone	pregabalin	flunitrazepam	methadone	oxycodone	morphine	fentanyl	buprenorphine	gabapentin	clobazam	lorazepam	bromazepam	heroin	methamphetamine
2007-08	1	36	5	3	10	6	0	43	12	7	2	1	5	6	2	9	4	2	0	0	22	6	27	0	1	0	0	1	0	22	8
2007-08	2	1	1	0	0	0	0	2	0	0	1	0	0	0	0	0	0	0	0	0	2	0	3	0	0	0	0	0	0	0	0
2007-08	3	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
2007-08	total	38	6	3	10	6	0	47	12	7	3	1	5	6	2	9	4	2	0	0	24	6	31	0	1	0	0	1	0	22	8
2008-09	1	61	13	7	16	13	1	62	29	19	19	2	2	14	5	13	7	2	0	0	26	21	40	1	0	0	0	0	2	25	11
2008-09	2	2	0	1	3	0	0	4	1	1	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	1
2008-09	3	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2008-09	total	64	13	8	19	13	1	68	30	20	19	2	2	14	5	14	8	2	0	0	27	21	41	1	0	0	0	0	2	25	13
2009-10	1	41	9	5	26	17	5	68	38	22	13	10	6	15	12	8	4	2	0	1	37	24	30	1	2	0	0	0	0	27	5
2009-10	2	2	0	0	1	4	0	8	2	3	0	0	2	1	1	3	1	0	0	0	3	3	4	0	1	0	0	0	0	1	1
2009-10	3	2	0	0	1	2	0	4	2	0	1	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	0	0	0	0	1
2009-10	total	45	9	5	28	23	5	80	42	25	14	10	8	16	13	11	5	2	0	1	42	28	35	1	3	0	0	0	0	28	7
2010-11	1	54	14	5	40	11	6	95	47	20	23	10	13	21	20	27	2	5	0	1	45	32	38	3	7	1	0	1	0	48	2
2010-11	2	2	0	0	1	2	0	7	7	0	1	0	2	2	4	1	1	0	0	0	2	3	3	0	1	0	0	0	0	1	1
2010-11	3	3	0	0	1	1	0	9	1	2	2	0	1	0	0	2	1	0	0	1	2	2	1	0	1	0	0	0	0	0	0
2010-11	total	59	14	5	42	14	6	111	55	22	26	10	16	23	24	30	4	5	0	2	49	37	42	3	9	1	0	1	0	49	3
2011-12	1	51	15	6	25	21	12	94	39	32	35	16	24	22	19	19	9	10	0	2	59	38	39	11	8	0	0	2	0	41	1
2011-12	2	3	1	1	4	2	0	6	4	2	1	1	2	2	0	5	0	3	0	0	6	0	4	0	1	0	0	0	0	0	1
2011-12	3	2	0	0	4	1	2	10	6	3	3	3	1	3	0	2	0	2	0	1	7	1	1	0	1	0	0	0	0	1	2
2011-12	total	56	16	7	33	24	14	110	49	37	39	20	27	27	19	26	9	15	0	3	72	39	44	11	10	0	0	2	0	42	4
2012-13	1	72	23	2	49	18	9	133	45	29	24	19	21	20	28	31	5	12	2	1	60	43	41	9	3	1	1	3	0	66	1
2012-13	2	4	0	0	2	3	3	10	4	2	1	4	0	2	0	1	2	2	0	0	3	1	5	0	1	0	0	0	0	2	0
2012-13	3	6	2	0	1	1	2	14	3	6	2	2	1	2	2	4	1	1	1	0	6	1	2	0	0	0	0	0	0	3	0
2012-13	total	82	25	2	52	22	14	157	52	37	27	25	22	24	30	36	8	15	3	1	69	45	48	9	4	1	1	3	0	71	1
2013-14	1	54	20	1	47	21	11	152	36	30	23	21	14	31	22	28	6	12	20	0	64	58	37	6	5	2	1	3	0	74	4
2013-14	2	2	1	0	3	0	1	15	2	4	3	4	0	3	1	2	0	1	2	0	5	1	5	0	1	0	0	2	0	3	0
2013-14	3	5	1	0	9	2	1	28	7	3	2	0	0	6	1	7	2	1	0	0	3	3	1	0	0	0	0	0	0	2	0
2013-14	total	61	22	1	59	23	13	195	45	37	28	25	14	40	24	37	8	14	22	0	72	62	43	6	6	2	1	5	0	79	4
2014-15	1	25	16	0	20	7	7	57	7	9	7	7	8	9	22	6	3	5	8	1	17	21	22	7	5	3	0	5	1	41	1
2014-15	2	3	2	0	4	2	3	6	0	2	1	1	0	1	0	2	0	0	0	1	2	3	3	0	0	0	0	0	0	0	0
2014-15	3	2	2	0	6	3	0	17	1	6	3	0	1	2	0	3	2	2	0	0	4	3	0	0	1	0	0	1	0	2	2
2014-15	total	30	20	0	30	12	10	80	8	17	11	8	9	12	22	11	5	7	8	2	23	27	25	7	6	3	0	6	1	43	3
all years	total	435	125	31	273	137	63	848	293	202	167	101	103	162	139	174	51	62	33	9	378	265	309	38	39	7	2	18	3	359	43

Table 4.4.2: Victorian NCIS contributed data; fatal toxicity index for drugs over time (2007-08 to 2013-14); deaths/million scripts

	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	*total period to 2013-14*
codeine	41.58	69.51	53.28	69.67	66.54	97.10	70.27	34.83	***66.61***
tramadol	11.58	25.59	18.54	28.75	31.93	47.17	37.20	32.38	***29.00***
fentanyl	0.00	12.41	9.47	24.91	81.10	63.11	41.14	41.14	***50.15***
quetiapine	94.66	132.96	160.35	197.94	122.12	162.34	161.19	86.27	***152.64***
olanzapine	23.49	46.80	83.44	51.24	85.06	75.66	75.13	75.13	***63.74***
risperidone	0.00	6.03	29.06	34.68	81.16	80.76	73.37	55.29	***44.97***
diazepam	74.55	104.72	123.29	171.57	168.87	236.34	273.18	107.96	***166.77***
alprazolam	55.43	129.78	182.85	242.20	228.12	269.22	283.78	117.84	***193.75***
temazepam	9.66	27.53	36.08	33.07	57.78	60.56	58.33	27.29	***39.40***
oxazepam	7.99	50.72	39.07	77.03	122.22	88.92	87.74	33.77	***65.33***
clonazepam	31.22	56.05	283.02	284.39	553.22	687.64	656.02	207.60	***373.75***
mirtazapine	20.03	45.25	50.31	67.66	69.75	55.75	81.38	22.06	***58.23***
amitriptyline	7.23	16.74	41.91	73.56	53.09	75.44	54.49	47.19	***48.60***
citalopram	24.86	38.62	31.83	85.83	69.35	99.07	96.63	28.83	***64.15***
zopiclone	123.50	107.25	108.86	237.82	680.00	744.40	618.40	315.19	***395.44***
pregabalin	0.00	0.00	0.00	0.00	0.00	84.95	59.40	13.03	***61.63***
gabapentin	0.00	0.00	0.00	35.85	0.00	28.22	50.50	81.16	***39.98***

Note 2014-2015 data is incomplete and therefore cannot be effectively interpreted.
Pregabalin and gabapentin not detected prior to 2012-13.

Figure 4.4.1: Victorian NCIS contributed data; fatal toxicity index for drugs over time (2007-08 to 2013-14); deaths/million scripts

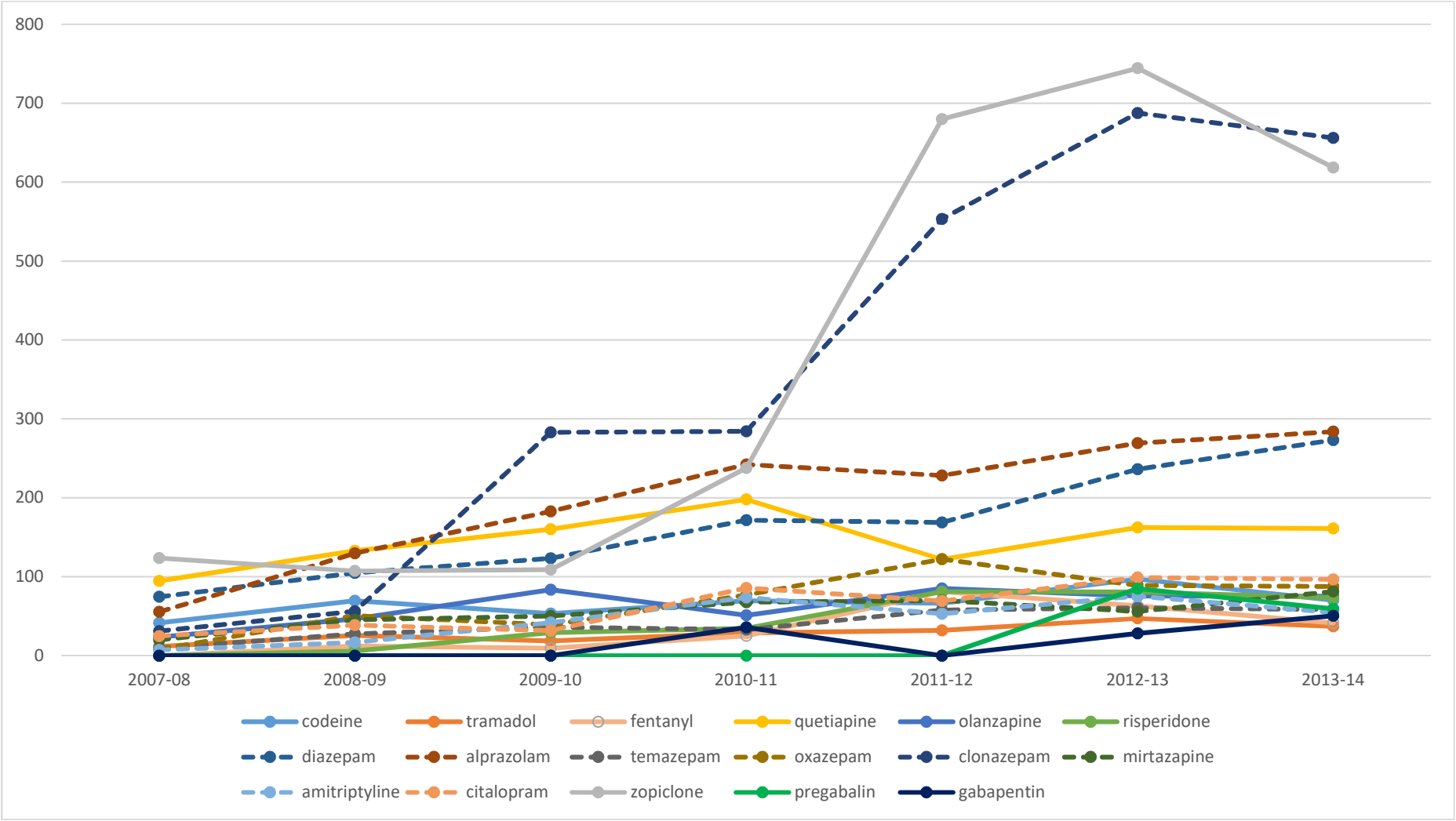
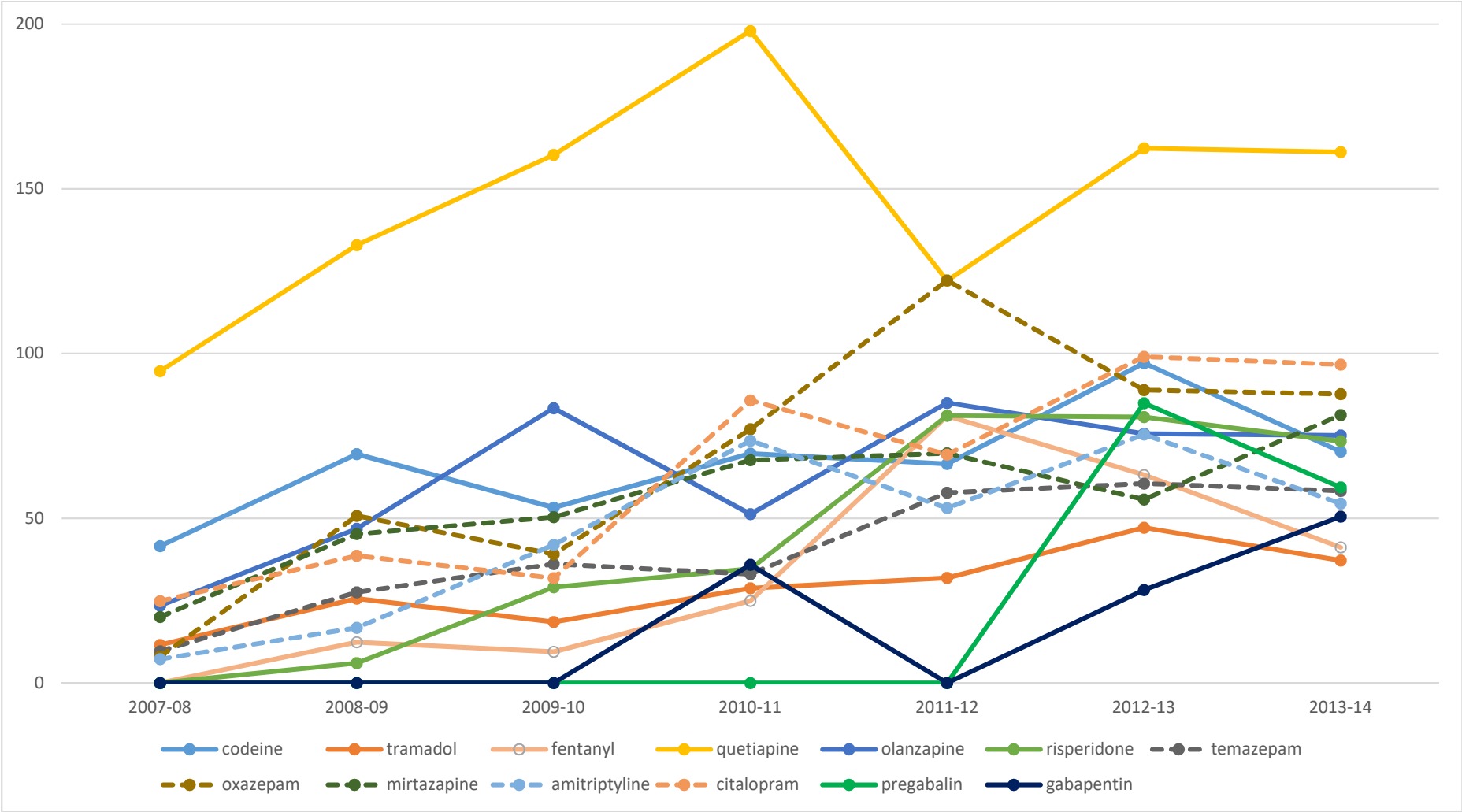


Figure 4.4.2: Victorian NCIS contributed data; fatal toxicity index for selected lower-risk drugs only over time (2007-08 to 2013-14) (highest ranked drugs zopiclone, clonazepam, alprazolam and diazepam excluded for graphical clarity); deaths/million scripts



This dataset was subsequently interrogated for combinations of relevance to the research question, to address specific concerns about the culpability of otherwise concerning agents.

Are antipsychotics culpable for deaths in people who are abusing illicit opioids, or are they merely 'bystanders'?

As previously articulated in chapter 4.1, it has been mooted whether quetiapine, rather than being culpable for deaths in people abusing heroin and methamphetamine, just happens to be more frequently present in these people when they overdose on heroin or amphetamine (and might even be mitigating harm through its putative effects on the recovery from use of these opioids). If a concern exists about a combination creating harm and biasing the apparent danger of a drug, one approach to resolve that is to remove the endpoints associated with the combination and then observe what harm remains, as this then is a lower limit estimation of the harm from the original drug alone. It is important to emphasise the lower limit nature of this, as it should be acknowledged that this population is at higher risk for prescription medication overdoses in general and that all prescription medications are likely to have contributions from this population, and thus such a subgroup cannot be compared to overall rates in other groups.

In this spirit, this report examined deaths attributable to quetiapine, olanzapine and risperidone where no heroin or methamphetamine was culpable.

The results are displayed on in Table 4.4.3 and Figure 4.4.3. For quetiapine, the majority of cases were culpable without either heroin or amphetamine. This is less evident for olanzapine and risperidone. Despite it being an inappropriate comparison, it is notable that quetiapine without heroin or amphetamine is largely above the overall rates for olanzapine, despite this being a comparison which biases against this outcome. A similarly inappropriate comparison with overall rates for fentanyl, a restricted Schedule 8 drug, shows higher rates for quetiapine (i.e. the lowest estimation of quetiapine-related mortality finds it more concerning than fentanyl).

These data would suggest that, even if in all deaths where quetiapine and at least one of methamphetamine or heroin were both deemed to be culpable (i.e. quetiapine was an 'innocent bystander'), then quetiapine still represents a threat compared to other drugs, even if none of the deaths associated with other drugs were due to methamphetamine, heroin or any other drug.

Table 4.4.3. Victorian NCIS contributed data for antipsychotics in cases where no heroin or methamphetamine was culpable.

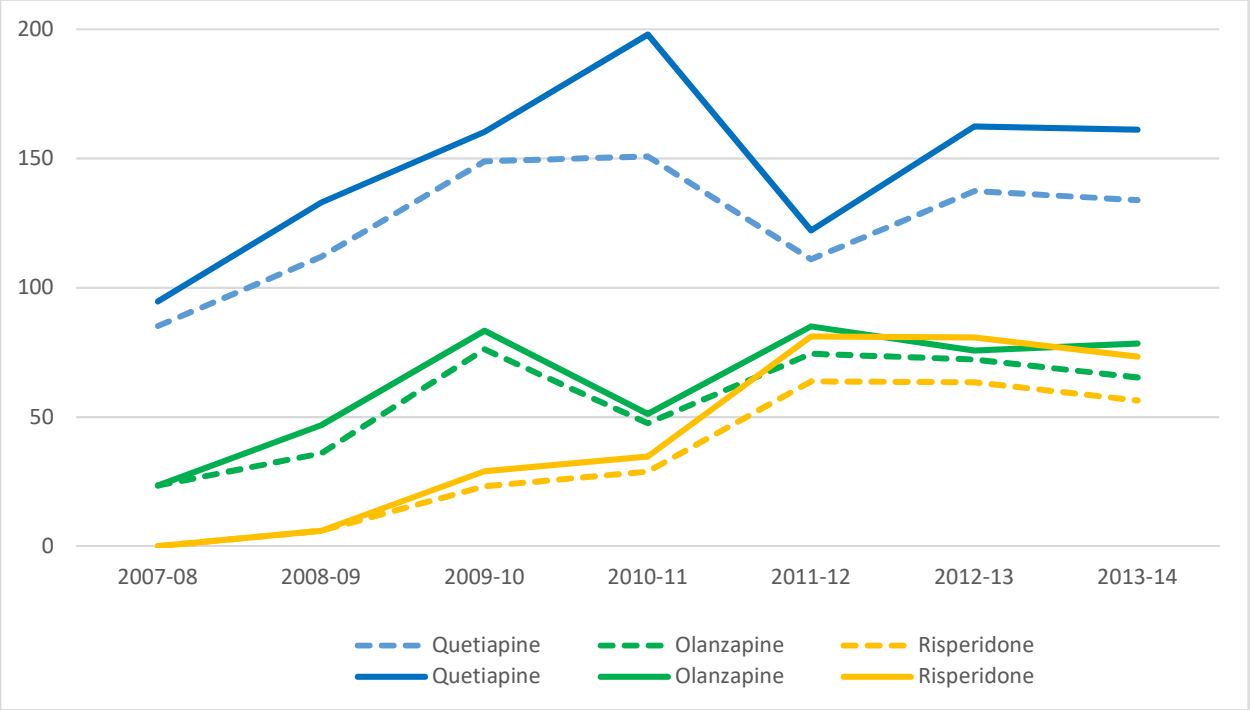
A. Overall number of antipsychotic-culpable deaths by year, for cases without 'illicit opioids' culpable and all cases
B. Antipsychotic-culpable deaths without 'illicit opioids' culpable as a proportion of all cases; estimated total prescriptions by year
C. Fatal toxicity index for antipsychotic-culpable deaths without 'illicit opioids' culpable, expressed as deaths/million prescriptions.

A	**Deaths**					
	Ilicits removed			*All cases*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2007-08	9	6	0	10	6	0
2008-09	16	10	1	19	13	1
2009-10	26	21	4	28	23	5
2010-11	32	13	5	42	14	6
2011-12	30	21	11	33	24	14
2012-13	44	21	11	52	22	14
2013-14	49	20	10	59	24	13

B	**Deaths as a proportion**			**Prescriptions**		
	Without ilicits as proportion of total			*Total (includes PBS and private)*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2007-08	90.0%	100.0%	-	105,640	255,406	144,689
2008-09	84.2%	76.9%	100.0%	142,900	277,749	165,877
2009-10	92.9%	91.3%	80.0%	174,623	275,643	172,051
2010-11	76.2%	92.9%	83.3%	212,188	273,206	173,014
2011-12	90.9%	87.5%	78.6%	270,237	282,164	172,491
2012-13	84.6%	95.5%	78.6%	320,321	290,783	173,349
2013-14	83.1%	83.3%	76.9%	366,022	306,141	177,176

C	**Fatal toxicity index**					
	Ilicits removed			*All cases*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2007-08	85.20	23.49	0.00	94.66	23.49	0.00
2008-09	111.97	36.00	6.03	132.96	46.80	6.03
2009-10	148.89	76.19	23.25	160.35	83.44	29.06
2010-11	150.81	47.58	28.90	197.94	51.24	34.68
2011-12	111.01	74.42	63.77	122.12	85.06	81.16
2012-13	137.36	72.22	63.46	162.34	75.66	80.76
2013-14	133.87	65.33	56.44	161.19	78.40	73.37

Figure 4.4.3. Victorian contributions to NCIS data for antipsychotics in cases where no heroin or methamphetamine ('illicit opioids') was culpable (deaths/million prescriptions). The complete lines represent all cases and the scored lines represent only the proportion of cases where 'illicit opioids' were not culpable, representing the lower limit of estimated harm. Even if in all deaths where quetiapine and an 'illicit opioid' were both deemed to be culpable, quetiapine was a 'innocent bystander', then quetiapine in 2016 (scored blue line) would still have a fatal toxicity index well in excess of fentanyl without combined 'illicit opioid' deaths excluded.



Do benzodiazepines lead to mortality in individuals not overdosing on opioids?

There has been significant evidence to suggest that the combination of opioids and benzodiazepines is the cause of benzodiazepine-related death, and there particularly has been concern regarding overdose deaths and combined toxicity in patients ingesting benzodiazepines and opioid replacement therapy(73) (see chapter 3.1). Further local data is cited in chapter 4.5 in a section of the same title as this one.

The significance of this speculative theory would be that, in the most optimistic interpretation, effective control of opioids (both illicit and licit) would abrogate the need to monitor benzodiazepines. To this end, we looked to determine whether benzodiazepines (and, given the purposes of this report, specifically schedule 4 benzodiazepines) were associated with death in the absence of culpability from any opioid, and then specifically opioid replacement therapy (ORT).

The results are displayed on Table 4.4.4. Of the large burden of mortality associated with benzodiazepines over the period between 2007-08 and 2013-14, 24.1% of cases had no culpability from any opioid. When only ORT was considered rather than all opioids, 76.1% of cases had no culpability from ORT. If a lower limit assumption is made in a similar manner to quetiapine and opioids, it would lead to fatal toxicity indices similar to that of risperidone. These data would suggest that benzodiazepines are capable of causing significant harm independently of a combination with opioids, and certainly independently of a combination with ORT. This is further explored in chapter 4.5 with a similar data set.

Schedule 4 benzodiazepine, with and without any opioid (heroin or pharmaceutical)

A Year	Deaths			
	S4 BZD without any opioid	**S4 BZD with opioid**	**S4 BZD total**	**Percentage without opioids**
2007-08	26	75	101	25.74%
2008-09	25	97	122	20.49%
2009-10	22	99	121	18.18%
2010-11	34	113	147	23.13%
2011-12	40	115	155	25.81%
2012-13	51	154	205	24.88%
2013-14	64	172	236	27.12%

Schedule 4 benzodiazepine, with and without ORT

B Year	Deaths			
	S4 BZD without any ORT	**S4 BZD with ORT**	**S4 BZD total**	**Percentage without ORT**
2007-08	81	20	101	80.20%
2008-09	101	21	122	82.79%
2009-10	91	30	121	75.21%
2010-11	115	32	147	78.23%
2011-12	106	49	155	68.39%
2012-13	154	51	205	75.12%
2013-14	179	57	236	75.85%

Table 4.4.4. Deaths in the Victorian contributions to the NCIS attributable to Schedule 4 benzodiazepines (BZD), expressed as total deaths, as classified by:
A. involvement of opioids, B. involvement of opioid replacement therapy.

4.5. Victorian Overdose Deaths Register (managed by the Coroners Prevention Unit)

The Coroners Court of Victoria (CCOV) runs the Coroners Prevention Unit (CPU), a group which has interest in drug overdose deaths in Victoria. To this end, the CPU established the Victorian Overdose Deaths Register to record trends associated with drug overdose deaths in Victoria. Cases, including open cases, are identified through ongoing monitoring of the CCOV case management system and death surveillance database. In pursuing a broad research agenda related to Victorian overdose deaths, many parameters are determined and recorded, including status of known injecting drug use (although this has been inconsistently recorded, and thus has not been used in this report) and status of known prescription shopping. No national direct equivalent exists. The rapidly responsive nature of this database allows for the inclusion of more recent data than other databases.

Determination of drug-related causality of death

Each case possibly for inclusion is assessed on the basis of its autopsy report, toxicology report and, for closed cases, finding. Attribution of causality is determined from these documents on the basis of recommendations from a consensus panel convened by the Substance Abuse and Mental Health Services Administration (SAMHSA)(74), a section of the United States Department of Health and Human Services. The methodology for this process is described in depth across two sources: as an appendix to CPU attachment to the CCOV Frood finding(75) and in an internal DHHS report authored by Dwyer et al.(76). This process has been confirmed in personal correspondence.

The application of causality is more inclusive than that from the NCIS in a number of different ways. First, deaths including drug effect combining with an ‘underlying natural disease process’ or ‘another (non-overdose) mechanism’ are included as contributory to a drug. Secondly, where no drug is not nominated by expert death investigators at all, any drug detected on toxicology is coded as contributory. Thirdly, when only a drug class is nominated as contributory rather than a specific drug, all drugs in that class are coded as contributory. These factors contribute to improved sensitivity of case detection and are important in a number of different common situations. This approach assists in trying to determine candidate drugs whose improved control would lead to reduced harm, but may slightly overrepresent class effects and commonly used drugs.

It is therefore useful to interpret this data by excluding, where possible, contexts in which ‘bystander’ drugs might be attributed to harm causality but in fact may be irrelevant to or even reducing harm. This report attempts to address these questions through subanalysis performed directly on the raw data. The authors gratefully acknowledge the contribution of Dr Jeremy Dwyer in this matter.

Overview of overall overdose death characteristics and patterns in overdose deaths by drug class

In the Dwyer report, cases were delineated into ones caused by a single drug versus ones due to multiple drugs, and the results for pharmaceutical overdose deaths are shown in table 4.5.1. Consistently over three quarters of the cases involved more than one drug, and this pattern became more accentuated over time. This underlines the importance of considering combination toxicity in preventing drug overdose deaths, but also in interpreting these data.

Table 4.5.1. Pharmaceutical overdose deaths, single versus multiple drug deaths. Reconstructed from the Dwyer report(76).

	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Single drug deaths	58	53	58	60	55	49	50
Multiple drug deaths	237	213	217	246	258	267	308
All overdose deaths	295	266	275	306	313	316	358

Prescription drug classes were also compared against each other and against illicit drugs and alcohol in terms of number of deaths caused in the whole cohort, and the results are displayed in Table 4.5.2. Benzodiazepines caused more deaths than illicit drugs, as did opioids, but of course this does not account for frequency of use in the population. Antidepressants, antipsychotics and non-benzodiazepine anxiolytics were the next most common prescription drug classes in order.

Frequency of contributing drug groups was examined in the Dwyer report, and the table is replicated in Table 4.5.3. The combination leading to the most deaths was the combination of benzodiazepines and opioids. Benzodiazepines were constituent in four of the five leading prescription drug combinations for total number of deaths.

Table 4.5.2. Contribution of drug classes to overdose deaths from the CPU cohort. Replicated from the Dwyer report(76).

	2009	2010	2011	2012	2013	2014	2015
	All overdose deaths						
Benzodiazepines	160	169	180	199	212	215	238
Opioids	177	145	183	212	192	186	199
Illegals	147	149	153	133	166	164	227
Antidepressants	122	106	101	142	134	144	161
Alcohol	94	85	88	80	94	94	106
Antipsychotics	63	64	65	78	75	81	91
Non-benzodiazepine anxiolytics	35	28	33	38	56	48	60
Non-opioid analgesics	26	25	30	52	41	49	46
Anticonvulsants	18	14	13	10	37	45	51
Total	379	342	362	367	380	387	453

Table 4.5.3. Combinations of contributing drug groups from the CPU cohort. Replicated from the Dwyer report(76).

Drug groups	n	%
Benzodiazepines and opioids	899	33.7
Benzodiazepines and antidepressants	675	25.3
Benzodiazepines and illegals	581	21.8
Opioids and antidepressants	551	20.6
Opioids and illegals	448	16.8
Benzodiazepines and antipsychotics	397	14.9
Benzodiazepines and alcohol	334	12.5
Opioids and antipsychotics	307	11.5
Antidepressants and antipsychotics	295	11.0
Antidepressants and illegals	265	9.9
Opioids and alcohol	241	9.0
Antidepressants and alcohol	218	8.2
Opioids and non-opioid analgesics	190	7.1
Alcohol and illegals	186	7.0
Antipsychotics and illegals	181	6.8
Opioids and non-benzodiazepine anxiolytics	173	6.5
Benzodiazepines and non-opioid analgesics	171	6.4
Antidepressants and non-opioid analgesics	158	5.9
Antidepressants and non-benzodiazepine anxiolytics	145	5.4
Benzodiazepines and anticonvulsants	141	5.3
Total	2670	100.0

Overdose deaths by individual contributing drugs

Drug-related overdose deaths, and their accompanying fatal toxicity indices (the normalised rate of deaths per million prescriptions) are expressed in Tables 4.5.4 and 4.5.5, and graphically compared in Figures 4.5.1 and 4.5.2. Benzodiazepines as a whole demonstrated a steady increase in toxicity over the time of the study, although this was heavily influenced by clonazepam, diazepam and nitrazepam. Alprazolam's toxicity continued to escalate until the time of rescheduling, after which its toxicity subsided, but still at a level higher than diazepam or nitrazepam. Temazepam's rate of toxicity was relatively stable and relatively low over the time period.

Tramadol has had relatively stable levels of toxicity, in contrast to fentanyl, whose toxicity increased dramatically in 2012 and largely maintained at a rate double that of tramadol. Codeine's toxicity escalated in 2012 and 2013 but subsequently subsided.

Zopiclone started with a very high fatal toxicity index, which overall escalated over the study period. Zolpidem has slightly fewer numbers of deaths compared with zopiclone, but given that its supply could not be estimated its fatal toxicity index was not calculated. Quetiapine had a much toxicity index compared with the other antipsychotics, although olanzapine demonstrated increases in 2015 and 2016. The antidepressants examined were largely stably low throughout. Pregabalin was only examined from 2013 onward but its toxicity actually subsided over time. Gabapentin did show an inconsistent increase in toxicity over the latter years of the study period.

Table 4.5.4. CPU prescription drug-related fatalities: benzodiazepines and opioids of interest

A. Drug-related fatalities in Australia captured by the CPU for selected prescription drugs, by year of notification and drug identified.
B. Fatal toxicity index on CPU data, for selected prescription drugs (deaths/million prescriptions).

Note deaths will total to greater than the number of total deaths as more than one of the drugs may have been identified.

A	diazepam	alprazolam	temazepam	oxazepam	nitrazepam	clonazepam	total BZD	codeine	tramadol	fentanyl
2009	104	62	28	18	17	7	160	76	22	1
2010	109	56	22	19	16	9	169	57	9	2
2011	124	43	48	44	11	14	180	66	15	5
2012	133	57	35	41	24	18	199	93	18	17
2013	164	45	22	17	26	19	212	71	24	11
2014	169	28	20	19	13	25	215	54	23	11
2015	192	23	25	34	17	33	238	64	32	23
2016	200	21	25	26	22	30	258	47	26	13
Fatal toxicity index per calendar year										
B	**diazepam**	**alprazolam**	**temazepam**	**oxazepam**	**nitrazepam**	**clonazepam**	**total BZD**	**codeine**	**tramadol**	**fentanyl**
2009	158.44	395.79	38.96	48.61	113.58	201.71	76.36	83.51	44.07	10.72
2010	168.88	369.92	32.45	54.44	115.01	251.29	84.24	67.46	18.51	17.35
2011	197.14	294.68	74.83	135.46	88.61	407.95	94.41	80.79	31.42	41.10
2012	190.51	382.40	52.64	121.86	199.51	472.73	98.83	103.57	33.68	115.83
2013	299.37	450.51	44.11	68.87	302.59	637.70	139.95	104.23	53.86	91.67
2014	208.48	316.55	28.84	53.30	112.23	591.15	101.65	55.73	34.46	69.39
2015	243.47	535.69	38.07	97.61	166.10	780.35	119.67	69.76	47.64	156.79
2016	290.18	375.98	44.58	87.01	284.01	812.72	149.62	60.19	44.40	107.60

Table 4.5.5. CPU prescription drug-related fatalities: antipsychotics, antidepressants, z-drugs and gabapentinoids of interest

A. Drug-related fatalities in Australia captured by the CPU for selected prescription drugs, by year of notification and drug identified.
B. Fatal toxicity index on CPU data, for selected prescription drugs (deaths/million prescriptions).

Note that zolpidem has not been on the PBS and thus supply data is not recorded in PBAC DUSC's ASM, although slightly more deaths are attributable to it compared to zopiclone.
Pregabalin was only recorded routinely post-mortem from 2013 onwards but the most recent data is available.
Note deaths will total to greater than the number of total deaths as more than one of the drugs may have been identified.

A	mirtazapine	amitriptyline	citalopram	quetiapine	olanzapine	risperidone	zopiclone	zolpidem	pregabalin	gabapentin
2009	23	24	17	28	19	6	6	11	-	0
2010	21	26	22	37	18	3	3	3	-	0
2011	23	22	21	34	17	11	6	5	-	0
2012	26	32	25	41	22	8	13	5	-	1
2013	30	25	24	41	15	10	14	4	17	1
2014	29	41	25	48	21	7	11	6	27	1
2015	50	28	26	49	30	9	17	11	34	4
2016	24	31	27	55	36	13	11	5	32	2
Fatal toxicity index per calendar year										
B	**mirtazapine**	**amitriptyline**	**citalopram**	**quetiapine**	**olanzapine**	**risperidone**	**zopiclone**	**zolpidem**	**pregabalin**	**gabapentin**
2009	73.39	77.14	46.65	173.86	67.39	34.81	330.59	-	-	0.00
2010	63.13	81.49	64.63	190.78	65.09	17.28	167.84	-	-	0.00
2011	66.70	67.67	63.04	151.41	63.42	65.01	295.37	-	-	0.00
2012	61.99	81.17	66.94	134.70	72.83	43.77	571.85	-	-	28.51
2013	82.86	74.77	80.42	147.60	62.36	71.40	838.08	-	132.96	32.83
2014	51.51	82.07	59.30	121.42	61.87	35.86	449.63	-	52.13	23.14
2015	82.53	54.75	63.92	131.44	91.34	46.93	716.25	-	44.61	97.74
2016	42.94	51.08	79.06	170.26	135.18	86.96	527.27	-	39.28	56.09

Figure 4.5.1. Fatal toxicity index by CPU detected data for selected drugs, 2009-2016, deaths per million prescriptions. Selected drugs include Schedule 4 drugs of interest, alprazolam and fentanyl. Clonazepam and zopiclone have escalating indices far above other drugs, and alprazolam, diazepam and nitrazepam also have elevated indices.

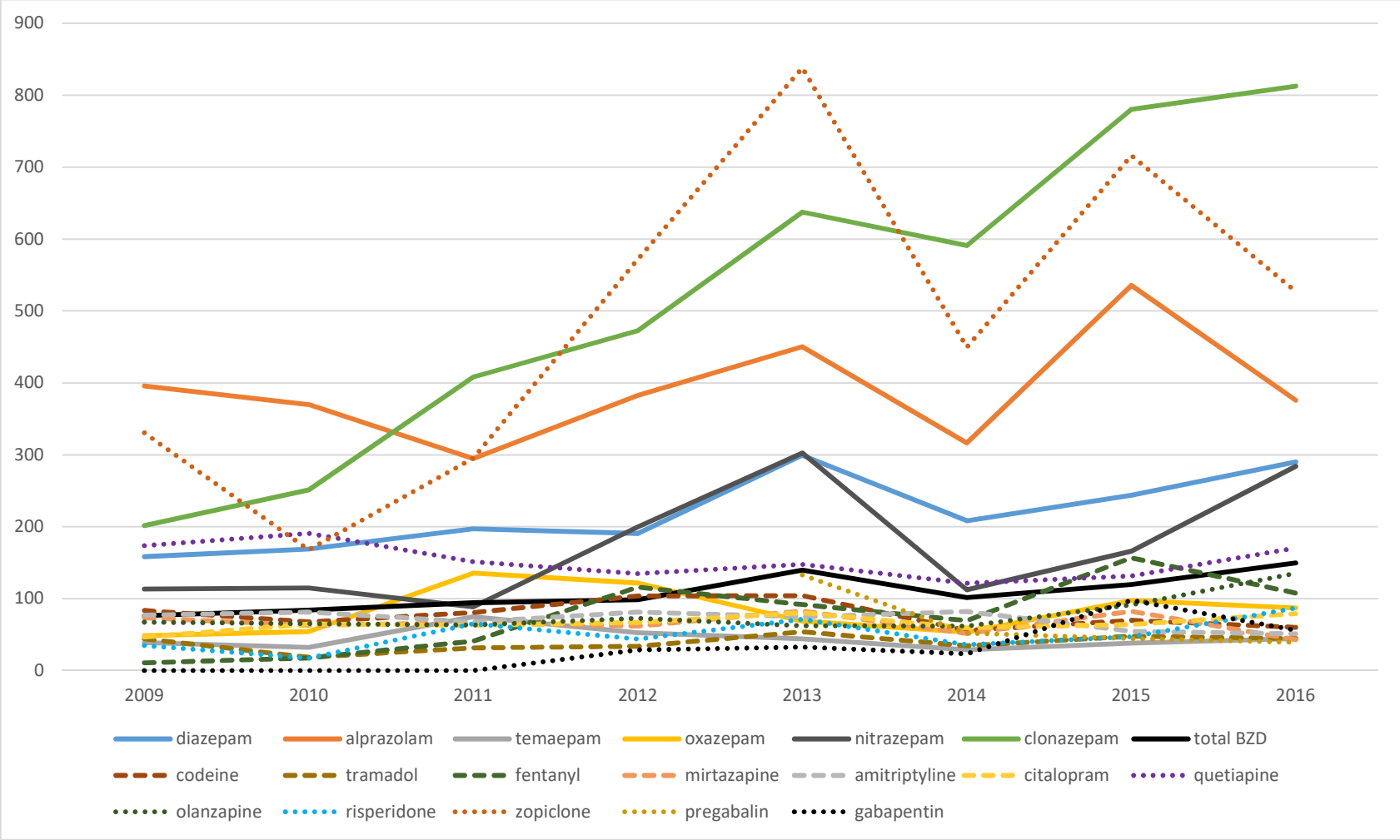
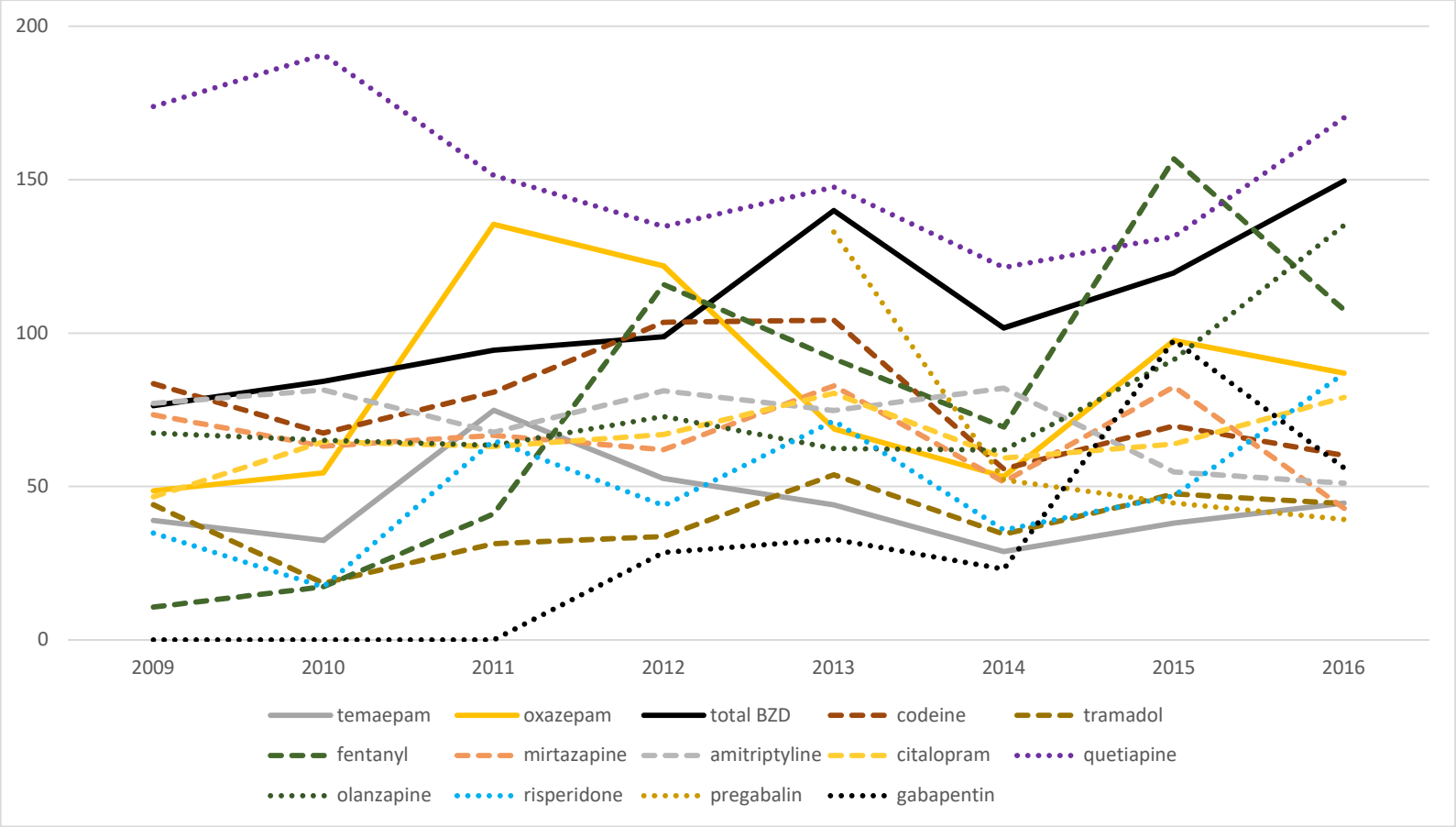


Figure 4.5.2. Fatal toxicity index by CPU detected data for selected drugs, 2009-2016, deaths per million prescriptions. Selected drugs are as per Figure 4.5.1., but excluding the highest scoring drugs (alprazolam, clonazepam, nitrazepam, diazepam and zopiclone) excluded for graphical clarity. Quetiapine consistently outscores the Schedule 4 drugs displayed on this graph. Fentanyl The majority of other drugs, apart from oxazepam, have similar trajectories although tramadol, pregabalin and risperidone have lower indices than other drugs.



In a similar way to this report's management of the data from the Victorian contribution to the NCIS, the data was subsequently interrogated for combinations of relevance with the assistance of Dr Jeremy Dwyer.

Are antipsychotics culpable for deaths in people who are abusing illicit opioids, or are they merely 'bystanders'?

As previously articulated in chapter 4.1, it has been mooted whether quetiapine, rather than being culpable for deaths in people abusing heroin and methamphetamine, just happens to be more frequently present in these people when they overdose on heroin or amphetamine (and might even be mitigating harm through its putative effects on the recovery from use of these opioids). If a concern exists about a combination creating harm and biasing the apparent danger of a drug, one approach to resolve that is to remove the endpoints associated with the combination and then observe what harm remains, as this then is a lower limit estimation of the harm from the original drug alone. It is important to emphasise the lower limit nature of this, as it should be acknowledged that this population is at higher risk for prescription medication overdoses in general and that all prescription medications are likely to have contributions from this population, and thus such a subgroup cannot be compared to overall rates in other groups.

In this spirit, this report examined deaths attributable to quetiapine, olanzapine and risperidone where no heroin or methamphetamine was culpable. The conclusions are similar to those found relating to similar analysis in chapter 4.4 but are replicated here.

The results are displayed on Table 4.5.7 and Figure 4.5.2. For quetiapine, the majority of cases were culpable without either heroin or amphetamine. This is less evident for olanzapine and risperidone. Despite it being an inappropriate comparison, it is notable that quetiapine without heroin or amphetamine is largely above the overall rates for olanzapine, despite this being a comparison which biases against this outcome. A similarly inappropriate comparison with overall rates for fentanyl, a restricted Schedule 8 drug, shows similar rates (i.e. the lowest estimation of quetiapine-related mortality finds it similar to fentanyl).

These data would suggest that, even if in all deaths where quetiapine and at least one of methamphetamine or heroin were both deemed to be culpable (i.e. quetiapine was an 'innocent bystander'), then quetiapine still represents a threat compared to other drugs, even if none of the deaths associated with other drugs were due to methamphetamine, heroin or any other drug.

Table 4.5.7. CPU data for antipsychotics in cases where no heroin or methamphetamine was culpable.

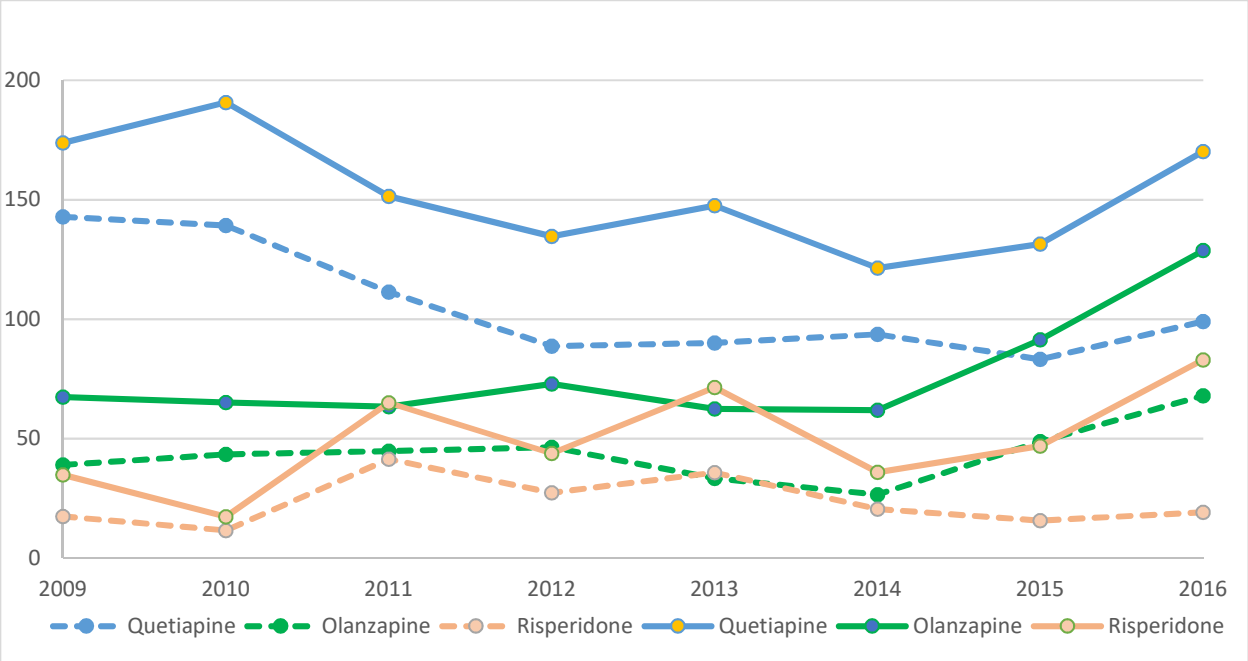
A. Overall number of antipsychotic-culpable deaths by year, for cases without 'illicit opioids' culpable and all cases
B. Antipsychotic-culpable deaths without 'illicit opioids' culpable as a proportion of all cases; estimated total prescriptions by year
C. Fatal toxicity index for antipsychotic-culpable deaths without 'illicit opioids' culpable (deaths/million prescriptions).

A	**Deaths**					
	Ilicits removed			*All cases*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2009	23	11	3	28	19	6
2010	27	12	2	37	18	3
2011	25	12	7	34	17	11
2012	27	14	5	41	22	8
2013	25	8	5	41	15	10
2014	37	9	4	48	21	7
2015	31	16	3	49	30	9
2016	32	19	3	55	36	13

B	**Deaths as a proportion**			**Prescriptions**		
	Ilicits removed as proportion of all cases			*Estimated total (includes PBS and private)*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2009	82.1%	57.9%	50.0%	161,053	281,923	172,346
2010	73.0%	66.7%	66.7%	193,936	276,533	173,625
2011	73.5%	70.6%	63.6%	224,549	268,042	169,198
2012	65.9%	63.6%	62.5%	304,378	302,087	182,773
2013	61.0%	53.3%	50.0%	277,770	240,521	140,049
2014	77.1%	42.9%	57.1%	395,323	339,427	195,216
2015	63.3%	53.3%	33.3%	372,789	328,442	191,757
2016	58.2%	52.8%	23.1%	323,035	279,651	156,650

C	**Fatal toxicity index**					
	Ilicits removed			*All cases*		
Year	Quetiapine	Olanzapine	Risperidone	Quetiapine	Olanzapine	Risperidone
2009	142.81	39.02	17.41	173.86	67.39	34.81
2010	139.22	43.39	11.52	190.78	65.09	17.28
2011	111.33	44.77	41.37	151.41	63.42	65.01
2012	88.71	46.34	27.36	134.70	72.83	43.77
2013	90.00	33.26	35.70	147.60	62.36	71.40
2014	93.59	26.52	20.49	121.42	61.87	35.86
2015	83.16	48.71	15.64	131.44	91.34	46.93
2016	99.06	67.94	19.15	170.26	128.73	82.99

Figure 4.5.2. CPU data for antipsychotics in cases where no heroin or methamphetamine ('illicit opioids') was culpable (deaths/million prescriptions). The complete lines represent all cases and the scored lines represent only the proportion of cases where 'illicit opioids' were not culpable, representing the lower limit of estimated harm. Even if in all deaths where quetiapine and an 'illicit opioid' were both deemed to be culpable, quetiapine was an 'innocent bystander', then quetiapine in 2016 would still have a fatal toxicity index similar to fentanyl without combined 'illicit opioid' deaths excluded.



Do benzodiazepines lead to mortality in individuals not overdosing on opioids?

There has been significant evidence to suggest that the combination of opioids and benzodiazepines is the cause of benzodiazepine-related death, and there particularly has been concern regarding overdose deaths and combined toxicity in patients ingesting benzodiazepines and opioid replacement therapy(73) (see chapter 3.1).

It is certainly the case that benzodiazepines and opioids are the most commonly co-culpable combination in the CPU data published in the Dwyer report, which examined data from 2009-2015 (see Table 4.5.3). Very few deaths in this cohort deemed caused by benzodiazepines occurred in isolation (see Table 4.5.6.). It is unclear from the previously reported data in this cohort as to whether benzodiazepines (or at least schedule 4 benzodiazepines) are able to lead to mortality without opioids.

Table 4.5.6. Number of single and multiple drug overdose deaths in the CPU cohort. Reconstructed from the Dwyer report(76).

Drug	Single drug deaths	Multiple drug deaths	Total deaths
diazepam	1	994	995
temazepam	10	190	200
oxazepam	2	190	192
clonazepam	2	123	125
nitrazepam	6	118	124

The significance of this speculative theory would be that, in the most optimistic interpretation, effective control of opioids (both illicit and licit) would abrogate the need to monitor benzodiazepines. To this end, we looked to determine whether benzodiazepines (and, given the purposes of this report, specifically schedule 4 benzodiazepines) were associated with death in the absence of culpability from any opioid, and then specifically opioid replacement therapy (ORT).

The results are displayed on Table 4.5.9 and Table 4.5.10. Of the large burden of mortality associated with benzodiazepines over the period between 2009-2016, 18.7% of cases had no culpability from any opioid. There was no trend in this respect noted over time (see Table 4.5.9). When only ORT was considered rather than all opioids, 74.7% of cases had no culpability from ORT. If a lower limit assumption is made in a similar manner to quetiapine and opioids, it would lead to fatal toxicity indices similar to that of risperidone.

These data would suggest that benzodiazepines are capable of causing significant harm independently of a combination with opioids, and certainly independently of a combination with ORT.

Table 4.5.9. Overdose deaths due to Schedule 4 benzodiazepines (BZD), with or without co-culpability of any opioid, expressed in absolute terms and with the proportion without opioid expressed as a percentage of total, in the CPU cohort.

Year	S4 BZD without any opioid	S4 BZD with opioid	S4 BZD total	Percentage without opioids
2009	20	110	130	15.38%
2010	28	111	139	20.14%
2011	25	136	161	15.53%
2012	36	138	174	20.69%
2013	42	159	201	20.90%
2014	27	178	205	13.17%
2015	50	179	229	21.83%
2016	50	201	251	19.92%

Table 4.5.10. Overdose deaths, supply and fatal toxicity index for Schedule 4 benzodiazepines (BZD), with and without opioid replacement therapy (ORT) in the CPU cohort. Fatal toxicity index expressed as deaths/million prescriptions.

	Deaths				***Supply***	***Fatal toxicity index***	
Year	**S4 BZD without any ORT**	**S4 BZD with ORT**	**S4 BZD total**	**Percentage without ORT**	**Estimated scripts (PBS + private)**	**S4 BZD**	**Proportion - without ORT***
2009	99	31	130	76.15%	1,938,565	67.06	51.07
2010	109	30	139	78.42%	1,854,700	74.94	58.77
2011	107	54	161	66.46%	1,760,626	91.44	60.77
2012	127	47	174	72.99%	1,864,552	93.32	68.11
2013	148	53	201	73.63%	1,414,931	142.06	104.60
2014	147	58	205	71.71%	2,026,717	101.15	72.53
2015	181	48	229	79.04%	1,945,915	117.68	93.02
2016	196	55	251	78.09%	1,668,493	150.44	117.47

Fatal toxicity index expressed in deaths/million prescriptions.

* Note this is an assumption which underestimates harm from target drug as denominator includes patients on confounder drug but numerator does not. It assumes that confounder drug patients are not particularly high risk and that the patients who died of target drug/confounder drug jointly culpable would not have died/be high risk for dying if confounder could have been withheld.

Do z-drugs have toxicity outside combination with benzodiazepines?

Z-drug pharmacodynamics appear dependent on action on the benzodiazepine subunit of the GABA-A receptor; benzodiazepines should not be combined with z-drugs. The introduction of z-drugs and subsequent popularity was with consideration to their supposed selectivity and shorter half-life, and it does appear clinically that they might lead to less problematic respiratory depression and residual daytime sleepiness. Given this, if benzodiazepines could be effectively regulated, would this supplant the need to regulate z-drugs (displacement i.e. substitution theory aside)? To determine this, it must be determined whether z-drugs have toxicity outside combination with benzodiazepines.

In a manner similar to the previous two combinations of relevance examined, we analysed z-drug related deaths in combination with benzodiazepines and those which did not.

The results are shown in Table 4.5.8. The co-culpability of benzodiazepines in z-drug related deaths is variable, but in recent years between 16-33% of z-drug related deaths did not involve benzodiazepines. This demonstrates they can have toxicity by themselves. In a lower limit comparison as previously described, using data from the PBAC DUSC-tracked zopiclone, z-drugs without benzodiazepines involved would still lead to a fatal toxicity index in 2016 in excess of all other non-benzodiazepines examined.

Table 4.5.8. Contribution of co-culpability of benzodiazepines to z-drug mortality in the CPU cohort. Fatal toxicity index expressed as (deaths/million prescriptions).

Year	z-drug deaths with BZD	z-drug deaths without BZD	% z-drug deaths without BZD	zopiclone deaths alone	zopiclone estimated supply	zopiclone fatal toxicity index	proportionate burden of fatal toxicity index from z-drugs without BZD involved*
2009	6	7	53.85%	6	18149	330.59	178.01
2010	5	1	16.67%	3	17874	167.84	27.97
2011	8	4	33.33%	6	20314	295.37	98.46
2012	12	5	29.41%	13	22733	571.85	168.19
2013	15	3	16.67%	14	16705	838.08	139.68
2014	12	5	29.41%	11	24465	449.63	132.24
2015	21	7	25.00%	17	23735	716.25	179.06
2016	10	5	33.33%	11	20862	527.27	175.76

Fatal toxicity index expressed in deaths/million prescriptions.

* Note this is an assumption which underestimates harm from target drug as denominator includes patients on confounder drug but numerator does not. It assumes that confounder drug patients are not particularly high risk and that the patients who died of target drug/confounder drug jointly culpable would not have died/be high risk for dying if confounder could have been withheld.

4.6. Victorian Poisons Information Centre

Overview of the service

The Victorian Poisons Information Centre (VPIC) is based in a major metropolitan hospital in Melbourne and has been in operation since 1962. VPIC receives telephone calls with queries about poison exposures, animal/insect stings/bites and overdoses both intentional and unintentional in nature. The service is available 24 hours a day, 7 days per week, however overnight shifts are shared between the other Australian poison information centres and therefore some calls from other states overnight may be recorded in the VPIC database. The trained operators provide advice to the caller (who may be a medical professional or member of the public) about what they should do to manage the exposure. VPIC aims to provide up-to-date advice to callers to achieve the best care for those who require treatment for their exposure as well as minimise unnecessary medical service usage. Each telephone call is recorded in an electronic database with details as listed below at the time of contact. This database is then used to report annual trends in exposures and the overall activity of the service to the public.

Understanding this database

There are a number of limitations to data from this source. First, this database replies on patient self-reporting. Each exposure is recorded at the time of the telephone call, which theoretically provides accuracy of the information, however the priority is always given to the management of the caller over completion of the record and therefore occasionally the data recorded may not be entirely complete. Some callers may give false reasons for the exposure, such as claiming an accidental overdose instead of an intentional overdose. Additionally, the recorded poisons are only as accurate to what the caller describes them to be. If a caller has taken a substance and they don't know what it was, then the record will reflect this.

Secondly, the nature in which these data are recorded is important to consider in their interpretation. In order to collate the data, some poisons are recorded as a class, such as benzodiazepines. To extract the separate benzodiazepines from the class is logistically difficult and, balanced against the context in which this information would be applied, it was considered of insufficient utility to make this delineation. Separate poisons can be extracted from the database if they are not captured by class, however this is not publicly available information and each request must be made to the manager of the poisons information service. The authors are grateful for the contribution of Jeff Robinson and Dr Shaun Greene in allowing us to analyse the raw data in order to assess selected medications.

It should also be noted that VPIC fields calls overnight from the catchments of other Australian poisons information centres (PICs) on a rotational basis for logistical reasons, and in this way Victorian calls are rotationally fielded by other poisons information centres. It therefore stands that the Victorian data collected could be contaminated with data from other PICs jurisdictions however this is unlikely to significantly skew the results as the rotation

(one in four nights) roughly approximates the proportion of burden conferred by the VPIC catchment.

The main utility of the VPIC data for this report is to detect trends in drug related exposures within the Victorian population, after normalisation for the quantity of drug dispensed. This data cannot show hard endpoints of death or hospitalisation but is likely to detect emerging sources of harm earlier than other local databases.

Drugs analysed in this report have been chosen as drugs of interest for determining emerging trends, based on trends seen in previous sections of this report. Given that benzodiazepines are likely to need to be considered as a group, given the already demonstrated risk of displacement of harm if drugs within that class are monitored in an uncoordinated manner (i.e. the substitution effect), they were considered for the purposes of this report as a group. One of the key indicators of emerging threats of harm, both in Australia and internationally, is reports to PICs, and thus it is useful to assess the evolution of PIC calls to determine emerging threats of harm, especially with changes in supply or use during that period.

Distribution of drug-related incidents

The data is illustrated in Table 4.6.1 and is graphically represented in Tables 4.6.1 and 4.6.2. The eight calendar years in which data was captured included a period of dramatically escalating pregabalin use, with the introduction of its use for neuropathic pain and the opening of access through the PBS, and it was thus unsurprising to see absolute number of calls for pregabalin jump from 5 to 204 as people inexperienced with its use began to start using it frequently, and this might seem alarming in passing observation. Nevertheless, when it was normalised for estimated supply, calls per million prescriptions actually reduced over time, suggesting not the escalating proportionate burden of harm one might expect to see with emerging misuse and abuse but in fact decreasing proportionate burden of harm that one might expect to see with familiarisation of appropriate use.

Zopiclone demonstrated a dramatic escalation in calls over this time despite a relatively stable rate of supply in Victoria during this period. This translated to a dramatic escalation in incident toxicity index, with the number of calls per million prescriptions over ten times that of pregabalin, tramadol or Schedule 4 codeine/paracetamol in 2016. Quetiapine-related calls demonstrated a progressive increase, roughly in keeping with increasing supply, with a rate which remained the second highest of any group. Benzodiazepines and gabapentin consistently demonstrated higher normalised rates of calls than codeine/paracetamol and tramadol, which both demonstrated stable normalised rates over this period.

Table 4.6.1. VPIC data for selected drugs and drug groups per year.

A. Total calls received by VPIC regarding poisonings by specific formulations.
B. Estimated total supply in Victoria (estimated aggregated PBS and private supply)
C. Incident toxicity index (calls/million prescriptions) – rates of calls normalised for supply.

A	tramadol	S4 codeine - paracetamol	BZD total	zopiclone	pregabalin	gabapentin	quetiapine	zolpidem
2009	106	203	945	0	5	11	238	49
2010	104	212	1,000	19	28	10	319	54
2011	103	237	959	35	21	19	361	56
2012	130	242	1,000	65	27	22	411	47
2013	112	226	977	57	67	22	471	43
2014	139	214	989	65	103	18	504	44
2015	155	281	1,128	96	175	16	552	45
2016	182	258	1,194	93	204	21	666	38

B	tramadol	S4 codeine - paracetamol	BZD total	zopiclone	pregabalin	gabapentin	quetiapine
2009	499,261	818,795	2,095,215	18,149	27,124	24,734	161,053
2010	486,271	758,956	2,006,086	17,874	32,682	25,962	193,936
2011	477,391	732,675	1,906,545	20,314	37,866	28,450	224,549
2012	534,387	810,898	2,013,610	22,733	50,776	35,081	304,378
2013	445,620	619,794	1,514,819	16,705	127,861	30,463	277,770
2014	667,374	867,501	2,115,169	24,465	517,925	43,207	395,323
2015	671,638	816,826	1,988,850	23,735	762,233	40,924	372,789
2016	585,606	695,400	1,724,347	20,862	814,572	35,659	323,035

C	tramadol	S4 codeine - paracetamol	BZD total	zopiclone	pregabalin	gabapentin	quetiapine
2009	212.31	247.93	451.03	0.00	184.34	444.74	1477.77
2010	213.87	279.33	498.48	1063.01	856.74	385.17	1644.87
2011	215.76	323.47	503.00	1722.98	554.59	667.83	1607.67
2012	243.27	298.43	496.62	2859.23	531.74	627.11	1350.30
2013	251.34	364.64	644.96	3412.17	524.01	722.20	1695.64
2014	208.28	246.69	467.57	2656.89	198.87	416.60	1274.91
2015	230.78	344.01	567.16	4044.73	229.59	390.97	1480.73
2016	310.79	371.01	692.44	4457.81	250.44	588.92	2061.69

NB: Zolpidem is only expressed in absolute calls as supply data is unable to be estimated as it has not previously been monitored by the PBAC DUSC. “S4 codeine-paracetamol” represents paracetamol 500mg/codeine 30mg formulations, “BZD” represents supply (cumulative BZD supply from PBAC DUSC-estimated drugs)

Figure 4.6.1. Incident toxicity index (normalised rates) for calls received by VPIC for selected drugs and drug groups by year (calls/million prescriptions).

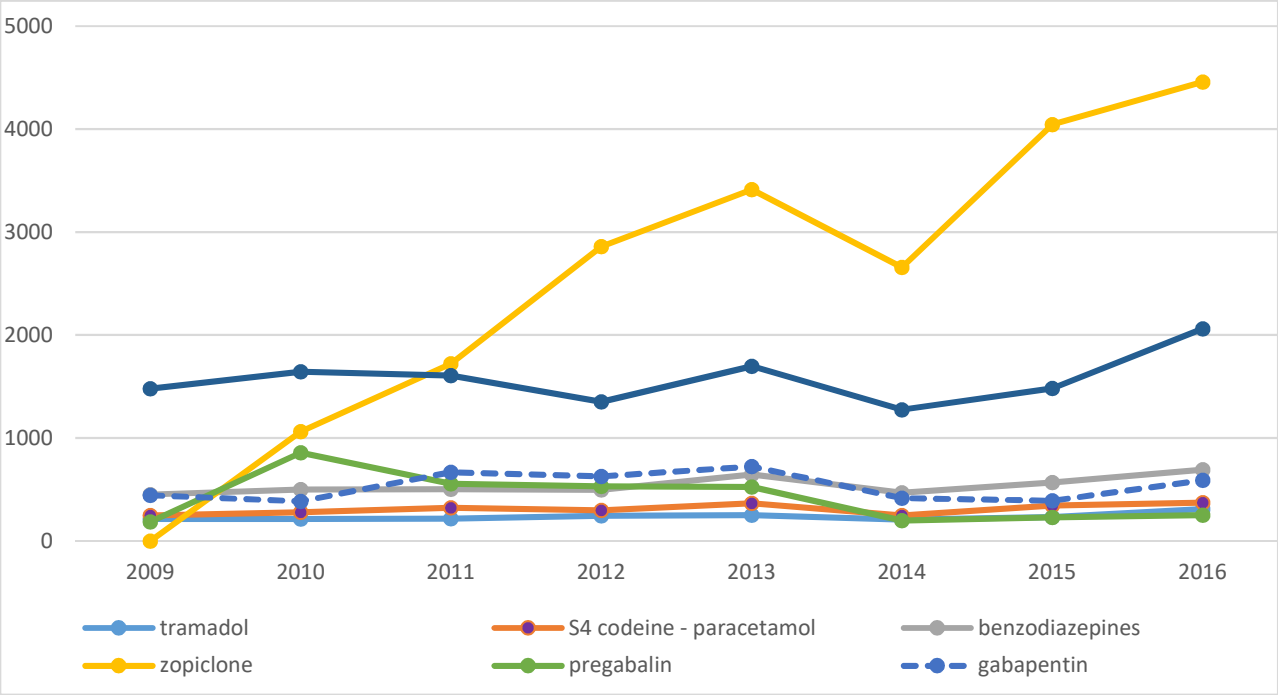
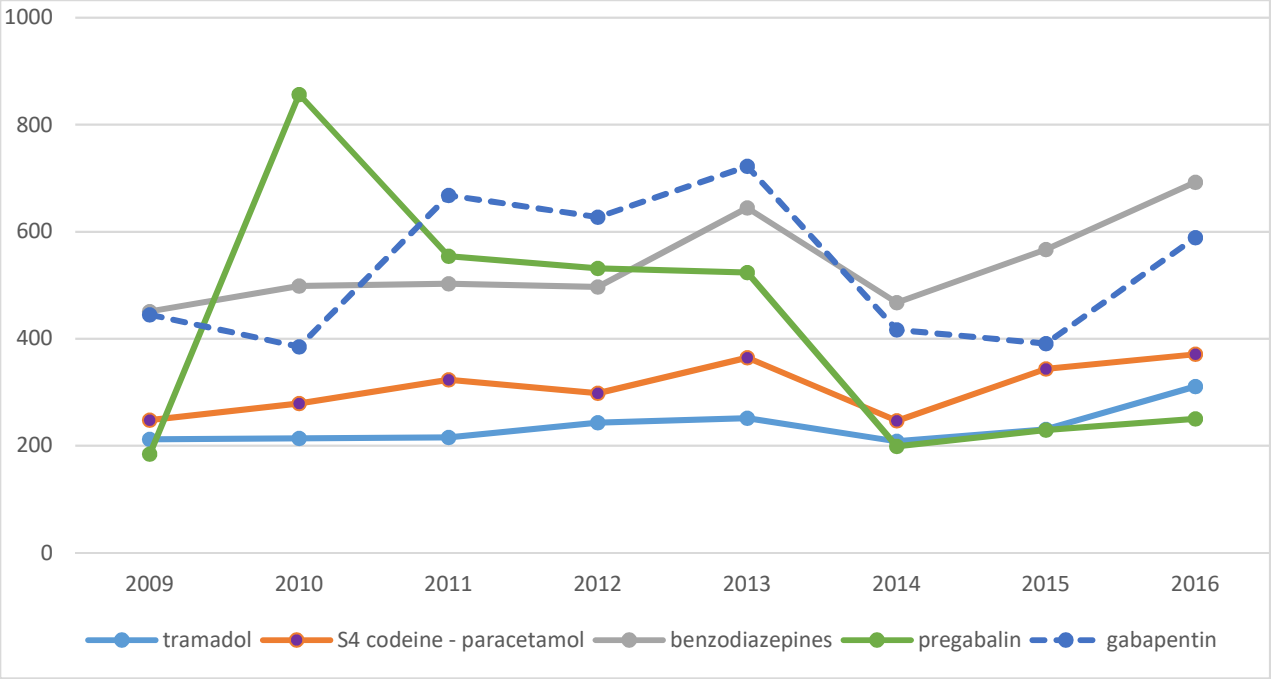


Figure 4.6.2. Incident toxicity index (normalised rates) for calls received by VPIC for selected drugs and drug groups by year (calls/million prescriptions); data as above but with highest ranking drugs zopiclone and quetiapine excluded for graphical clarity.



4.7. Ambo Project by Turning Point

The Ambo Project is an ongoing project which monitors ambulance attendances for alcohol and drug-related events attended by Ambulance Victoria. It is administered by Turning Point, with data collected by Ambulance Victoria as part of data recording for attendance reports. It is funded by the DHHS. It has been in place since 1998, although it has only been in its current form since July 2011. A caveat to its interpretation is therefore that only six months of data was recorded in 2011. Additionally, as part of industrial action in 2014, data was not recorded for three months. Broad details from this database are available online at the Ambo-AODstats website but this gives no granularity on individual drugs, the importance of which is discussed in Chapter 3.1. The Ambo Project data was therefore supplied as provided data tables under an Eastern Health Human Research Ethics Committee extension approval. We gratefully acknowledge Sharon Matthews for making this data report available, and Dr Cherie Heilbronn and A/Prof Belinda Lloyd for their advice.

Notably the Ambo Project by Turning Point is currently the only database in a suite of DHHS-supported databases managed by Turning Point that gives granular detail on specific drugs involved. The Victorian Drug Statistics Handbook was published for periods up until June 2011, after which it was ceased and drug statistics were captured by drug class.

Ambulance callout data is of note particularly as it may detect emerging trends earlier than other databases, as notably seen with quetiapine in 2009 when increased overdose-related mortality had yet to emerge but increased ambulance callouts had. As seen in the earlier parts of this chapter, quetiapine overdose-related mortality has subsequently emerged and stabilised. In trying to determine which prescription medications may pose a threat in the near future, identifying trends in this database may help flag emerging problem drugs.

Determination of drugs culpable in ambulance callouts

Benzodiazepines, opioid analgesics, antidepressants and pregabalin were interrogated in this data set, the aggregated results of which are on Table 4.7.1, and the incident toxicity indices on Table 4.7.2, and in Figures 4.7.1 and 4.7.2. There was a broad spectrum of rates of calls per million prescriptions, with zopiclone progressively rising as high as 10,296 ambulance calls per million prescriptions in 2013 i.e. a greater than 1% chance that an individual episode of dispensing zopiclone would lead to an ambulance callout. This rate has subsequently plateaued, notably while deaths continue to emerge in other data sets. This data set was one of the few to differentiate codeine/paracetamol from plain codeine, codeine/ibuprofen and codeine/aspirin, although it did not differentiate Schedule 4 codeine/paracetamol (i.e. codeine 30mg/paracetamol 500mg) from combinations with lower amounts of codeine. If one presumes that the totality of call-outs in this data set for codeine/paracetamol were for Schedule 4 rather than Schedule 2 or 3 medications, it achieved incident toxicity indices comparable to oxazepam, nitrazepam and temazepam. Plain codeine achieved similar levels, but progressively escalating. Tramadol, gabapentin and pregabalin demonstrated stable, relatively low indices with no clear progression over the course of the study period.

Table 4.7.1: AOD Ambo ambulance callouts (aggregated) per calendar year, drugs of interest

	July-Dec 2011	2012	2013	Jan-Sep 2014	2015	2016
Percentage of a year	**50%**	**100%**	**100%**	**75%**	**100%**	**100%**
Opioid analgesics						
tramadol	91	199	196	144	204	245
aspirin and codeine	N<5	8	8	6	6	N<5
ibuprofen and codeine	31	78	80	51	101	65
paracetamol and codeine	291	690	684	489	755	661
codeine	28	43	56	81	79	107
Benzodiazepine (all)	1776	4194	3890	2849	4137	4106
alprazolam	409	923	784	296	271	300
bromazepam	7	9	8	8	18	6
clobazam	N<5	N<5	0	0	0	0
clonazepam	74	171	151	145	269	278
diazepam	815	2104	2091	1659	2511	2418
flunitrazepam	N<5	16	8	13	18	20
lorazepam	13	54	53	54	75	126
midazolam	N<5	N<5	9	N<5	7	10
nitrazepam	60	124	120	86	100	80
oxazepam	119	252	203	217	322	312
temazepam	259	696	564	414	632	621
triazolam	N<5	0	N<5	0	0	0
zolpidem	61	136	121	83	134	129
zopiclone	76	186	172	152	215	204
benzodiazepine_other	100	126	78	58	74	98
Antidepressants						
mirtazapine	86	215	213	173	266	292
amitriptyline	75	182	162	127	162	174
citalopram	19	66	69	45	47	48
gabapentin	8	14	15	7	10	14
Anticonvulsant						
pregabalin	7	38	79	108	251	336

Table 4.7.2: AOD Ambo ambulance callout incident toxicity index by calendar year (calls/million scripts), drugs of interest

	2011	2012	2013	2014	2015	2016
tramadol	381.24	372.39	439.84	287.69	303.74	418.37
codeine - paracetamol (Schedule 4*)	794.35	850.91	1103.59	751.58	924.31	950.53
codeine (plain)	709.23	523.60	957.26	1102.52	804.19	1277.51
benzodiazepines (all)	1992.81	2215.17	2722.39	1899.96	2192.94	2493.19
alprazolam	5605.86	6192.20	7848.80	4461.89	6311.80	5371.12
bromazepam	2029.87	1345.77	1397.13	1339.35	2357.69	1149.27
clonazepam	4312.61	4490.90	5068.06	4571.58	6361.02	7531.23
diazepam	2591.39	3013.74	3816.92	2728.72	3184.19	3508.28
oxazepam	732.72	749.01	822.35	811.65	924.40	1044.10
nitrazepam	966.64	1030.78	1396.55	989.95	977.09	1032.75
temazepam	807.55	1046.76	1130.69	795.94	962.35	1107.25
zopiclone	7482.67	8181.80	10296.38	8284.04	9058.51	9778.43
mirtazapine	498.79	512.62	588.29	409.69	439.04	522.48
amitriptyline	461.39	461.64	484.50	338.94	316.78	286.72
citalopram	114.07	176.73	231.22	142.31	115.54	140.55
gabapentin	562.38	399.07	492.41	216.01	244.35	392.61
pregabalin	369.73	748.38	617.86	278.03	329.30	412.49

Notes:

1. (*) As data is not disaggregated for Schedule 4 preparations (versus Schedule 2/3 preparations), it has been assumed that all toxicity in this group is from Schedule 4 codeine – paracetamol combinations.
2. These data have been manipulated to compensate for only six months being recorded in 2011 (initiation of database) and nine months in 2014 (paramedic industrial action).
3. The 2016 DDD not yet published, and thus 2015 DDD ratio transposed to 2016 in order to calculate the incident toxicity index.

Figure 4.7.1: Incident toxicity index (calls/million scripts) over time (2011-2016), drugs of interest

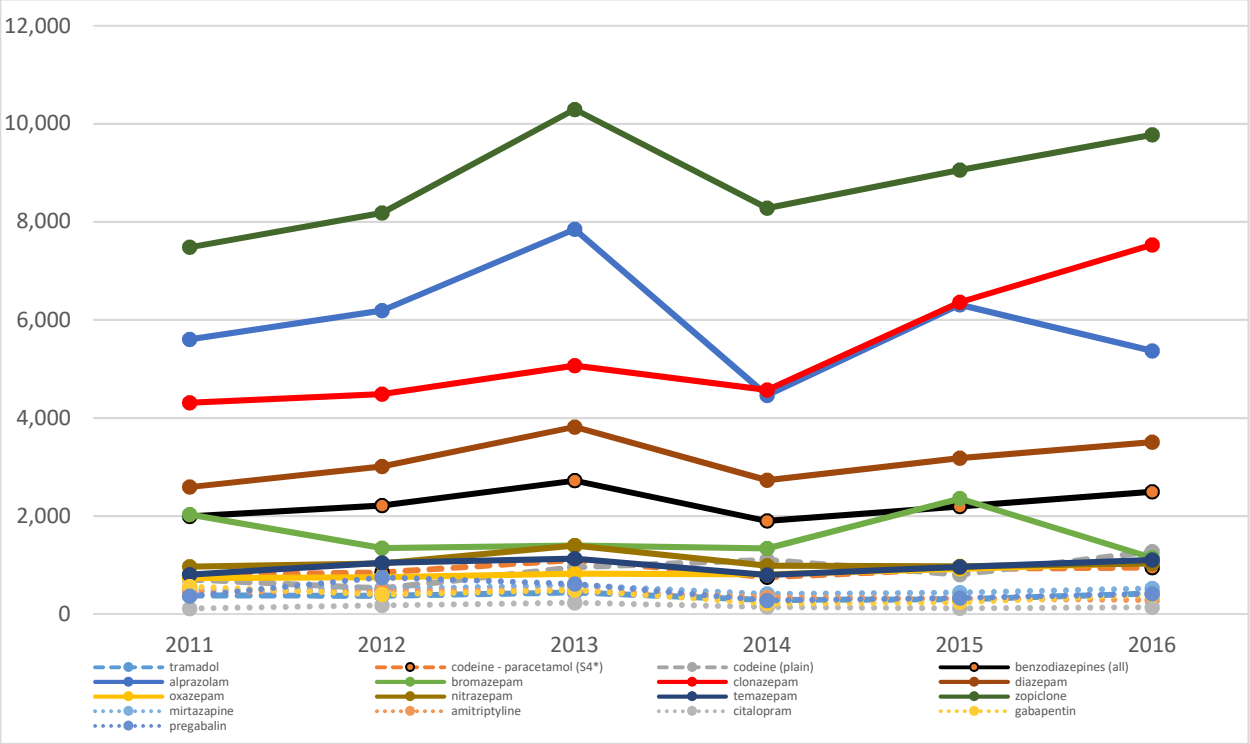
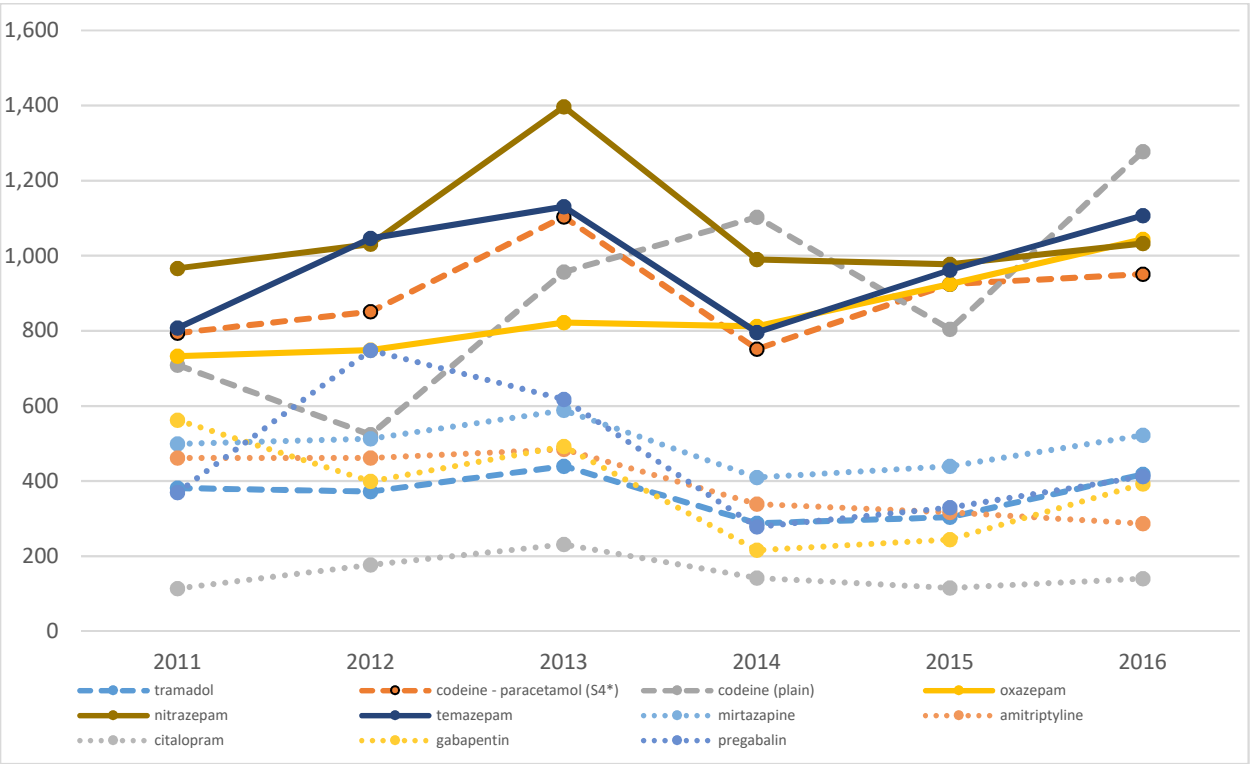


Figure 4.7.2: Incident toxicity index (calls/million scripts) over time (2011-2016), drugs of relatively low impact (excluding zopiclone, alprazolam, clonazepam, diazepam, cumulative BZD and bromazepam)



4.8. Victoria Police Forensic Services Department data

Victoria Police's Forensic Services Department collects data regarding all pharmaceutical drugs analysed after being seized by Victoria Police in the period 2012-2016 (see Appendix 3). Of note in this dataset, within the top ten most frequently detected drugs, the drugs of interest to this report are alprazolam (ranked 1), diazepam (ranked 3), quetiapine (ranked 8) and clonazepam (ranked 9). This would suggest that these drugs may well be associated with diversion or abuse in Victoria, although this relationship is unclear. Notably, alprazolam was 7.8x more frequently detected than the fifth most common agent, sildenafil.

4.9. Conclusions from this chapter

The evidence for harm from individual drugs can be understood as a spectrum, with the peer reviewed literature and mortality databases detecting more established prescription medicine sources of harm, and ambulance and poisons information detecting trends as they emerge from misuse and abuse to deliver harm. Throughout this, context is important – particularly in the weight of supply, availability and existing regulation. The peer reviewed literature reflects the key changes across these domains in recent years. This is particularly clear with benzodiazepines, where the burden of harm as a class is evident across multiple measures of morbidity and mortality. In addition, changes that have come about from the rise, regulation and fall of harm from alprazolam have influenced other drugs, particularly the other benzodiazepines, to which the burden of harm that used to sit with alprazolam has been displaced (the substitution or 'squeezed balloon' effect). Harm from opioids is a rising threat, and while codeine's large burden of mortality in the context of an even broader base of possible abuse has been described in the literature, there is little to support the threat of harm from tramadol. Similarly, within antipsychotics, quetiapine has displayed a concerning escalation out of proportion to its supply beyond that offered by others in its class, whereas the literature is overall reassuring on harm from anti-depressants in Australia. There is little said about other sedatives and anticonvulsants, but the established patterns of harm from benzodiazepines, quetiapine and codeine are hard to ignore.

It is in the data from the local databases that we have been able to view a lot of the evidence from the peer reviewed literature in the context of overall supply, and to compare relative harms between drugs, as well as durability and escalation of rates of harm. Zopiclone has consistently suggested escalating and high levels of death proportionate to supply across multiple mortality cohorts although ambulance callouts have plateaued, and there is no reason to think that zolpidem is any different. Clonazepam has also followed a similar pattern, and while there is a hierarchy across the different individual benzodiazepines, as a whole their normalised rates of harm sit above antidepressants, Schedule 4 opioids and gabapentinoids and they deliver harm independent of opioids. Quetiapine is consistently more harmful proportionate to supply than other antipsychotics, with a mature level of harm now evident and a clear harm independently of heroin or methamphetamine. Apart from a slight escalation with plain codeine in ambulance callouts, there is no other local data for emerging trends proportionate to supply, with no such signals from tramadol, pregabalin or gabapentin.

Chapter 5. Trends in misuse and abuse of Schedule 4 medications in Australia and internationally

Summary estimation of concern from trends of use, misuse and abuse globally

Note: this does not supplant the importance of the qualitative analysis of this report

Definite concerning trends	Probable concerning trends	Possible concerning trends	Unlikely concerning trends
diazepam clonazepam quetiapine zolpidem pregabalin codeine (S4)	midazolam temazepam zopiclone gabapentin tramadol dextropropoxyphene testosterone	oxazepam lorazepam nitrazepam bromazepam olanzapine phenobarbital venlafaxine amitriptyline frusemide hydrochlorothiazide benzhexol levodopa oxybutynin baclofen clonidine epoetin tamoxifen mesterolone nandrolone	clobazam risperidone amisulpride aripirazole chlorpromazine clozapine haloperidol lurasidone paliperidone ziprasidone trifluoperazine asenapine droperidol periciazine fluphenazine flupenthixol zuclopenthixol levetiracetam lamotrigine topiramate sodium valproate carbamazepine zonisamide vigabatrin tiagabine perampanel oxcarbazepine lacosamide phenytoin primidone citalopram fluvoxamine fluoxetine sertraline escitalopram paroxetine dapoxetine desvenlafaxine duloxetine dosulepin imipramine doxepin clomipramine nortriptyline mirtazapine reboxetine moclobemide

			agomelatine mianserin vorioxetine phentermine biperiden orphenadrine apomorphine selegeline amantadine atomoxetine lithium doxylamine darbepoetin methoxypegepoetin β anastrazole letrozole exemestane toremifene

5.1. Benzodiazepines

There is extensive peer reviewed literature available for the misuse of benzodiazepines between the years 2005-current. It is presumed that extension of the timeframe for which this search was conducted to earlier years would result in an extremely large cohort of articles describing the evolution of benzodiazepine use and misuse from their first discovery of misuse potential in the 1960s.(1)

The difficulty in conducting a peer reviewed literature search on the topic of misuse of benzodiazepines lies in both the large numbers of articles returned, as well as the dearth of literature which separates individual benzodiazepines from their class. Of the 493 articles which were picked from screening of title and abstract from 2159 articles across the databases searched, 129 were excluded based on relevance to the research question, 75 based on language other than English, 31 due to unavailability of the full text article and 4 others were excluded based on improper format for this review or duplicates discovered at this stage leaving 254 included articles. Thirteen articles were based on the Australian experience. One hundred and eighty of these articles focussed on benzodiazepines as a class without separation. This issue of publication of benzodiazepines as a class poses some challenges with interpretation of the literature for the purpose of this review, as two benzodiazepines, alprazolam and flunitrazepam are currently listed under schedule 8 in Australia and therefore already form part of the proposed RTPM. It is widely known that both alprazolam and flunitrazepam have previously caused harm both in Australia and overseas, which resulted in the listing under schedule 8 and therefore the authors intend to interpret the class-based literature with caution. Following on from this issue, this means that interpretation of the literature via the whole class of benzodiazepines as a whole is not sufficient to comment on the harm from schedule 4 benzodiazepines both here and overseas. However, given the extensive publication of literature about benzodiazepines as a class it would also be imprudent to ignore this subsection of the cohort simply because it is possibly contaminated with the inclusion of two schedule 8 benzodiazepines. Therefore these articles about benzodiazepines as a class are discussed in the first section of this chapter of the report, followed by more specific literature on the various other benzodiazepines under schedule 4 in Australia.

Benzodiazepine class

Australian publication

Within the general class of benzodiazepine literature there were eight articles returned.

Two studies focussed on presentation to emergency departments. The first article is set in New South Wales, and describes the increasing ED presentations between the years 2007-2011 due to benzodiazepines, albeit alprazolam was detected as the benzodiazepine showing the steepest incline in numbers.(2) The second study was based in Victoria which included comment on the high frequency of benzodiazepines implicated in overdose presentations to one ED and showed that 68% of overdoses involved were acquired via

medical practitioner prescription, which is a promising statistic for the implementation of a RTPM system program.(3)

Further information on the sources of misused benzodiazepines in Australia is included in two articles. Best et al describes the patient source of benzodiazepines to be 79.5% prescribed for real symptoms, 50% for fake symptoms and other sources identified to be trade for other drugs (61%), street purchase (74.7%), purchase from friend or partner (69%) or free from friend or partner (83%).(4) Percentages do not add to 100% as participants often reported multiple sources of benzodiazepines.(4) Another study across four states (Victoria, Tasmania, Western Australia and Queensland) reports 78% of benzodiazepines are acquired via prescription from a medical practitioner in patients who are admitted to a drug treatment service, and frequency of prescription forgery is reported as extremely low.(5) These higher numbers of prescription as the source of benzodiazepines are promising when reflecting on the theoretical usefulness of an RTPM.

One study was found in the Victorian setting which reported roadside testing of drivers suspected of drug impaired driving, which showed benzodiazepines were present in 8% of those tested within 853 specimens.(6) One of the more common benzodiazepines present was alprazolam and therefore the applicability of this study to the research question is limited.(6)

The use of benzodiazepines alongside heroin, within New South Wales, has been associated with increased criminal behaviour (OR=2.77) or poor health (OR=2.04).(7) Deaths involving alprazolam were also studied by the same author in the setting of New South Wales, and it was found that co-ingestion of other benzodiazepines occurred in 44.4% of fatalities.(8)

Other harm described in the Australian setting from benzodiazepines included one study which correlated the use of benzodiazepines to violent behaviour, however this study implicated alprazolam as the main perpetrator.(9)

Abuse

Potential for abuse was described in more than 35 articles within this cohort. The knowledge of benzodiazepines as a drug of abuse has been around since 1966 when the Rolling Stones released their hit “Mother’s Little Helper” which allegedly gives reference to the use of benzodiazepines in middle-class housewives of the United States.(1, 10) The abuse potential appears to be a challenge when prescribing this class of effective anxiolytics in a population of patients with mental health issues.(11) Benzodiazepine abuse appears to be worldwide with literature in the form of review, case reports and epidemiological studies on general abuse ranging from the United Kingdom, France, Finland, Ireland, Canada, U.S.A, Japan, Korea, Australia and Norway . (12-25) One study from Scotland found relatively low rates of benzodiazepine abuse compared to other regions of the world, at 0.8% of the population between the ages of 15-54 years.(26) One French study looked at the frequency of forged prescription for benzodiazepines, which was reported as high.(27)

Subpopulations of abuse are noted within the cohort, however applicability to this research question is limited, as an RTPM will include all Australian regardless of their risk factors for abuse. Some exploration of the risk factors for benzodiazepine abuse has been conducted in three studies which showed that people are at higher risk if they display characteristics of neuroticism, introversion, ineffective coping mechanisms, previous trauma, lower persistence, high levels of harm avoidance and lower self directedness.(28-30) Abuse has been described in groups of students and adolescents within the U.S., Ecuador, Nepal, and Ireland in seven studies.(31-37) Two articles describe the issue of abuse in pregnant women and mothers with established substance abuse issues.(38, 39) Description of abuse in older persons is also worth noting as this is mentioned in 3 articles including a systematic review which shows that this phenomenon requires further investigation to quantify harm.(40-42)

Dependence

Dependence on benzodiazepines is well known. 41 articles were included which related to dependence syndromes. The majority of these articles were studies of the prevalence of dependence syndromes and described symptoms of withdrawal such as increased mechanical pain sensitivity, anxiety, muscle spasms, tension and insomnia.(24, 43-62) Risk factors for dependence syndrome are available in some studies which include some mixed evidence for older persons, middle aged persons, persons with pre-existing mental health issues, disability pensioners, coexisting with alcohol dependence and anxiety or post-traumatic-stress- disorder or panic disorder as a co-morbidity.(63-80) One study addressed the relatively low stigma of benzodiazepine dependence in mothers from families with existing opioid dependence, compared to male family members.(81)

Emergency department presentations and poisoning exposures

Two articles describing emergency department presentations in Australia have been previously mentioned. Four other articles on this topic have been included. One study found benzodiazepines to be contributing to 29% of all non-medically prescribed drug presentations in the U.S.(1) In Santiago, Chile, the class of benzodiazepines were involved in 22.2% of overdose presentations.(82) In Brazil, the prevalence of benzodiazepine use in trauma presentations was 4.2%.(83) According to two studies, presentations to EDs for benzodiazepine related exposure appear to be higher in patients who have had benzodiazepines prescribed for them in an outpatient setting and patients who are also on buprenorphine opioid replacement therapy.(84, 85) Two studies found a non statistically significant difference in workplace accidents in those who use benzodiazepines during the work day.(86, 87) Poisoning exposures to benzodiazepines in Hong Kong between the years 2009 to 2015 saw an increased exposure rate with benzodiazepines rising from 4th most frequent exposure to 2nd most frequent after paracetamol.(88, 89)

Traffic accident control

Benzodiazepines are known to be sedating and to slow reflexes, which is part of the reason why this class is topical in studies which look at motor vehicle accidents and suspected driving under the influence of drugs (DUID).(90) Some studies have implicated

benzodiazepines in motor vehicle accidents and injuries.(91-94) A few studies from U.S.A, Switzerland, Sweden and Finland report a range of 2.8% to 33.3% of those suspected for DUID tested positive for benzodiazepines. (95-98) Three studies report on the common combination of benzodiazepines in drivers with alcohol and opioids, and one concluded that benzodiazepines as a sole agent did not increase the risk of arrest for DUID in Finland.(97, 99, 100)

Combination with other drugs

One of the areas of interest when examining the harm from benzodiazepines as a class is their common combination with many other drugs for various purposes, which can increase the risk of fatality.

Benzodiazepines can be used in combination with opioids to “boost” the opioid high, for anxiety, to induce sleep and to reduce symptoms of opioid withdrawal and the two classes are often used long term in combination.(1, 12, 101-107) The misuse and dependence on both opioids and benzodiazepines can go hand in hand with benzodiazepine use associated with early refills of opioid prescriptions.(108) Overdose deaths due to this drug combination are frequently reported but the exact mechanism behind why this combination can be so lethal is not well described apart from increased risk of respiratory depression.(103, 109-118) One study reported this combination to be present in 20% of patients who were admitted to a trauma centre in the U.S.A.(119) Patients who are on opioid replacement therapy frequently use benzodiazepines, which increase their risk of mortality.(111, 120-127) One report showed a prolonged QTc interval with the combination of methadone and benzodiazepine.(128) It is postulated that increased stress, perceived unmet needs, poor sleep or childhood trauma increase the likelihood that patients who are on opioid replacement therapy use benzodiazepines.(129-132) Benzodiazepine use in those who are on methadone opioid replacement therapy was also demonstrated to be associated with poorer treatment outcomes.(133) Benzodiazepine use alongside heroin is also associated with a higher all cause mortality.(134)

Another common combination is methamphetamine with benzodiazepines. This combination can be found in case reports for death or epidemiological studies in specific patient groups such as adolescents.(135-137) The reason for this common combination of stimulant and sedative is not clear in the literature which was included.

Benzodiazepines are also frequently found in combination with alcohol, with once study stating that this combination was found in 27.2% of benzodiazepine related ED visits and 21.4% of benzodiazepine related deaths in the U.S.A. (138) The reason for this combination to be frequently found together is likely to be due to benzodiazepine prescribing for alcohol withdrawal. Benzodiazepine can also be found in combination with tricyclic antidepressants in two articles. This combination can actually be beneficial for the patient as it is hypothesised that the presence of a benzodiazepine can reduce the risk of seizure and cardiotoxicity due to the tricyclic antidepressant.(139) The misuse of benzodiazepine with amitriptyline is found to be common in one cohort of patients undertaking opioid replacement

therapy.(140) Other combinations mentioned in the literature include novel psychoactive substances and marijuana.(141, 142)

Other related harm

The literature describes a range of different forms of harm related to benzodiazepine use.

Impulsivity due to benzodiazepine use amongst prison inmates has been explored with an OR 1.87 [95% confidence interval 1.03-3.38].(143) The risk of violent behaviour in benzodiazepine users is also characterised in two studies which show a possible increase in partner violence.(144, 145)

Injection of benzodiazepines has been associated with risky behaviours such as needle sharing, which can lead to increased risk of contracting HIV, limb ischaemia, infection and amputations.(146-148)

Other miscellaneous harm described in the includes fetal malformations in pregnant women, cognitive dysfunction, changes to sleep architecture and decreased quality of life.(149-153)

Overdose and toxicity

Examination of the peer-reviewed literature for harm from overdose is not the most accurate way to quantify harm as the risk of overdose is well known and therefore the publication of death from overdose is less likely in recent years. Nineteen articles were included which describe overdose from benzodiazepines in the form of case reports, review articles and epidemiological studies. Epidemiological studies show the frequency of benzodiazepines overdose is high relative to other prescription medications and some studies show it to be on the increase.(154-162) One study showed a decrease in the frequency of benzodiazepine related deaths in Florida, U.S.A. between 2011-2012.(163) This may have been attributed to the implementation of a prescription-drug-monitoring-program.(163)

Some articles describe those who are at a higher risk of overdose such as older patients, younger patients who inject drugs and those who are also on opioids. (115, 116, 164-166)

Harms in overdose are reported to include death, anterograde amnesia, QTc prolongation, need for intensive care admission.(167-169)

<u>Diazepam</u>

When looking at the cohort of articles which specify individual benzodiazepines in misuse, diazepam was the most frequently published. Of 253 articles about benzodiazepines, 49 articles were about diazepam.

Abuse and dependence

Diazepam is known to have high abuse potential and toxicity in overdose.(170) Illegal activity surrounding diazepam has been examined with diazepam's doctor shopping index shown to be high, with around 4.4% of diazepam illegally obtained in France and street prices in Nevada, U.S. for diazepam are the second highest of all the drugs sold.(171-173) Four articles show diazepam to be a frequently misused prescription medication in the U.K., France and also Iran. (174-177) When specifically examined due to suspicion, high rates of abuse have been not been shown in Rwandan youths and truck drivers in France.(178, 179) The intravenous route of administration was described in one case to produce withdrawal effects of palpitations and insomnia and intravenous administration is often used in conjunction with promethazine and buprenorphine and referred to as a "South Asian Cocktail."(180, 181)

Combination with other drugs

Six studies described the combination of benzodiazepines with opioids such as heroin and buprenorphine, and showed increased death rates in co-ingestion which is previously demonstrated in combination with benzodiazepines as a class.(103, 126, 181-184)

Diazepam has also been reported to be used with ecstasy. One study in the U.S.A showed that 9.6% of people testing positive for ecstasy over a range of settings, also tested positive for benzodiazepines, however it is unknown if this is partly due to contaminants in the ecstasy pill.(185) One other study in Florida, U.S.A. showed that 30% of ecstasy users also intentionally use diazepam.(186)

Traffic accident control

Diazepam has been found to be a common drug present in those who are suspected of DUID in Finland, Switzerland, England, Wales, Korea, Sweden, Norway and Australia (Victoria).(6, 187-194) In those who are involved in an accident, diazepam is also commonly found to be present in up to 7.4% of those tested.(137, 195-198)

Poisoning

Seven articles about overdose were included. Diazepam was found to be amongst the top ten drugs involved in prescription overdose deaths.(199-201) Some case reports with overdose combinations were represented in the literature specifically for diazepam, with 172 cases of oxycodone poisoning, one poisoning in combination of paraquat and one poisoning with valproate.(115, 202, 203) One study showed a decreasing trend in deaths from diazepam in Scotland, however the authors note that this may be due to changes in pathological reporting and better titration of methadone doses.(204)

Other related harm

Diazepam may increase aggression and violence with or without alcohol presence based on three articles, one of which was published in Australia. (205-207) Diazepam implication in

sexual assault cases has also been explored in two studies, which were based in Norway and the U.K.(208, 209)

Midazolam

There were 17 articles specifically about midazolam misuse. Eight articles described high rates of intravenous midazolam abuse in Bangkok, Thailand.(210-217) Midazolam has also been found in used syringes at an injecting centre in Switzerland.(218) The intranasal route has also been implicated in misuse of midazolam in those who have a history of substance abuse.(219)

One case report of fatal overdose was found with a combination of zolpidem and propofol in an anaesthetist.(220) Combination with buprenorphine was found to be common in Singapore and Malaysia with risk of fatality.(183, 221, 222)

Other miscellaneous harm included driving under the influence of midazolam in 5% of cases in one Swiss study, increased risk of HIV infection from injecting behaviour and syringe lending behaviours.(188, 223, 224)

Clonazepam

27 articles were included on clonazepam misuse.

Abuse

Clonazepam has been flagged as an “emerging drug” of abuse based on results of the OPPIDUM (Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse) survey in France.(225) In Norway, clonazepam has overtaken flunitrazepam as the most common illegal benzodiazepine abused.(226) Some other settings for abuse of clonazepam include prisoners on Reunion Island, France, Iran and the U.K.(176, 177, 227-230)

Studies of illegal behaviour surrounding clonazepam showed mixed results with only intermediate abuse potential based on a doctor shopping index of 1.8-1.9%, but a more recent study revealed that it is the second most frequent benzodiazepine implicated in doctor shopping in France.(172, 173, 231) Clonazepam also had the highest street price of benzodiazepines in Nevada, U.S.A.(171) Clonazepam was shown to have the second highest benzodiazepine risk of diversion next to flunitrazepam.(232)

Dependence

Only two articles addressed dependence in the context of bipolar depression alongside other medicines and megadose dependence.(233, 234)

Poisoning

Four articles were included on overdose which involved one paediatric patient with atrioventricular block and three cases of polydrug overdoses.(235-238)

Combination with other drugs

Two articles were found which included combination with opioids and clonidine.(239, 240)

Other harm

Three articles outlined the use of clonazepam in DUID in Norway and Denmark.(192, 198, 241) One case report showed possible involvement of clonazepam in a sexual assault case.(209)

Oxazepam

There were 11 articles included on the topic of oxazepam misuse.

Abuse

There is some evidence for abuse occurring in French, Iranian and Norwegian studies.(176, 177, 242) However, two studies postulate that oxazepam has a lower abuse potential than other benzodiazepines due to slow absorption rates, no active metabolites, no accumulation in chronic dosing, lower risk of drug interactions and the metabolism of the drug not being affected by age.(170, 243)

One French study showed oxazepam to be illegally obtained 5.7% of the time based on survey.(173)

ED presentations and poisoning exposures

One study from Victoria showed that between 2003-2004 in one hospital emergency department, 6% of benzodiazepine overdoses included oxazepam.(3)

Other related harm

Three articles describe oxazepam present in those who are found to be DUID in Norway and Switzerland.(188, 192, 241) One case of reinforced irritability in high dose oxazepam dependence was reported.(244)

Lorazepam

There were five articles included on the topic of lorazepam misuse. Two articles regarded lorazepam to have high abuse potential and toxicity in overdose.(170, 176) One article showed rare misuse in the population of the U.K. via survey.(174) The OPPIDUM French survey also found that low levels of the drug were obtained illegally.(173) One overdose

case report listed lorazepam in combination with a selective serotonin reuptake inhibitor and codeine.(245) One article implicated lorazepam in a small number of cases of motor vehicle accidents in Ontario, Canada.(246)

Nitrazepam

There were four articles included on the topic of nitrazepam misuse. One study found that the risk of abuse after initial prescription was higher for nitrazepam than for diazepam.(242) In combination with other drugs, nitrazepam was the second most common benzodiazepine implicated with buprenorphine in overdose deaths in Singapore.(183) In the Australian setting, it was found that 10% of the patients who presented with overdose on benzodiazepines to a Melbourne hospital had taken nitrazepam.(3) Nitrazepam was also found amongst other substances in people who were DUID in Norway.(192)

Temazepam

There were four articles included on the topic of temazepam misuse. One study found that temazepam has a high abuse potential and toxicity in overdose.(170) In the Australian setting, it was found that 20% of the patients who had presented with overdose on benzodiazepines to a Melbourne based hospital had taken temazepam.(3) In combination with other drugs, previous availability of gel-caps in Australia resulted in injection with heroin to increase pleasure and intoxication.(247) Temazepam gel-caps have since been taken off the Australian market. Temazepam has also been implicated in a small number of sexual assault cases in the U.K.(208)

Clobazam

There were two articles included on the topic of clobazam misuse. One article showed that physiological dependence is possible in use for epilepsy but not psychological dependence.(248) Only one case report of overdose was found and this was a polydrug overdose.(249)

Bromazepam

Nine articles were included on the topic of bromazepam misuse. Two French studies described potential abuse of bromazepam.(177, 250) In the same setting, doctor shopping behaviour was classed as intermediate although one European study listed bromazepam as one of the most frequently forged prescriptions. (172, 173, 251)

Two case reports of megadose dependence were included.(252, 253) There were two articles about overdose, with descriptions of usage in the elderly and one case report of deep coma.(201, 254)

5.2. Antipsychotics

Quetiapine

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, 63 articles related to quetiapine. Twenty-eight articles related to the misuse of quetiapine in various formats including case series and epidemiological studies through survey and poison information systems. Two Australian studies were identified within the cohort. (255, 256)

Abuse

Abuse of quetiapine is relatively well characterised in the literature compared to other antipsychotics. The route of administration of quetiapine during abuse can be oral, intravenous, smoked or intranasal.(257-265) A case report of adverse effects of “snorting “quetiapine indicate that this behaviour can lead to dyskinesia, myoclonus, and akathisia as is often seen in toxic overdose.(259) There has been one report on the lower risk of abuse via the intranasal route in the extended release formulation due to the crushed tablets causing an unpleasant sensation when snorting because the powder can congeal in the nasal passages.(264) There is evidence of frequent abuse in the literature and case reports of recreational use describe the main reasons for using quetiapine in detail, including mood elevation, anxiolytic effects and sedation.(257, 258, 266-272) The reason for the preference for quetiapine over other atypical antipsychotic agents has been postulated to be related to the antihistaminergic effects and related rewards pathways. (258)
There is some literature available on the increased abuse of quetiapine in the prison population of the U.S. Some incarcerated patients are reported to give “vague symptoms” such as “hearing voices” in order to receive prescribed quetiapine for misuse.(273) There is some suggestion that quetiapine is more prone to misuse in the prison population due to lack of availability of other drugs to use as anxiolytics.(274) The knowledge of quetiapine as a drug of misuse in prison is well spread, with one published impact study on the successful removal of the drug from a prison formulary in New Jersey without psychiatric or disciplinary adverse effects.(275)

Dependence

Dependence syndromes are commonly reported with withdrawal symptoms of palpitations, anxiety, irritability, insomnia and dysphoria.(266, 267, 274, 276-279)

In combination with other drugs

In combination with other licit and illicit drugs, quetiapine can be used for various psychoactive effects. The street names for quetiapine include “Susie Q”, “baby heroin” and “Quell”.(258) Quetiapine is often mixed with other illicit substances in order to act as an anxiolytic whilst the person experiences the “come down” effects of the other drug, for example in combination with cocaine, quetiapine may be referred to as a “Q ball” and has the effect of mitigating dysphoria and inducing hallucinations in some people who inject this combination intravenously.(263) One case report also describes a similar combination with

marijuana, as referred to as a “Maq ball” which is smoked.(260) In the Australian setting, the Illicit Drug Reporting System-2013, which surveyed 868 people who inject drugs showed that 31% of respondants misused quetiapine and this was also associated with the use of benzodiazepines OR= 4.26 (95%CI=2.06-8.52) or non prescription opioids OR=2.76 (95%CI=1.47-5.19).(256) Patients enrolled in a methadone program in Halifax, Canada were surveyed on this topic of quetiapine combinations and it was found that 20% of patients reported using quetiapine to “experiment”, 25% to “enhance the effect of other substances” and overall 75% of patients had misused quetiapine for sedative effects.(280) This is also reflected in a study on addiction treatment inpatients in the state of New York, U.S. that reported that 96% of inpatients abuse quetiapine and around 67% of these inpatients used quetiapine to “recover from other substances.”(281) One case showed a patient using buprenorphine/naloxone as opioid replacement therapy who sought out both quetiapine and gabapentin in combination to potentiate buprenorphine and lead to “euphoria”.(282)

Poisoning

One study described misuse of quetiapine as not a current issue using interrogation of the National Coronial Information System (NCIS) to analyse overdose deaths between the years 2001-2009, however this particular study does refer to the fact that quetiapine misuse beyond 2009 is not shown in this report and the authors recommend further monitoring beyond this year.(283) Please refer to the section of NCIS data analysis for quetiapine contribution to death beyond 2009.
Overdose of quetiapine is frequently documented via case reports in the literature and is often associated with polydrug overdose. This search returned 35 articles outlining the toxicity of quetiapine in overdose. Of these 35 articles, 1330 cases of overdose were reported in various degrees of detail. Reported toxicity in overdose of varying degrees of frequency included delirium, central nervous system depression, tachycardia with or without increased QTc interval, coma, rhabdomyolysis, sedation, seizures, hypotension, increased creatine kinase levels, increased C-reactive protein levels, hypothermia, neuroleptic malignant syndrome, hypokalaemia, flexion myelopathy, sudden cardiac death, gastric pharmacobezoar (extended release formulation), diabetes insipidus, myoclonus, respiratory depression and death.(284-317) Quetiapine is one of the least cardiotoxic atypical antipsychotics in overdose. Despite the large cohort of case reports for overdose, this source of peer-reviewed literature is not the optimum source of information when determining harm from this drug to the population with regard to the outcome of death.

<u>Olanzapine</u>

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, 29 articles related to olanzapine. Only 4 articles described misuse of olanzapine. Two case reports describe a dependence syndrome with dose escalation and symptoms of withdrawal upon trial of dose reduction, which included increased anxiety, dysphoria, insomnia and nervousness.(318, 319)
The reasons for misuse were described in two articles which included delivering “a buzz” or euphoria when combined with either alcohol or benzodiazepines.(320) Olanzapine has also been described as an effective “trip terminator” when used with other illicit drugs.(321)

Overdose of Olanzapine with or without other drugs was described in 25 articles which included a total of 107 cases in various levels of detail. Toxic effects described by these case reports included seizures, coma, coagulopathy, abnormal plantar response, choreoathetosis, diabetes insipidus, cardiotoxicity, tachycardia, central nervous system depression, miosis, delirium, neuroleptic malignant syndrome, myoclonus, hyperreflexia, muscle rigidity, leukocytosis, increased creatine kinase, extra pyramidal effects, hyperprolactinaemia, atrial fibrillation and death.(285, 306, 315, 322-342) Olanzapine is known to be non cardiotoxic in overdose.(343)

Risperidone

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 9 articles related to risperidone. There were no articles related to risperidone misuse. There were 8 articles describing overdose with 124 cases. Reported toxicities in overdose include delayed respiratory depression, myoclonus, hypokalaemia, tachycardia, dystonia and death.(237, 285, 305, 315, 344-347) Benign outcomes were noted in some case studies.(237, 347) Risperidone is known to have some cardiotoxic effects in overdose.(343)

Aripiprazole

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 8 articles related to aripiprazole. There were no articles describing aripiprazole misuse. There were 7 articles describing overdose toxicity in 14 cases, which included effects of mild sedation, some facial muscle paralysis, prolonged central nervous system depression and one fatality in a paediatric patient.(285, 315, 352-356) Overall, most aripiprazole overdoses produced a benign clinical picture. Aripirazole is not known to cause cardiotoxicity in overdose.(343)

Chlorpromazine

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 5 articles related to chlorpromazine. It is suspected that adjusting the date range to earlier that 2005 may lead to a much larger cohort, especially in the area of overdose toxicity, however for the purpose of this research question for *current* harms related to misuse and overdose this is unnecessary.

All five articles related to chlorpromazine in overdose, and no articles referred to misuse. Toxicity in the presence of supratherapeutic ingestion of chlorpromazine included cardiac arrest, neuroleptic malignant syndrome and death.(333, 357-360) Chlorpromazine appears to have significant risk of harm in overdose, however the frequency of overdose reported in the literature is relatively low compared to other antipsychotic agents.(360)

Clozapine

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 5 articles related to clozapine. There were no articles which described misuse of clozapine.
There were four articles describing 54 cases of clozapine overdose.(285, 361-363) Six cases were fatal.(285, 361) Clozapine is known to have some cardiotoxic effects in overdose.(343) The likelihood of harm from overdose or misuse in Australia for clozapine is low given that this drug is tightly controlled. Patients visit one prescriber, attend regular pathology tests to measure full blood count in order to obtain further prescriptions and only receive the exact number of tablets per dose until their next scheduled pathology.

Haloperidol

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 1 article related to haloperidol. This article describes one case report of myocarditis after overdose of haloperidol.(364) It is presumed that prior to 2005 there may be more extensive literature on overdose of haloperidol given the drug has been around for a long time. There were no articles found on misuse of haloperidol between the years 2005-2017.

Lurasidone

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 1 article related to lurasidone. This article related to overdose and resulted in no harm to the patient.(365) Lurasidone is considered a new drug and therefore lag time in publication may be evident in the absence of literature.

Paliperidone

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 4 article related to paliperidone. There were no articles which described misuse of paliperidone.
Paliperidone in overdose is described in four articles which describe four case studies. These case studies described acute dystonia, delayed onset tachycardia and acute renal failure as associated toxicities of paliperidone in overdose.(366-368) One study showed no serious harm after an overdose of 756mg.(369)

Ziprasidone

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only 13 articles related to ziprasidone. There were no articles related to misuse.
There were twelve articles describing 99 cases.(237, 285, 315, 370-378) Toxicity in overdose is described as QTc prolongation, torsades de pointes, coma, drowsiness, drooling, poor muscle tone and/or death.(237, 285, 315, 370-378) Ziprasidone is known to cause prolonged QT in overdose.(343)

Trifluoperazine

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis, only one article related to trifluoperazine. This article described one case of dependence syndrome with associated weakness, restlessness and dysphoria upon withdrawal.(379) There were no articles found about trifluoperazine in overdose for the time period 2005-2017.

Asenapine, droperidol, flupenthixol, fluphenzine, pericyazine and zuclopenthixol

Of the 131 articles about antipsychotics included in the peer-reviewed literature analysis none were included about misuse or overdose for the schedule 4 medications asenapine, droperidol, flupenthixol, fluphenazine, pericyazine or zuclopenthixol.

5.3. Z-drugs

Ninety nine articles were included about Z-drug (zolpidem and zopiclone) misuse and overdose after excluding 23 articles which were found to be irrelevant to the research question, 18 which were in a language other than English, six which were in an inappropriate format, two duplicates and nine where the full text was not available. Some of the literature about worldwide overdose included Z-drugs as a class rather than the individual drugs of interest, zolpidem or zopiclone. The literature about class effect is briefly summarised first in this section, then the literature on the individual drugs follow.

Z-drug class

Z-drugs are known to decrease sleep latency, improve sleep quality and work by increasing GABA transmission at GABA A receptors.(380) These drugs are known as sedative hypnotics, which is a popular class for misuse.

Abuse

Two articles were included on the potential for abuse of Z-drugs as a class, which both demonstrate known abuse of Z-drugs in the setting of the European Union and one more specifically in South London nightclubs.(175, 381)

Dependence

Three articles were found on the topic of dependence to Z-drugs. One article argues for the possibility of dependence.(63) Conversely, one other article argues that dependence syndrome is mild and withdrawal reactions can include craving, insomnia, anxiety, tremor, palpitations, delirium, seizures (rare) or psychosis.(15)

Poisoning

One article is included on overdose of Z-drugs as a class which reports some symptoms of overdose to include sedation or coma, but rarely deaths unless in polydrug overdose.(380)

Other related harm

Four articles were included on the topic of contribution to road related harm with the use of Z-drugs in Norway, Sweden, Belgium and Denmark.(198, 382-385) One article categorises Z-drugs as one of the least likely to contribute to road related harm in a study from six European countries.(386)

Zolpidem

Abuse

Twenty articles outline the potential for abuse of Zolpidem.(15, 170, 387-405) The coveted effects of Zolpidem were explained in the literature to include euphoria/feeling “high”, visual hallucinations and pleasant delirium.(397, 399) One systematic review concluded that the potential of abuse was low in short-term use.(406)

Dependence

Twenty eight articles outline the potential for dependence to Zolpidem. (233, 392, 400, 403, 405, 407-430) Three articles contest this theory of potential for dependence in short-term use of Zolpidem and deem it unlikely to cause dependence syndrome.(406, 431, 432)

Source of acquisition

Frequent prescription fraud in France is reported for zolpidem.(27, 433, 434) In Taiwan, one study showed high levels of doctor shopping behaviour associated with zolpidem.(433)

Other harm

One study implicated zolpidem in a single sexual assault case.(435) Digit ischaemia was also reported in one case study after crushing and injecting the tablets.(436) In pregnancy, fetal neural tube defects have been found in those taking high doses of zolpidem.(437) In addition, five articles explored the harm related to driving under the influence of zolpidem in Finland, Switzerland and Sweden.(97, 188, 193, 438, 439)

Combinations with other drugs

Zolpidem misuse in combination with alcohol has been associated with an increased risk of an admission to an intensive care unit.(440)

Poisonings

Ten articles were included on the topic of overdose with zolpidem.(154, 199, 220, 254, 441-446) Published harms in these cases included coma, self-stabbing or myocardial injury.(442-444)

<u>Zopiclone</u>

Abuse

Five articles highlighted the potential for abuse of zopiclone, all of which demonstrated only moderate risk overall and lower relative risk than benzodiazepines.(170, 387, 447, 448) Two articles listed zopiclone to have a relatively low risk of abuse.(397, 449)

Dependence

Three articles showed risk of dependence to zopiclone with associated withdrawal effects.(409, 450, 451) One article comments on the lower risk of dependence to zopiclone over zolpidem.(409)

Other related harm

Four articles explored the harm related to driving under the influence of zopiclone in Sweden and Norway.(97, 439, 452, 453) Zopiclone was found to be involved in sexual assault cases infrequently in one study from the U.K.(454)

Poisoning

Ten articles were included on the topic of overdose with zopiclone.(88, 89, 168, 200, 455-460) Reported harms in these cases included QTc prolongation (in polydrug overdose with an SSRI) and haemolytic anaemia.(168, 456, 459, 460)

5.4. Anticonvulsants

One hundred and fifty seven articles were included in the final review on anticonvulsant schedule 4 medications with 8 excluded for formatting, 27 for language other than English, 15 for relevance to the research question, one animal study and 7 for full text not available.

The majority of the literature gave detail on specific anticonvulsants and only one relevant article was found which did not separate the anticonvulsants drugs in question. This article was based in Melbourne and showed trends in ambulance call-outs for specific drugs including the anticonvulsants between the years 2000-2009, during which no upward trends in anticonvulsants was found.(461)

Pregabalin

Abuse

Abuse of pregabalin has been found in several settings around the world including in the United Arab Emirates, India, U.K., Europe, U.S., Turkey and Jordan. (462-489) Reasons for abuse have been described as inducing euphoria, increasing energy levels and dissociative effects.(463, 480, 490) One case found increased sexual desire and excitement with pregabalin abuse.(491) The reinforcing effects of pregabalin are thought to be mediated through GABAergic pathways.(463, 490) Compared to gabapentin, pregabalin is known to be more potent, more quickly absorbed, and have a higher bioavailability, which makes it more prone to abuse.(490) Methods of delivery for abuse may include oral, rectal plugging and parachuting (emptying the contents of the capsule into a pouch for administration.)(478) Tolerance can develop quickly.(478) One cross-sectional study, which was based on a French pharmacovigiliance database showed pregabalin to have a low level of abuse, however a limitation to this investigation was that the data was based on spontaneous reporting.(492)

Dependence

Dependence has been described in seven articles in the setting of India, U.S., Germany and Lebanon.(463, 470-473, 493, 494) Some withdrawal effects noted were palpitations, restlessness and dysphoria.(463)

Combination with other drugs

Pregabalin abuse has been found in a high proportion of patients who use opioids or opioid replacement therapy, with reported rates of co-ingestion to be between 7-22%.(472, 495-501) A reported reason for use with opioids is to “potentiate the high” that the person gets from opioids or opioid replacement therapy.(495) In one study of post-mortem medico-legal cases from Finland, it was found that in 91.4% of cases where pregabalin was involved, there was also an opioid present.(498)

Other combinations found with pregabalin include alcohol, cannabis and benzodiazepines.(472)

Poisoning

There was limited literature available on the effects of pregabalin in overdose. Six articles were included that focussed on overdose or poisoning from pregabalin.(502-507) In overdose, pregabalin has been reported in these articles to cause neurological depression, coma or atrioventricular block.(502, 507)

Other related harm

One article showed 206 pregabalin positive samples across a 1 year period in people suspected to be driving under the influence of drugs in Finland.(508) Most of these cases had taken pregabalin alongside other drugs.(508) This is of concern due to pregabalin's sedating properties which are likely to impair driving.

Gabapentin

Abuse

Sixteen articles were included which focussed on the abuse of gabapentin including one systematic review, case reports and some epidemiological studies, which interrogated pharmacovigilance databases.(466-468, 470, 474, 478, 485, 488, 490, 509-515) Reasons for abuse include sedative and dissociative properties with reinforcing effects and reported withdrawal syndrome including one case of known delirium.(478, 490, 510, 514) One article argued that gabapentin had a low risk of abuse compared to other drugs such as alcohol, benzodiazepines or opioids.(516)

Dependence

Two articles describe a dependence syndrome to gabapentin, which included cravings and toxic delirium or confusion in withdrawal.(513, 517)

Combination with other drugs

Like pregabalin, gabapentin use with opioids and opioid replacement therapy appears to be commonplace with reported rates between 15-26% of users.(282, 495, 498, 499, 501, 518-521) The co-ingestion of gabapentin with opioids is apparently to "potentiate the high" that the user seeks from the opioid component.(282, 495) One study reports that the use of opioids alongside gabapentin is relatively safe.(522)

Other combinations found were with quetiapine for sedation and euphoria, and with alcohol or benzodiazepines.(520, 523)

Poisoning

Six articles were included which focussed on gabapentin in overdose or poisoning.(506, 524-528) Reported harms in these cases were mild central nervous system depression, cardiac conduction abnormalities (in combination with nefazodone) and death from gabapentin as a sole agent.(524-526)

Levetiracetam

Abuse

One article was included which described the relatively low potential for abuse of levetiracetam.(511)

Poisoning

Eight articles focussed on levetiracetam in overdose.(506, 524, 528-533) Levetiracetam appears to be one of the least toxic anticonvulsants in overdose.(506, 529, 531)

Lamotrigine

Abuse

One article was included which described the relatively low potential for abuse of lamotrigine.(511)

Poisoning

Fourteen articles focussed on lamotrigine in overdose.(503, 506, 524, 528, 534-543) Lamotrigine appears to be one of the most toxic anticonvulsants in overdose with reported reactions of myoclonus and spasticity, heart block, central nervous system depression, dyskinesia, seizures, oculogyric crisis or death.(506, 524, 534, 537, 538, 540, 542)

Topiramate

Abuse

There were no articles found about topiramate abuse.

Poisoning

Ten articles focussed on topiramate in overdose.(506, 524, 528, 544-550) The main toxic effects included seizures, metabolic acidosis, visual hallucinations, slurred speech, ataxia, drowsiness, dizziness, agitation, confusion or nausea and vomiting.(544-547)

Sodium Valproate

Abuse

There were no articles found about abuse of sodium valproate.

Poisoning

Thirty-two articles were included which focussed on sodium valproate in overdose.(202, 237, 334, 539, 551-577) Main toxic effects include central nervous system depression, loss of protective airway reflexes, loss of thermoregulation leading to hypothermia, coma, cerebral oedema or hyperammonemia.(202, 552, 559)

Carbamazepine

Abuse

One article was included which describes abuse of carbamazepine for euphoric effects.(578)

Poisoning

Twenty-five articles were included which focussed on carbamazepine in overdose.(441, 539, 558, 559, 569, 579-598) Some toxic effects of note were cardiotoxicity, anticholinergic effects and neurological complications.(559, 590)

Zonisamide

Three articles were included which focussed on overdose only, which showed toxic effects such as hypotension, respiratory depression, seizures, coma, bradycardia or vomiting.(524, 599, 600) There were no articles found which demonstrated zonisamide abuse.

Vigabatrin

No articles were found which highlighted abuse of vigabatrin. One article was included on vigabatrin in overdose which was a case series of 21 cases from 1996-2000 with no reported fatalities.(528)

Tiagabine

No articles were found which highlighted abuse of tiagabine. Seven articles were included on tiagabine in overdose with the main toxic effects listed as seizures, central nervous system depression, coma, agitation, drowsiness, confusion or tachycardia.(506, 524, 528, 601-604)

Oxcarbazepine

No articles were found which highlighted abuse of oxcarbazepine. Four articles were included that focussed on oxcarbazepine in overdose, and seizures were the more commonly reported toxicity.(506, 524, 605, 606)

Lacosamide

No articles were found which highlighted abuse of lacosamide. Two articles were included that focussed on lacosamide in overdose, and cardiac conduction abnormalities were the more commonly reported toxicity.(532, 607)

Phenytoin

One article highlighted the low risk of abuse relative to other anticonvulsant medications.(511) One case study was found on a patient who had become dependent on phenytoin, with dose escalation, cravings and withdrawal effects such as restlessness, jitters and irritable mood.(608)

Seven articles were included which focussed on phenytoin in overdose.(539, 557, 582, 609-612)

Perampanel

There were no articles included about perampanel, a relatively new drug on the Australian market.

5.5. Barbiturates

Two barbiturates are currently under schedule 4 in Australia, which include phenobarbital and primidone. Of the 36 articles included after the initial screen of title and abstract, 16 articles were included after removal of five articles with little relevance to the research question, eight articles in a language other than English, two duplicates and five articles when the full text article was not available. These low numbers are to be expected due to the date range 2005-current which was used in the search. Publication for barbiturates peaked in the 1970s and has declined every year since then.(613)
Most of the literature was available only by class not by individual drug. There were no articles which addressed primidone misuse specifically. There were no articles about phenobarbital misuse.

Barbiturate class misuse

Misuse was shown in some patient populations which included patients with other known substance abuse, adolescents to get “high” and to use in suicide, those residing in urban Afghanistan, HIV positive gay and bisexual men in the U.S.A and older adults attending emergency psychiatric services.(40, 614-618) One article showed low risk of abuse in patients with epilepsy when used for seizure control.(248) In coal miners it was found that there was no increased risk of workplace accident with barbiturate use.(87)

Barbiturate class overdose

One article showed an increased risk of overdose in barbiturate users compared to benzodiazepine or Z-drug users and one other article confirmed the use of barbiturates could predict drug related premature death in a Swedish study.(155, 619) Symptoms of overdose are described in one study as central-nervous-system, cardiovascular and respiratory depression with hypothermia and possible miosis/nystagmus.(615) Two epidemiological studies in Egypt and Iran describe 199 barbiturate overdoses.(558, 620)

Phenobarbital poisoning

There were three articles outlining two fatal cases of Phenobarbital poisoning.(359, 621) Phenobarbital was reported to be the sixth most common poison after autopsy in Japan between the years of 2003-2006.(622)

5.6. Codeine

The potential for misuse of codeine containing compounds both in Australia and overseas is well known. The difficulty in capturing misuse in the literature lies in the multiple different codeine combinations available both here and overseas, which do not necessarily match with Australian schedule 4 codeine containing products. The other issue for consideration is the impending up-scheduling of all codeine containing schedule 3 products in Australia during 2018, however this issue is considered out of scope for this review which focuses on current schedule 4 medications in Australia.(623) Due to these difficulties, codeine containing combinations were considered for this section on trends and all attempts were made to decontaminate the included literature of all schedule 8 pure codeine products or schedule 3 combination products where possible.

Twenty-five articles were included in the final review of codeine for this section from 92 screened for full text. Eight were excluded for inappropriate formatting, three for language other than English, 19 for relevance to the research question, one duplicate and seven full text not available and 29 articles were considered to be out of scope due to focus on over-the-counter schedule 3 codeine containing products.

Abuse

Some studies refer to codeine alone when discussing misuse and therefore it is not possible to determine whether this codeine is on prescription or purchased over the counter. This section will discuss relevant findings from these articles.

Case studies for abuse of codeine are commonly published. One case series described the reason for abuse in some cases was to obtain a “hazy feel good high.”(624) Internet forums often show misuse for dulling of physical or emotional pain.(625) Routes of administration may include snorting, oral or rectal use.(624, 625) Three particular cases made note of the fact that most users began with a legitimate therapeutic need for codeine, which then evolved into misuse.(624, 626) In Norway, it appears that 0.5% of the population engage in problematic use of codeine based on findings from their prescription database.(627) In the U.S. and Canada, codeine is reported to be commonly used recreationally in opioid addicted patients, rural residents and street drug users.(628-630) In France, there were significant levels of doctor shopping behaviour for codeine on prescription and it was found to be abused commonly in combination with benzodiazepines.(631) One study argued for low risk of abuse in weak opioids for those initiating treatment.(632)

Combinations with other drugs

Pleasurable effects from taking codeine combinations may include feeling a “buzz” and in those who are dependent, avoiding symptoms of withdrawal.(633)

In combination with paracetamol specifically, there appears to be high levels of abuse in the U.S., particularly in College students and middle aged and elderly populations.(634-636) One study reported people who abuse this combination commonly take prescriptions from

family members who legitimately use this product for pain.(637) This particular combination is concerning, given the risk of liver toxicity from chronic paracetamol ingestion over time.(637) Intravenous abuse of combination paracetamol and codeine in combination with diphenhydramine is known to be a new problem in Uzbekistan.(638)

In combination with alcohol, codeine containing products have been used to “get drunk faster” and save money.(624) In combination with marijuana, codeine is taken to “feel good”.(624) One Irish study found high levels of misuse of codeine in patient who were being treated on a methadone program.(639) In France, codeine is commonly abused alongside benzodiazepines HR=3.12 [95% CI 1.55-6.26].(631)

Other Harms

Some case reports of deafness, occupational violence and risky sexual behaviours associated with codeine use were found.(640-642)

Poisoning

The liver toxicity from chronic overdose in combination with paracetamol are well known. Acute overdose was only the focus for five articles found, however it is likely that this phenomenon is relatively common.(245, 643-646) What is unknown, is the extent of harm from schedule 4 codeine products without contamination of data from schedule 3 or 8.

5.7. Tramadol

Abuse

Given that opioids have known abuse potential, there has been investigation into the abuse liability of tramadol as a member of this class and concern by medical experts that it may be misused.(647) There have been some studies which show potential for addiction and abuse of tramadol, including case reports, epidemiological studies in patients who attend rehabilitation programs in Europe, and surveillance programs.(381, 648-655) Tramadol does appear to have some reinforcing potential in higher doses.(656) The reasons for abuse have been explored in one study with rather vague descriptions such as “feel drug effect” and interest in taking the drug again after the first dose.(657) Another survey in the U.K. found 75% of tramadol users required the drug for pain, 31% used it to relax, 26% used it to aid sleep and 25% used it to get high, with multiple uses in participants leading to a more than 100% total.(658) The use of tramadol to prevent premature ejaculation further increases the likelihood of non-medical usage.(659) Reported risk factors for abuse of tramadol are comorbid mental health issues.(660) Abuse of immediate release formulations appears to be preferred to extended release, which is likely to be due to the delayed absorption and less profound effects of the extended release tablets.(661) Abuse of tramadol appears to be common in literature from Middle Eastern countries such as Egypt, Yemen and Iran.(462, 662-669) There were studies which included reports of seizure activity and serotonin syndrome in people who abuse tramadol.(670-672)

On the other hand, some studies reported low levels of abuse risk, with one study even demonstrating the abuse potential to be comparable to Non-steroidal Anti-inflammatory Drugs.(655, 673-677) Low risk of abuse could be attributable to tramadol falling under the category of being a weak opioid.(632) Minimal rates of abuse were reported in one study which investigated the effect of release of a cheaper generic, with no change to abuse risk.(661) However, there was a reported 10% reduction in tramadol use after changes to scheduling in Scotland during 2014.(678) In developed countries such as the U.S. and New Zealand, the levels of tramadol abuse were found to be low in those on combination tramadol-paracetamol and attending rehabilitation centres.(679, 680) In France, there were low numbers of tramadol users in self reports to a drug rehabilitation program.(681) Chinese men who have sex with men (a patient group which is known to have higher levels of substance misuse) were also found to have low levels of tramadol abuse.(682) There have been some case reports of tics and seizures in those who abuse tramadol.(683) The probability of abuse in one U.S. pre and post study remained the same regardless of the level of restriction via rescheduling.(684)

Dependence

Dependence to tramadol is evident in some studies, including one which highlights high numbers of dependent patients in drug rehabilitation in Colombia and 104 reports from a systematic review of articles from the European Union.(381, 685-695) The mechanism of dependence has been postulated to be due to poor efficacy of tramadol as an analgesic, leading to dose escalation which then results in dependence.(381) Tolerance is also

demonstrated in repeated doses.(696) Withdrawal symptoms after cessation of tramadol were described in some of the literature, and in up to 10% of users in the U.K.(655, 658) Symptoms of withdrawal may include feeling emotionally unwell.(658)

Despite this evidence for dependence, the risk of physical dependence to tramadol was found to be low in one study.(673)

Sources of acquisition

Diversion rates of tramadol appeared to be low during 2002 in the U.S.A, according to one study.(697) Drug trafficking is a problem, however, in Gaza where the drug is known to have higher levels of abuse.(698)

Doctor shopping index for tramadol was reported as low in France and the U.S.A.(13, 699, 700) However, one study showed that prescription fraud for tramadol is relatively common in Europe and drug sharing practices are common in the U.K.(173, 251, 701) One survey from the U.K. showed that 64% of tramadol was prescribed by a medical practitioner, 34% was from a friend, 3% was from a dealer and 3% came from the internet.(658) The availability of tramadol for internet purchase also appears to be high due to low restrictions on supply in some parts of the world.(702)

Combinations with other drugs

Tramadol combinations appeared infrequently in the articles included in this review. Tramadol has been found in combination with cannabis or opium in adolescents in Iran.(703) The combination of tramadol with cannabinoids has been associated with reduced renal function.(704) In combination with alcohol, some people who abuse tramadol experience enhanced pleasurable effects.(658) One Australian study which reported on deaths from serotonergic drugs commented on the dangerous combination of tramadol alongside others which may cause serotonin toxicity.(705)

Poisonings

Reported toxicity in overdose cases included acute respiratory acidosis, seizure, trauma from seizure, cardiogenic shock, serotonergic toxicity, multiple organ failure, hyperglycaemia, hypoglycaemia, Brugada ECG pattern, hyponatraemia, shock, asystole, central-nervous-system depression, nausea, vomiting, tachycardia, respiratory depression, acute renal impairment, hyperamylasemia or liver injury when in combination with paracetamol.(705-725) Unintentional overdoses appear to be fairly common, with one Finnish study reporting 55% of tramadol overdoses to be accidental.(726) One factor which may increase overdose risk is the metabolism of tramadol by CYP2D6, which is known to have varying genetic polymorphisms resulting in some poor or extensive metabolisers.(727, 728) In some areas such as Iran, England and Wales, the rate of overdose is seen to be on the increase.(729-732) Other reports of overdose deaths come from Sweden, Belgium, Denmark, Finland, Norway, Iceland, Italy, South Korea, Singapore, Ireland, Iran.(196, 199, 504, 733-743)

A reduction in tramadol poisoning exposures occurred after rescheduling to U.S.A. schedule II in Kentucky, U.S.A.(744, 745)

Other related harm

Tramadol appears in cases of sexual cases in low levels in the U.K.(454) Tramadol misuse has also been associated with risky sexual behaviours in Egypt.(642)

In an Australian study of random roadside testing, tramadol appeared in 1.2% of subjects, but the rate of misuse is not known from this information.(6) In Sweden and Denmark, tramadol was present in some subjects suspected of DUID.(193, 198, 384, 746)

One study showed increased risk of contracting hepatitis C virus or liver disease when co-injected with heroin in the Egyptian setting.(747)

5.8. Dextropropoxyphene

34 articles were included in the analysis for dextropropoxyphene misuse. The relative risk of dextropropoxyphene in the Australian setting is estimated to be low despite the known toxicity of the schedule 4 drug, as medical practitioners must provide a Prescriber Confirmation Form with each new prescription which has could result in more rational prescribing decisions.(748)

Abuse

The abuse potential for dextropropoxyphene is well known.(749) There have been a few studies in the setting of India and Bahrain which show abuse in the population, particularly in those who inject drugs and high rates of use in those who attend drug rehabilitation.(750-753) It was also found that abuse is more common in rural parts of the U.S.A. versus urban.(754)

Despite known abuse, theoretically weak opioids such as dextropropoxyphene have been shown to have lower risk of problematic usage and have reduced morbidity risk.(632, 755)

Poisoning

In overdose, dextropropoxyphene is known to cause respiratory and cardiac conduction abnormalities, with prolonged QTc interval and increased seizure activity.(753, 756-759) Dextropropoxyphene was also measured to have a 10 times higher mortality in overdose than any other combination analgesic and is a prominent feature of poison centre exposures during the 2000s in the U.S.A.(760, 761) In the 90s, dextropropoxyphene was responsible for 766 overdose deaths in the UK over a three year period, but at the time was available without a prescription.(753) There were six other articles which described cases of intentional dextropropoxyphene poisoning in Finland, England, Sweden and Wales.(644, 762-766)

Other Harms

Dextropropoxyphene use was not shown to increase workplace accidents in one study of coal miners.(767)

Risky sexual behaviours were shown to be higher in some users of dextropropoxyphene in one study in India, such as multiple sexual partners or paid sexual partners.(768)

Withdrawal from the market

Due to known toxicity, dextropropoxyphene has been withdrawn from the market and many user settings or restricted, with publication about these events from the U.S.A., U.K., France and Denmark with some positive results regarding suicide rates.(769-779) The withdrawal from the market has not been welcomed by some patients, with one survey reporting that 48% of users were not happy to change to another analgesic.(780)

5.9. Selective serotonin reuptake inhibitors

Fifty-one articles were included about selective serotonin reuptake inhibitors (SSRI) misuse and overdose after excluding seven articles which were found to be irrelevant to the research question, six which were in a language other than English, three which were in an inappropriate format and five full text unavailable. The majority of the literature about overdose worldwide was commenting on SSRIs as a class rather than the individual drug. The literature about class effect is briefly summarised first in this section, then the literature on the individual drugs follows on.

There were no articles found which described either abuse of SSRIs as a class, or combinations of drugs which increased risk of harm.

Selective serotonin reuptake inhibitor class

Dependence

One article was found which related to dependence syndrome to SSRIs, with associated difficulty in cessation of treatment.(781)

Poisoning

Eight articles were included on the topic of overdose and poisonings from SSRIs. (360, 782-788) SSRIs were found to be safer in overdose than tricyclic antidepressants and some serotonin-noradrenalin reuptake inhibitors with a lower risk of cardiotoxicity.(360, 782-784, 786, 788) Despite this relative safety, one study found that after the introduction to SSRIs to the market in Nordic countries, there was no correlating decrease in suicide rates as would be expected.(785) In overdose, there has been reported serotonin syndrome, some QTc prolongation and seizures.(786, 787)

Suicide rates

There has been some speculation about the risk of SSRIs in increasing suicide ideation in patients, particularly in the adolescent population. Five articles were found disputing this theory, and contending that SSRIs do not lead to increased risk of suicide.(789-793) One study was found which supported this hypothesis by observation of higher rates of suicide in those who are adolescents, although this is only relative to other age groups who were also taking SSRIs.(794)

Citalopram

There were no articles found which highlighted abuse, dependence or harmful combinations with citalopram.

Nineteen articles were found on the topic of overdose on citalopram and associated harms.(312, 331, 543, 783, 795-809) Reported harms in overdose include hypoglycaemia, seizures, QTc prolongation, ventricular tachycardia, metabolic acidosis, drowsiness, hypertension, vomiting, coma, cardiac arrest or death.(312, 331, 795-801, 804, 805, 807, 809)

Suicide risk was variable when initiating and continuing citalopram when examined in one study.(810)

Fluvoxamine

There were no articles found which highlighted abuse, dependence or harmful combinations with fluvoxamine.

There were two articles included on the topic of overdose with fluvoxamine, one of which was fatal in polydrug overdose and one which included a patient with status epilepticus.(441, 811)

Fluoxetine

There were no articles found which highlighted abuse, dependence or harmful combinations with fluoxetine.

There were three articles included on the topic of overdose with fluoxetine, one with a benign outcome, one with fatality from serotonin toxicity in combination with moclobemide and one with hypotension in combination with trazodone.(812-814)

Sertraline

There were no articles found which highlighted abuse, dependence or harmful combinations with sertraline.

There were six articles included on the topic of overdose with sertraline.(238, 245, 294, 672, 815, 816) Harms from overdose were reported as serotonin syndrome and one fatal diabetic ketoacidosis.(672, 816)
One study investigated the risk of suicidality with the use of fluoxetine and concluded that there was no increased risk with administration of the drug.(817)

Escitalopram

There were no articles found which highlighted abuse, dependence or harmful combinations with escitalopram.

There were seven articles included on the topic of overdose with escitalopram.(168, 801, 804, 818-821) Harms from overdose were reported as prolonged QTc interval, seizures, drowsiness, hypertension, vomiting or bradycardia.(168, 801, 804, 818, 821)

Paroxetine and dapoxetine

There were no studies included which addressed these two SSRIs specifically.

5.10. Serotonin-noradrenalin reuptake inhibitors

Forty-four articles were included about serotonin-noradrenalin reuptake inhibitors (SNRIs) misuse and overdose after excluding eight articles which were found to be irrelevant to the research question, eight which were in a language other than English, one duplicate and two where the full text was not available.

Venlafaxine

Abuse

Three articles were found on the topic of abuse of venlafaxine. One article reported snorting the capsules in high doses for stimulant and psychedelic effects.(822) Two other cases of abuse were found.(823, 824)

Source of acquisition

One article was found which highlighted the wide availability of venlafaxine for internet purchase.(822)

Dependence

Two articles were found on the topic of dependence to venlafaxine.(825, 826)

Overdose and poisoning

Thirty-two articles were found on the topic of venlafaxine poisonings and overdose.(312, 458, 783, 788, 827-854) Venlafaxine appears to have significant cardiotoxicity in overdose.(829, 830, 832-834, 836, 838, 844, 848-850) Other harms reported in overdose include rhabdomyolysis, seizures, nystagmus, neuroleptic malignant syndrome, hypoglycaemia, gastric bezoar, confusion, mydriasis, cognitive deterioration, psychosis, anticholinergic effects or acute eosinophilic pneumonia.(312, 788, 827, 837, 839, 840, 842, 846, 847, 851, 853, 854)

Desvenlafaxine

There were no articles found on the topic of abuse, dependence source of acquisition or common risky combinations for desvenlafaxine.

Overdose and poisoning

There were two articles found on the topic of overdose to desvenlafaxine, one of which argues a lower risk of harm than venlafaxine and one with a case report of Tako tsubo cardiomyopathy.(838, 855)

Duloxetine

There were no articles found on the topic of abuse, dependence source of acquisition or common risky combinations for duloxetine.

Overdose and poisoning

There were six articles included on the topic of overdose to duloxetine.(238, 856-860) Duloxetine appears to have lower toxicity in overdose than venlafaxine.(856)

5.11. Tricyclic antidepressant

Eighty-six articles were included about tricyclics antidepressant (TCA) misuse and overdose after twelve articles were excluding for relevance to the research question, eight in a language other than English, two in an inappropriate format or two for full text was not available. The majority of the literature about overdose worldwide was commenting on TCAs as a class rather than the individual drug. The literature about class effect is briefly summarised first in this section, then the literature on the individual drugs follows on.

Note: There were no articles which mentioned abuse or dependence of TCAs.

Tricyclic antidepressant class

Poisoning

The toxicity of TCAs in overdose is well known worldwide and this class is considered to be one of the least safe antidepressants on the market.(782) There were 31 articles including case series, poison information centre information and epidemiological studies which focussed on toxicity in overdose by TCAs.(82, 139, 169, 360, 782-784, 786, 791, 794, 861-881) Several studies showed the cardiotoxicity of TCAs in overdose including Brugada ECG and QTc prolongation.(139, 862, 865, 869, 877) Other harms include cerebellitis in a paediatric patient, coma, death, seizures and intractable hypotension.(861, 862, 864, 880)

Other harm

One article was included which was an Australian study looking at the ambulance callouts for non-fatal accidents, of which TCAs were a common reason for attendance.(882)

Combination with other drugs

In combination with methadone, tricyclics antidepressant users were found to have increased risk of accidental overdose.(160) When taken in overdose alongside benzodiazepines, the risk of seizure can be reduced.(139) This combination is commonly found. No other combinations were explored in the included literature within the broad class of TCAs.

Amitriptyline

Amitriptyline is demonstrated to be by far the most widely discussed TCA in the included literature due to its wide availability and the fact that the drug has been on the market for many years. Twenty-six articles were included on the topic of overdose with amitriptyline and associated harms.(355, 833, 883-906) The main harms that were discussed in these articles were Brugada ECG, acute myocardial infarction, seizure, cardiac arrest or death.(884, 889, 892, 896, 897) Common overdose symptoms such as sedation are less likely to be discussed as the timeframe specified in this review precludes the earlier literature which is likely to contain common overdose toxicities.

Five articles highlighted the potential for abuse of amitriptyline for euphoric effect; however the frequency of abuse is likely to be rare.(907-910)

Three articles commented on amitriptyline misuse in combination with other drugs such as morphine, methadone, clonidine, benzodiazepines and buprenorphine for aggregate calming effects.(140, 908, 911)

One article characterised other harm from amitriptyline, in fatally injured drivers in Washington State where a relatively small number of drivers tested positive to amitriptyline which is a known sedative and may impair driving.(195) The extent of misuse in this situation is unknown.

Dosulepin (dothiepin)

Eight articles were included on the topic of overdose on dosulepin.(783, 912-918) Compared to other TCAs, dosulepin is known to have a higher level of toxicity in overdose.(783) Harms described in these articles include atrial flutter in a paediatric patient and Brugada ECG.(912, 916, 917)

One article mentioned abuse of dosulepin to induce mania in a case study.(919)

Imipramine

Eight articles were included on the topic of overdose with imiprimine.(312, 791, 913, 920-924) Harms described in these articles include cardiovascular and neurological complications in a paediatric patient and seizures.(312, 922)

There were no articles included on abuse of imiprimine or combinations with other drugs.

Doxepin

There were no articles included on abuse of doxepin or combinations with other drugs.

Five articles were included on the topic of overdose on doxepin.(307, 783, 791, 925, 926) Harms included QTc prolongation and syncope.(926) Doxepin is considered one of the least safe TCAs in overdose despite lower levels of publication on overdose captured in this review.(783)

Clomipramine

There were no articles included on abuse of clomipramine or combinations with other drugs. Two articles were included on the topic of overdose on clomipramine.(358, 927)

Nortriptyline

There were no articles included on abuse of nortriptyline or combinations with other drugs. One article was included on the topic of overdose with nortriptyline which mentioned Takotsubo cardiomyopathy.(928)

5.12. Mirtazapine

Eleven articles were included in this analysis, which were based on mirtazapine misuse. Overall, the rate of misuse and attributed harm appears to be low.

Abuse

Two articles describe potential for abuse of mirtazapine. One article is in the context of a women's prison in the U.K. where mirtazapine is reported to be used for mind altering properties and "pleasure".(929) Dose escalation in a patient with known substance abuse has been reported in one case report.(930) Overall, the literature does not show a high level of misuse.

Other harm

Mirtazapine was found in less than 1% of cases of impaired drivers in one study based in Switzerland. (188) No other harm was found in the literature returned in this search.

Poisoning

Eight articles included information on mirtazapine in overdose. In most cases, the level of harm from overdose was low.(931-934) In a study on completed suicides in Canada, mirtazapine was found to be involved in only 1 case out of 397.(935) Despite these figures, mirtazapine was reported to have a higher case fatality ratio than selective serotonin reuptake inhibitors.(783) Two cases of serious harm including death and cardiac arrest were found in the literature, however these cases were in polydrug overdose and it is unclear what role mirtazapine played in the outcomes for these patients.(357, 936)

5.13. Other antidepressants

Of twelve articles screened for full text on the topic of “other” antidepressants, four were included with two excluded for language other than English, five excluded for relevance to the research question and one duplicate.

Reboxetine

One article was included on the topic of reboxetine in overdose which was asymptomatic.(937) There were no articles found about misuse of reboxetine.

Moclobemide

There were three articles found on the topic of overdose with moclobemide which showed serotonin toxicity in combination with other serotonergic drugs taken and two fatalities.(814, 845, 938) There were no articles outlining moclobemide misuse.

Agomelatine, mianserin, vorioxetine

No articles were found about these three schedule 4 “other” antidepressants

5.14. Anorectic agents

Diuretics and phentermine were searched together for this relatively small volume section. Thirty five articles were screened for full text and 13 articles were included, with five articles excluded for relevance to the research question, seven for language other than English, and ten duplicates.

Diuretics

Abuse

Diuretic abuse in people aiming to lose weight for cosmetic reasons or competitive sport is well known despite the low numbers of articles published after 2005. In this small group of articles returned, frusemide and hydrochlorothiazide were the most common agents abused, presumably because of their short half life.(939, 940) Diuretics can be abused for competitive sports which require a slim body type or the competitor to fit within a weight category such as in ballet, wrestling, boxing, gymnastics, dance or body building.(939, 941, 942) In the general population, diuretics can be abused for weight loss.(943, 944)

Combination with other drugs

In body building, diuretics are often used in combination with anabolic androgenic steroids which can cause fluid retention.(939)

Poisoning

Two articles outlined cases of diuretics in overdose, which were commonly part of a polydrug overdose and taking the diuretic appeared to be opportunistic rather than intentional to achieve toxicity.(605, 945)

Other related harms

Abuse of diuretics as part of purging for weight loss can lead to dehydration, exhaustion, muscle cramps, electrolyte imbalances, ototoxicity, interstitial nephritis, impaired vasodilation, hyperuricaemia, arrhythmias, myocardial infarction or death.(939, 946, 947)

Phentermine

One article described the low risk of abuse or dependence with phentermine, explaining that people who take phentermine do not have cravings to take more, and experience no withdrawal effects.(948) There were no articles included which supported the theory of potential for phentermine abuse or dependence. One article from South Korea, outlined that phentermine is currently being illegally sold on the internet, but the drug was not found to be present in samples of hair from drug suspects and therefore misuse cannot be proven from these samples.(949) There was one article which mentioned a case of phentermine induced psychosis.(950)

5.15. Anticholinergic and antiparkinson agents

Of the 52 articles which were screened for full text on the topic of anticholinergic and antiparkinson agents of misuse, 28 were included in the final review, with four excluded for language other than English, six excluded for relevance to the research question, two excluded for inappropriate format, and eleven duplicates.

One article made comment on anticholinergic agents in general, stating that there is lack of evidence for misuse of anticholinergic agents for Parkinson's Disease after interrogation of the Norwegian Prescription Database.(951)

Benzhexol

Abuse

Abuse of benzhexol was described in five articles to achieve the effects of hallucinations and euphoria due to anticholinergic effects.(952-956)

Dependence
Two articles describe dependence syndrome with the use of benzhexol, one case in intermittent explosive disorder where the patient was unable to withdraw from treatment without worsening effects and one case of psychosis with cessation.(953, 957)

Source of acquisition

Benzhexol was reported to be sourced through some illegal avenues in France, with known theft and internet purchase without prescription according to a survey.(958)

Combination with other drugs

Benzhexol was found to be used in combination with Red Bull Energy Drink to prolong the psychostimulant effect and in combination with alcohol and benzodiazepines.(952, 954)

Levodopa

Abuse

In patients who are being treated with levodopa for Parkinson's Disease a small proportion have been found who feel compelled to take excessive amounts of levodopa due to an aversion to the "off" state when the medication levels drop.(959-963) This compulsive behaviour is explained by the reinforcing pathway of levodopa in the brain inducing possible psychological dependence.(964) One study surveyed patients with Parkinson's disease to investigate the excessive use of their medications and found that both levodopa and dopamine agonists were abused to "feel good" in a significant but small group of patients.(965)

Poisoning

One article focussed on one case of poisoning with controlled release levodopa-carbidopa which resulted in mydriasis, urinary retention, psychomotor agitation, delirium, visual hallucinations, tachycardia and xerostomia. (966)

Biperiden

One article was included of a case study of biperiden abuse and dependence with withdrawal symptoms of dysphoria, psychomotor agitation, anxiety, headache and insomnia.(967)

Oxybutynin

Three case studies were included on the topic of abuse and dependence with oxybutynin, with one reported motivation to induce a feeling of a “floating sensation” with high doses.(952, 968, 969)

Orphenadrine

One article was included on the topic of orphenadrine misuse, which stated that there is no evidence for misuse when a German Pharmacovigilance Database was interrogated but the literature shows potential for abuse.(970)

Apomorphine

Two articles were included on the topic of apomorphine abuse which resulted in one case of loss of significant impairment in functioning and loss of control of consumption and one case of dyskinesias.(971, 972)

Selegeline

Two articles were included on the topic of selegeline overdose with some reported effects of hallucinations and convulsions lasting up to two weeks after overdose.(973, 974) There were no articles included on the topic of abuse or dependence.

Amantadine

Four case studies of amantadine overdose were included with symptoms reported as seizures, acute renal failure, hyperkalaemia and cardiotoxicity.(377, 975-977)

5.16. Atomoxetine

Of the 40 articles which were screened on the topic of atomoxetine misuse, 14 were included in the review with 17 excluded for relevance to the research question and nine duplicates.

Abuse

One article supported the theory that atomoxetine has some potential for abuse but states that this risk is lower than that of methylphenidate.(978) Six articles mentioned the low potential for abuse of atomoxetine with one explaining that pharmacologically this drug has no affinity for receptors which are commonly involved in the reward pathway (GABA A, μ-receptors or dopamine transporters).(979-984)

Poisoning

Five articles covered seven cases of overdose with atomoxetine and showed symptoms of drowsiness, agitation, hyperreflexia, hyperactivity, gastrointestinal upset, tremor, tachycardia, hypertension and/or seizure.(985-989)

One Australian article reported 83 exposure calls for atomoxetine to the NSW poison Information Centre over an eleven year period, a figure which is relatively low.(990) In the U.S. there were 20,032 registered cases between the years 2002-2010 in the National Poison Database System which showed a relatively benign picture in overdose.(991)

5.17. Baclofen

Twenty articles related to baclofen were deemed relevant after screening full text. Seven of these articles involved misuse of baclofen and 13 articles describe overdose. One case series was from the Australian setting.(992)

Misuse

Baclofen is known to be structurally and pharmacologically similar to gamma-hydroxybutyrate, an illicit drug which is known for its euphoric and sedative properties.(993) There has been evidence of misuse potential in areas of Europe including evidence within pharmacovigilance data in Germany.(994) Another study by survey of misuse of baclofen was conducted in the UK in 2010 by the European Monitoring Centre for Drugs and Drug Addiction which showed lifetime prevalence of misuse of baclofen to be 1.3% of respondents.(995, 996) This is complemented by another survey conducted in South London, UK specifically in the population of males who have sex with males, which reported a 2.5% rate of baclofen misuse.(466)Two case studies were included in the cohort reflecting misuse. One case of dose escalation and doctor shopping in order to “think more clearly” resulted in mania, psychomotor agitation and consequential withdrawal delirium.(997) Another case involved a teenage girl who was prescribed baclofen therapeutically, however it was then used by the girl recreationally to induce “controlled” vanishing consciousness leading to multiple comas.(998)

Overdose

Thirteen articles describe baclofen in overdose across 98 case reports. The observed effects of baclofen in overdose case reports include coma, bradycardia, hypotonia, non-convulsant status epilepticus, reduced brainstem reflexes mimicking brain death, decreased Glasgow Coma Scale, delirium, miosis or dilated pupils, reduced reflexes, bradycardia, hypertension, diabetes insipidus, flaccid paralysis, respiratory distress and associated aspiration pneumonitis.(313, 992, 999-1009) There were no reported deaths within the cohort of overdose articles.

5.18. Lithium

Of the 23 articles screened for full text on the topic of lithium misuse, 1 was excluded for full text not available, 3 for language other than English and one for relevance to the research question.

No articles were found on the topic of lithium abuse or dependence.

Poisoning

Eighteen articles were included which focussed on lithium in overdose.(360, 597, 794, 1010-1024) Some reported symptoms of overdose were renal failure, encephalopathy, rare ECG

changes or bradycardia, neurological toxicity and seizures.(1012, 1017-1021) One article describes lithium overdoses to have a serious prognosis OR 4.3 [95% CI 1.6-11.6].(360)

5.19. Clonidine

Of the 19 articles screened for full text on the topic of clonidine, eight articles were included with three articles excluded for relevance, one for language other than English and seven duplicates.

Abuse

Five articles showed potential for abuse of clonidine.(239, 501, 994, 1025, 1026) One epidemiological study from a German pharmacovigilance database showed some potential for abuse.(994) Clonidine is also known to be used more commonly in the population of injecting drug users and those seeking detoxification for opioid dependence.(501, 1026)

Dependence

One article was found which reported one case of dependence on clonidine with associated withdrawal effects of rebound hypertension and increasing the symptoms of opioid withdrawal (as this patient was also opioid dependent).(1027)

Combinations with other drugs

One case study recorded a patient who used clonidine alongside amitriptyline and buprenorphine to achieve a “mood altering state”.(1025) It was found that 10% of patients seeking opioid inpatient detoxification in the setting of the U.S. were also using clonidine.(501) In combination with benzodiazepines, one case stated it enhanced and prolonged the benzodiazepine effects.(239)

Poisoning

There were two articles which focussed two cases of clonidine in overdose which included the symptoms of depressed sensorium, bradycardia and paradoxical hypertension followed by hypotension.(985, 1028)

5.20. Doxylamine

Doxylamine is available under schedule 4 in Australia in combination with codeine and paracetamol and marketed as an analgesic. Given that doxylamine is available in differing combinations around the world, the applicability of the articles found to this research question is limited. Five articles were included on the topic of doxylamine misuse. One French cross-sectional study was found on the topic of dependence to doxylamine in combination with codeine.(1029)

One article showed potential harm from doxylamine use in U.S. aviation accidents between 1990-2005, where some pilots were found to test positive to the substance, however the preparation of doxylamine may have been different to what is found in Australian schedule 4.(1030)

Three articles were included on the topic of doxylamine overdose which showed symptoms of rhabdomyolysis or syndrome of inappropriate antidiuresis.(1031-1033)

5.21. Erythropoiesis stimulating agents

The search for erythropoiesis stimulating agents as available in Australia on schedule 4 (epoetin, darbepoetin, Methoxy pegepoetin beta) proved to have significant “noise” and the actual agents were quite diluted in the list of articles generated. Twenty-two articles were included in the final analysis, nine excluded as the full text was unavailable, four for language other than English, 23 for relevance to the research question and two duplicates. There were a significant number of textbooks which covered the topics of doping in sports in a general way, and it appears that this topic as part of a set of illegal agents is well known. The availability of each of these textbooks has been a limitation to this review, however it appears that the abuse of erythropoiesis stimulating agents on prescription in Australia is likely to be low and therefore the benefits of obtaining these hard copies is questionable in elucidating the overall picture of harm. A large proportion of the studies returned during this search focused on the ethical implications or psychology of doping in sports, and were therefore deemed in appropriate for inclusion in this review.

After reviewing the available literature, the picture of misuse appears to be present in only niche populations, and the source of acquisition is unlikely to be directly from medical practitioners and therefore monitoring of these agents on a RTPM system is likely to not have a good evidence base.

Abuse

Erythropoiesis stimulating agents are known as peptide hormones in the sporting industry and can be abused in a variety of sports including athletics and cycling.(1034-1046) The popularity of these peptide hormones in sports is due to their effects on stimulating red blood cell production and therefore oxygen transport around the body to improve aerobic capacity. Detection of these peptide hormones in the body has been historically difficult which adds to the popularity, however as technology to detect them improves their popularity has seen a decline with top up blood transfusion becoming more favourable for their instant effects and lower levels of detectability.(1036, 1038, 1047, 1048)

In the non-sporting population, erythropoiesis stimulating agents can be misused in overcorrection of anaemia in renal patients.(1049)

Other Harms

Erythropoiesis stimulating agents are known to increase the risk of thrombosis and vascular accident.(1050-1052) Other adverse effects in misuse include increased levels of neuroticism from baseline and potentially increased risk of cancer as one study showed some evidence for favouring of tumour survival.(1053, 1054)

Combination

Erythropoiesis stimulating agents, when abused in sport, often come in combination with multiple other agents to enhance performance or for cosmetic use to counteract side effects

such as growth hormones, human chorionic gonadotropin (HCG), amphetamines, clenbuterol, insulin, thyroxine, anabolic androgenic steroids, diuretics and analgesics.(1055)

5.22. Oestrogen modulators

Of five articles screened for full text on the topic of misuse of oestrogen modulators two were included in the review, with two excluded for language other than English and one for relevance to the research question.

Oestrogen modulators such as aromatase inhibitors and selective oestrogen receptor modulators are known to be used by men who abuse anabolic androgenic steroids to reduce excess testosterone metabolism to oestrogen resulting in gynecomastia as well as after a cycle of anabolic androgenic steroids to help restore the body's endogenous testosterone.(1056, 1057) In women, these same agents are used to block the endogenous oestrogen and achieve a more favourable testosterone: oestrogen ratio for building muscle mass.(1056, 1057)

5.23. Androgenic agents

The misuse of androgenic steroids is well characterised in the literature and multiple synthetic derivatives of testosterone exist. In Australia, schedule 4 androgens of abuse may include testosterone, mesterolone and nandrolone. When performing a literature search for misuse of these agents the results return exceptionally large numbers of articles which describe misuse of androgenic anabolic steroids in general without specification as to the type of agent or the source, illicit or prescription. It is therefore difficult to quantify exact levels of harm from a literature search due to significant "noise" diluting the results from illicit sources, however it is well known that there is extensive illegal trade of steroids within the community of gymnasiums and therefore inclusion on a RTPM system is unlikely to change levels of use significantly. The full search returned 407 potentially relevant articles, however the majority of these articles did not specify the schedule 4 agents available in Australia and therefore could not be included. Overall 18 articles were included, 364 excluded for potential irrelevance, 5 for full text not available, 39 for language other than English, and 1 duplicate.

Harm from androgen misuse

There was an exceptional amount of literature describing the harms from chronic misuse of androgenic agents, however the exact harm from available schedule 4s in Australia is not commonly specifically described. Some positive effects from chronic use may include increased libido, deepening voice (in males), increasing fat free muscle mass, erythropoiesis, elevated mood, elevated self esteem and increased energy levels.(1058) Reported negative effects include hirsutism, alopecia, acne, testicular atrophy, gynecomastia, azoospermia, thyroid hormone inhibition, tendon rupture, dyslipidaemia, hypertension, fluid retention, cardiomyopathy, stroke, pulmonary embolism, hepatic tumours, irritability, aggression, hostility, paranoia and less frequently pulmonary peliosis.(1058-1061)

Source of acquisition

Some articles discussed the various sources of androgen acquisition in those misusing, however the exact proportion from each source in Australia is difficult to investigate as it relies on self reporting and no articles which specify these sorts of detailed results were found. It appears that it is easy to obtain androgens online through a multitude of websites, with the main origins reported as Mexico and Thailand.(1058, 1062, 1063) One German study found large quantities of steroids seized at customs between the years 2010-2013 with 83% of these androgens including testosterone and nandrolone.(1064) Despite these androgens matching those available on schedule 4 prescription in Australia, this clearly shows that these agents were not being obtained from a prescription source. Other sources may include veterinarians, mail order catalogues and other steroid users.(1058) Elaborate operations were described in one article where users would exchange cash and drugs through lockers at a business park in the U.S., resulting in no actual contact between the user and dealer.(1065) Quality of androgens supplies through illegal sources is questionable with some illegally manufactured, stolen and known circulating counterfeit steroids.(1066)

Misuse of androgens

Misuse in the sporting industry and security industry is well described in the literature for body building properties.(1066-1070) Some case reports of abuse of testosterone specifically were mentioned in the literature, mostly in young athletes or body builders.(1071-1073) Again, it is difficult to pinpoint the source of these androgens. It has been found that the prevalence of misuse of anabolic androgenic agents in Australian students is around half that of those in the U.S.(1066)

Another subgroup of misusers is middle aged and older men who seek androgens to treat “andropause” a condition of middle age testosterone depletion.(1066, 1074-1076) An Australian article depicts the ongoing misuse of testosterone for “andropause” as less prevalent in Australia as this country has national prescribing guidelines which are aimed at quality prescribing habits for this condition, which is difficult to diagnose.(1074) However, in Ireland, the U.S., Sweden, the U.K. and Canada, testosterone prescribing in on the increase for this condition despite the fact that the use of testosterone has a poor evidence base.(1074) One study revealed that the inappropriate prescribing of testosterone in Canada could be put down to both physician factors including ambiguity of diagnostic criteria for androgen deficiency and patient factors which include drug-seeking and improved patient access to information about these agents(1075)

5.24. Conclusions from this chapter

There is a wide range of peer-reviewed literature available which investigates the harm from misuse of specific Schedule 4 medications internationally. Certain classes of drugs can be harder to separate to individual drugs in order to establish their respective harm, such as the benzodiazepines and anabolic steroids, whereas other classes are often reported via drug and are therefore easier to draw conclusions. However, from such a large cohort of articles which are found in such a broad search, it is possible to rule out the possibility of harm from certain drugs or classes by the absence of literature captured. This chapter has managed to, on one hand, conclude that there is a lack of evidence for harm for certain drugs of interest such as SSRIs, while on the other hand describing the likelihood of harmful trends for other drugs of suspicion such as quetiapine.

Through predominantly quantitative review of the literature, we can conclude that based on peer-reviewed literature search there is evidence of definite concerning trends in harm for benzodiazepines (when examined as a whole class), diazepam, clonazepam, quetiapine, pregabalin, zolpidem and, to some extent, Australian schedule 4 codeine-containing products; evidence surrounding Australian Schedule 4 codeine is still somewhat difficult to distil from a breadth of literature which encompasses codeine products as a whole. On a relatively lower scale of harm there is evidence of probably concerning trends with midazolam, temazepam, zopiclone, gabapentin, tramadol (although there is disagreement as to the risk of harm), dextropropoxyphene and testosterone. There is some evidence to support possible concerning trends in oxazepam, lorazepam, nitrazepam, bromazepam, olanzapine, phenobarbital, venlafaxine, amitriptyline, frusemide, hydrochlorothiazide, benzhexol, levodopa, oxybutynin, baclofen, clonidine, epoetin, tamoxifen, mesterolone and nandrolone, however, this low level of evidence is unlikely to be sufficient to support these drugs' inclusion into a RTPM system except where necessary from a displacement point of view.

Chapter 6. Identifying the characteristics of other prescription drug monitoring programs

6.1. United States

Forty-nine states in the United States of America (US), the District of Columbia and one US territory, Guam, have operational prescription drug monitoring programs (PDMPs). Missouri is the only US state without an operational PDMP. The US classes controlled substances by its own system, defined by the Drug Enforcement Agency (DEA)'s Controlled Substances Act. Schedule 1 US contains drugs that are classed as illicit substances, for example methamphetamine. US Schedule 2-5 contain drugs that have a potential for abuse in a gradient of harm, with US Schedule 5 drugs showing the lowest potential (see Table 6.1.1.). Different US states monitor a different range of schedules and some states monitor additional medicines (see Table 6.1.2).

Gabapentin

Gabapentin is a drug of increasing concern in the US, where certain jurisdictions have noted escalations in poisons information phone calls and overdose deaths (see Figure 6.1.1., 7.1.1). It is not currently a controlled substance, and thus is not routinely monitored, but is currently being monitored by four states, and will be monitored by Kentucky from July 1. A survey of 1749 licensed pharmacists in Kentucky showed that 78% were concerned about the abuse and diversion of gabapentin, 64% felt patients frequently sought multiple prescribes for gabapentin, and 72% supported reclassifying gabapentin as a controlled substance (personal correspondence).

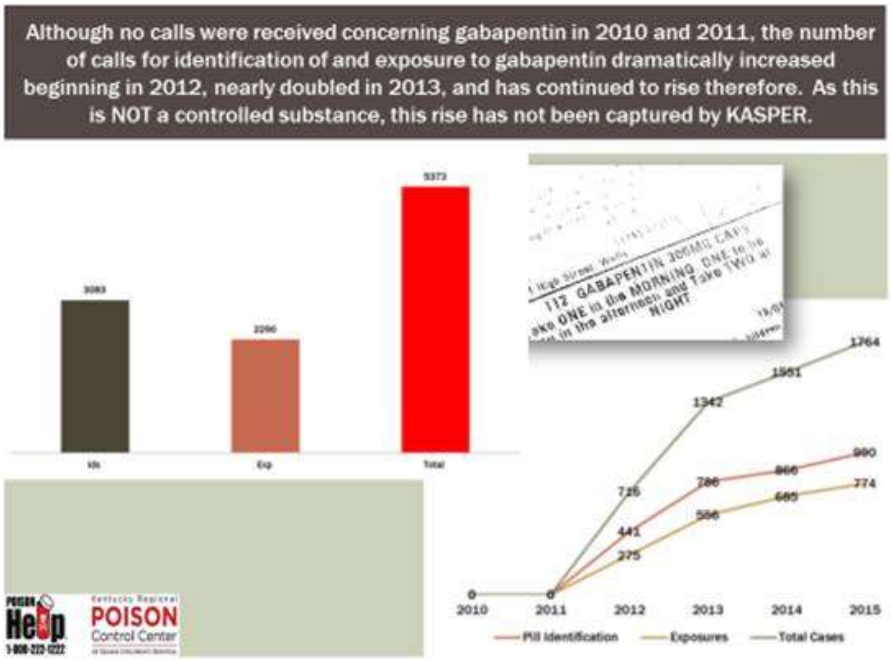


Figure 6.1.1. Poisons information calls to the Kentucky Regional Poison Control Center for gabapentin, 2010-2015. From personal correspondence with David Hopkins, KASPER Program Manager, Kentucky Cabinet for Health and Family Services.

Table 6.1.1. Australian Schedule 4 medications and their correlation with the US Controlled Substances Act

US DEA Schedule	**Australian Schedule 4 drug of interest**
Schedule 2	codeine (plain)
Schedule 3	barbiturates, codeine combination products, testosterone, anabolic agents
Schedule 4	benzodiazepines, tramadol, dextropropoxyphene, zolpidem, zopiclone, modafinil, phentermine
Schedule 5	codeine cough preparations, pregabalin, lacosamide
Not scheduled	quetiapine, baclofen, gabapentin, doxylamine

United States Drug Enforcement Administration. Drug Scheduling [Internet]. United States of America. U.S. Department of Justice; [cited 26/3/2017] Available from https://www.dea.gov/druginfo/ds.shtml

Table 6.1.2 PDMPs in the United States and their characteristics

State	**Drugs monitored**	**Frequency of data transmission**	**Mandatory use by prescriber (P) or dispenser (D)**	**Date of implementation**
Alaska	Sched 2-4	Weekly	P= Yes D= Yes	2012
Alabama	Sched 2-5 & codeine cough syrups, anabolic steroids, butalbital products and combinations, chlordiazepoxide and combinations	Daily	P= No D= No	2007
Arkansas	Sched 2-5 & Nalbuphine	Weekly	P= Yes D= No	2013
Arizona	Sched 2-4	Daily	P= Yes D= No	2008
California	Sched 2-4	Weekly	P= No D=No	2009
Colorado	Sched 2-5	Daily	P= No D=No	2006

Connecticut	Sched 2-5	Daily	P= Yes D= No	2009
District of Columbia	Sched 2-5 & Cyclobenzaprine, Butalbital	Daily	P= No D=No	2016
Delaware	Sched 2-5	Daily	P= Yes D=Yes	2012
Florida	Sched 2-4	Weekly	P= No D=No	2011
Georgia	Sched 2-5	Weekly	P= Yes D= No	2013
Hawaii	Sched 2-5	Weekly	P= No D=No	1996
Idaho	Sched 2-5	Daily	P= No D=No	1996
Illinois	Sched 2-5	Daily	P= No D=No	1999
Indiana	Sched 2-5 Ephedrine and Pseudoephedrine	Daily	P= Yes D= No	2007
Iowa	Sched 2-4	Weekly	P= No D=No	2009
Kansas	Sched 2-4 & Butalbital/acetaminophen/caffeine (Fioricet), prescription pseudoephedrine products, promethazine with codeine	Daily	P= No D=No	2011
Kentucky	Sched 2-5 & gabapentin, nalbuphine	Daily	P= Yes D= No	1999
Louisiana	Sched 2-5 & butalbital, ephedrine products are schedule 5	Daily	P= Yes D=Yes	2009
Massachusetts	Sched 2-5 & gabapentin	Daily	P= Yes D=No	1994
Maryland	Sched 2-5	Daily	P= Yes D=No	1994

Maine	Sched 2-4	Daily	P= Yes D=Yes	2005
Michigan	Sched 2-5	Daily	P= No D=No	2003
Minnesota	Sched 2-4 Butalbital, gabapentin, Human growth hormones are schedule 3	Daily	P= Yes D= No	2010
Missouri	-	-	-	-
Mississippi	Sched 2-5 & ephedrine and pseudoephedrine are schedule 3	Daily	P= Yes D= No	2005
Montana	Sched 2-5	Weekly	P= No D=No	2012
North Carolina	Sched 2-5	3 business days	P= No D=No	2007
North Dakota	Sched 2-5 & gabapentin	Daily	P= Yes D=Yes	2008
Nebraska	Sched 2-5 & All prescription medications	Daily	P= No D=No	2012
New Hampshire	Sched 2-4	Daily	P= Yes D= No	2014
New Jersey	Sched 2-5 & Human Growth hormones	Daily	P= Yes D=Yes	2012
New Mexico	Sched 2-5	Daily	P= Yes D= No	2005
Nevada	Sched 2-4	Daily	P= Yes D= No	1997
New York	Sched 2-5 & Chorionic Gonadotropin (HCG) is sched 3	Daily	P= Yes D= No	1973
Ohio	Sched 2-5 & gabapentin	Daily	P= Yes D=Yes	2006

Oklahoma	Sched 2-5	Daily	P= Yes D=Yes	2006
Oregon	Sched 2-4 & pseudoephedrine	3 business days	P= No D=No	2011
Pennsylvania	Sched 2 -5	3 business days	P= Yes D=Yes	1973
Rhode Island	Sched 2-4	Daily	P= Yes D= No	1979
South Carolina	Sched 2-4	Daily	P= Yes D= No	2008
South Dakota	Sched 2-5	Weekly	P= No D=No	2012
Tennessee	Sched 2-5	Daily	P= Yes D= No	2007
Texas	Sched 2-5	Weekly	P= No D=No	1982
Utah	Sched 2-5 & butalbital with paracetamol	Daily	P= Yes D=Yes	1997
Virginia	Sched 2-4	Daily	P= Yes D= No	2006
Vermont	Sched 2-4	Daily	P= Yes D=Yes	2009
Washington	Sched 2-5	Daily	P= Yes D= No	2012
Wisconsin	Sched 2-5	Daily	P= Yes D= No	2013
West Virginia	Sched 2-4 & opioid antagonists	Daily	P= Yes D= No	1995
Wyoming	Sched 2-4	Daily	P= No D=No	2004

6.2. Canada

Eleven of Canada's provinces or territories currently have operational prescription monitoring programs. The coverage for monitoring varies from a relatively simple triplicate system in Alberta, to the Pharmanet system in British Columbia which covers all prescription medications in real-time (see Table 6.2.1).

Table 6.2.1. Prescription monitoring programs in Canada and their characteristics

Province/territory	**Australian Schedule 4 drugs monitored**	**Real time?**
British Columbia	All Canadian prescriptions dispensed included in *Pharmanet*	Y
Alberta	Dextropropoxyphene, benzodiazepines, codeine, zolpidem, zopiclone	N
Saskatchewan	Anabolic steroids, barbiturates, benzodiazepines, codeine as a single dose form or in combination (except those containing 20 mg per 30 ml or less of codeine in liquid for oral administration), gabapentin, phentermine, dextropropoxyphene	N
Manitoba	Dextropropoxyphene, phentermine, barbiturates, tramadol, codeine (all forms), clonidine, benzodiazepines, modafinil, atomoxetine	Y
Ontario	Codeine, apomorphine, dextropropoxyphene, barbiturates, benzodiazepines, anabolic steroids, zolpidem, tramadol	Y
New Brunswick	Codeine, apomorphine, dextropropoxyphene, barbiturates, benzodiazepines, anabolic steroids, zolpidem, tramadol, clozapine, olanzapine	Y
Nova Scotia	Codeine, apomorphine, dextropropoxyphene, barbiturates, anabolic steroids (except topical testosterone), zolpidem,	N
Prince Edward Island	Codeine, apomorphine, dextropropoxyphene benzodiazepines and gabapentin	Y
Newfoundland & Labrador	Tamper-resistant pads only (not a monitoring program) for codeine, phenobarbital	N
Yukon	See Alberta (both managed by the College of Physicians & Surgeons of Alberta)	N
Northwest territories	Electronic medical record (2016), no PDMP	Y- EMR

Beth Sproule. (2015). Prescription Monitoring Programs in Canada: Best Practice and Program Review, Ottawa, ON, Canadian Centre on Substance Abuse. The *Controlled Drugs and Substances Act Canada*

In addition to separate province prescription monitoring there is also the Non-Insured Health Benefits system which focuses on benzodiazepines, stimulants, gabapentin and opioids and prompts the dispensing pharmacist when the patient has had a recent refill of the drug in question.(1) This allows the pharmacist to make an informed decision about whether or not to supply. The program also aims to reduce doctor shopping. It covers all areas of Canada except for Quebec.

6.3. Norway

Norway has a nationwide prescription database which contains all drugs dispensed in Norwegian community pharmacies.(2) The information in transmitted to the database on a monthly basis and therefore the system is not classified as 'real time'. The aim of the prescription database is to improve prescribing practices and provide a rich data source for researching wishing to describe drug trends. This database is therefore not comparable to the proposed Australian RTPM as the aim of the program differs and this system is not real-time to provide feedback to those who supply medicines.

6.4. Conclusions from this chapter

The monitoring of prescription drugs is a longstanding concept and has been in place worldwide in many different forms since the 1970s. The main pioneers of prescription drug monitoring are in the United States, where all states except one have an individual monitoring system, however the process for decisions behind inclusion of drugs for monitoring can be variable in each state. When comparing monitoring systems from overseas to a potential Australian RTPM, it is important to consider the context: the differences in scheduling of drugs and the lack of direct comparison in two very different healthcare systems. The utility of prescription drug monitoring systems can also vary between jurisdictions, with Norway's database serving more as a research tool to detect concerning trends as they emerge, compared to those in North America which are intended to serve quality and punitive goals. Overall, there is extreme variability in which Australian Schedule 4 drugs are included in monitoring systems overseas and in the systems that are in place to include them.

Chapter 7. Peer-reviewed literature describing and assessing the success of prescription drug monitoring programs outside of Australia

While prescription drug monitoring programs (PDMPs) have been put into place extensively in the United States and Canada, trying to appreciate whether they are effective or not has rarely been a simple question. The diversity of different approaches and environments amongst the different PDMPs has made this particularly challenging, and despite attempts to standardise the approach to assessment(1), metrics and their interpretation vary. There are inherent challenges to the assessment of PDMPs which have been proven difficult to overcome, not least of all the difficulty of comparison against controls. The majority of studies have been ecological studies or time series analyses in a period of time where overall trends have signalled the worst escalation of pharmaceutical drug abuse in contemporary times.

[redacted from public release]

Figure 7.0.1: The controlled substance abuse in the United States has progressively escalated. Published in Manchikanti et al(2).

The implications of this for the Victorian RTPM are even harder to determine. Apart from the multiple fundamental differences in existing health infrastructure and the technology that is to be implemented, as well as the nature of the Victorian RTPM, the social context of drug use, misuse and abuse varies with each precedent. It should be emphasised that a RTPM system is important, but not sufficient in isolation and needs to be part of a co-ordinated response to drug threats. Progressive innovation and improvement has led to progressive but dramatic reductions in doctor shopping multiple US states (see Figure 7.0.2, 7.0.3).

[redacted from public release]

Figure 7.0.2. Doctor shopping in Oklahoma over the period 2010-2016. Multiple interventions, with a real-time prescription monitoring service at the nidus, led to successive gains over time leading to a two-thirds reduction in doctor shopping. From personal correspondence with Don Vogt, PMP Program Manager, Oklahoma Bureau of Narcotics.

[redacted on public release]

Figure 7.0.3. Total number of doctor shoppers in Ohio, 2011-2016. The number of doctor shoppers in Ohio has reduced from 2205 in 2011, to 1639 in 2012, 1172 in 213, 963 in 2014, 720 in 2015 and 357 in 2016. Since the initiation of legislation to increase use of the PDMP in June 2011, Ohio has progressively rolled out a number of initiatives and innovations: a live monitoring website in July 2011, co-ordinated sharing live prescription data with neighbouring states Indiana in August 2011, Michigan in January 2012 and Kentucky in August 2013, access to medical directors of Medicaid managed plans in September 2013, new features to support chronic pain opioid prescribing guidelines in October 2013 including display of an 'active cumulative morphine equivalent' to simplify recognition for prescribers of total opioid dosing, allowing prescribers to review their own history in January 2014, connecting to West Virginia's PDMP in April 2014, adopting daily reporting in May 2014, graphically representing opioid usage to health care providers in August 2014, allow access to mother's PDMP file for prescribers treating opioid dependent newborns in September 2014, data linkage to overdose deaths to identify high-risk prescribers in March 2015, mandatory checks prior to prescribing in April 2015, Veterans Health Administration data linkage in April 2015 and integration with a large pharmacy chain's computer platform in August 2015. Doctor shopping has subsequently been curtailed and, in 2016, was one-sixth of the frequency of 2011. New York state has realised an even more dramatic effect. Opioid and benzodiazepine usage of slowly decreased in contrast to the national US trend. Published in the OARRS 2016 Annual Report(3).

As far as this report is concerned, the implications are even harder to determine. This report is explicitly tasked with determining the evidence that surrounds the possible inclusion of Australian TGA Schedule 4 medications on the RTPM. This is clearly not a distinction that has been directly assessed by North American investigators, nor is it one which is easy to retrospectively delineate. As previously articulated, the Australian Poisons Standard traverses drug classes in a way that is not true for other countries. In the United States, the within-class grouping of benzodiazepines is maintained within Schedule 4, and thus investigators have had no reason not to address benzodiazepines as a class. Furthermore, some drugs such as codeine are less problematic in North America, primarily due to a combination of cultural differences and accessibility of alternatives such as hydrocodone. Overall control of opioid abuse has been another key public health focus in North America and this has been the other focus for investigators; other areas have been relatively neglected by investigators in trying to manage the challenges which are greatest by volume.

This chapter will first address the assessment of PDMPs as a whole, and then look at assessments of benzodiazepines and opioids in turn. It has been supported by review of the peer-reviewed literature. In addition, attempts at contact were made to administrators of all PDMPs in the United States, as well as the PDMP Training and Technical Assistance Center (TTAC) at Brandeis University and the six Canadian provinces with available program contacts. The assistance of all corresponding colleagues is gratefully acknowledged.

7.1. How might we learn from the experience of other PDMPs?

Part of the difficulty in knowing whether a PDMP is effective in reducing any particular type of prescription medication related harm is the heterogeneity in the observed success of programs. An analysis of PDMPs published in 2014 compared the success of states with a PDMP between 1999-2008 versus those who did not, and attempted to adjust for year, geographic region, poisoning mortality rate from other substances, unemployment rate and medical examiner type. Of the states with a PDMP active during this time, the adjusted risk ratio for drug overdose mortality varied from 0.65 in Michigan to 3.37 in Nevada(4), a phenomenon that had previously been appreciated(5) and a phenomenon also observed in opioid dispensing(6). This heterogeneity may well be attributable to various methodological differences, but also different environments and additional supporting measures, especially given some states' PDMPs have been able to realise impressive benefit in management of monitored drugs (see Figure 7.1.1). It should be noted that subgroup analysis trended benefit to systems where the Department of Health governed versus the Board of Pharmacy, where statutory requirements for committee oversight were in place, where there were no laws explicitly excusing practitioners from expectation, and where there was statutory authority to monitor non-controlled substances. It has been noted in another overview study of all fifty states that increased legislative strength of a PDMP reduces opioid overdose deaths(7). These data would support the careful consideration of legislative and logistic design mechanisms in the implementation of any prescription monitoring program, but also illustrates how apparently subtle variations can underlie large differences in outcomes. While more in-depth discussion of this issue lies outside the scope of this report, it nevertheless is relevant to conceptually consider its effect on interpretation of the North American experience and its applicability here.

[redacted on public release]

Figure 7.1.1. Kentucky resident drug overdose deaths by drugs involved, before and after the implementation of a PDMP at the beginning of 2012. Deaths related to llicit and commonly diverted drugs increased in line with national trends, but deaths related to regulated drugs (including selected prescription opioids and alprazolam) decreased. In this time, gabapentin emerged as a significant threat (from 6 deaths to 53 deaths). Published in Data-Driven Multidisciplinary Approaches to Reduce
Prescription Drug Abuse in Kentucky: Second Action Team Meeting Data Update 2015(8).

First, the quantitative assessment of a PDMP's success is subject to many potential confounders. In the previously mentioned review, the adjusted risk ratio for drug overdose mortality was actually significantly higher in states with a PDMP implemented than those without (adjusted RR 1.11, (95% CI 1.02-1.21))(4). This is not incompatible with benefit from PDMP implementation: apart from the reasons potentially driving heterogeneity similarly being applicable, the trend of escalation in prescription medication abuse was not a temporally consistent one. Coordination with other initiatives and adequate health care professional training influence broad measures such as overdose mortality(2, 9); it has been speculated that when PDMPs are perceived to be mainly used for law enforcement purposes that drug users adopt riskier practices more prone to drug overdose-related death(10). In addition, while efforts can be made to adjust for potential confounders, as happened in this study, more subtle differences can act as significant confounders, not least of all the selection bias derived from states with emerging prescription medication abuse problems being more likely to adopt a PDMP, and states with an emerging problem with a specific drug being more likely to look to monitor it. In this way, it is hard to interpret data which derive from real life as if they came from a controlled experiment.

Secondly, it is important to consider possible flow-on effects in assessing success. Notably, from a previous generation of interventions in paper-based triplicate prescription programs, it was shown in New York in 1989 that an initiative to reduce benzodiazepine use succeeded by measures directly addressing benzodiazepine use but also led to a corresponding increase in alternative drugs (the substitution effect) which represented suboptimal therapy(11, 12), although it is likely that the reduction in benzodiazepines outweighed the substitution effect(13, 14). In addition, while it led to a reduction in benzodiazepine use in problematic users, it also led to a greater relative reduction in access to those non-problematic users(15), a probable consequence of prescribers becoming more reluctant to appropriately prescribe monitored or restricted drugs (the chilling effect), and may have precipitated unnecessary emergency psychiatric presentations(16), although these observations may be affected by confirmation bias. Implementation in this case was

particularly hampered by the mechanism of monitoring, which required that prescribers purchase and use dedicated triplicate prescription forms. Consideration of indirect consequences of regulation and its mechanisms should be therefore considered(17). This study illustrates not only the importance of the substitution effect, but the difficulty in assessing a program in its entirety of effect.

Thirdly, it is only recently that we have been able to start to appreciate the benefit of PDMPs as they become more widespread and supporting technology becomes effective, a key improvement from the New York triplicate prescription program experience. Successive US government initiatives have also stimulated the expansion of PDMPs to 49 of the 50 states in the US, as well as the District of Columbia and Guam. The Harold Rogers PDMP initiative and the National All Schedules Prescription Electronic Report Act have helped to financially support the growth of PDMPs(4) and this led to an intensive rollout of programs between 2010 and 2014. The impact of many of these have not yet been publicly documented, although some data is available from personal correspondence.

These limitations make it hard to apply every piece of available evidence as a direct precedent for success or otherwise of specific types of monitoring, however lessons can be learned from examining selected relevant examples.

7.2. Monitoring benzodiazepines

As detailed in the previous section of this chapter, a 1989 attempt during an earlier generation of prescription monitoring to monitor benzodiazepines in New York had mixed outcomes, and this remains a cautionary tale for monitoring implementation. Nevertheless, a number more contemporary examples of benzodiazepine monitoring may be more applicable to the potential impact of benzodiazepine monitoring in Australia.

One of the most pertinent examples of a co-ordinated intervention with a PDMP at its nidus is Florida. Florida had previously been one of the most problematic states for the illegal distribution of prescription drugs, and had seen a progressive escalation in prescription drug-related death, with a near doubling of the rate for overall prescription drugs between 2003 and 2009, and a benzodiazepine-related death rate which tripled in the same time period (see Figure 7.2.1). A number of interventions were subsequently initiated in a co-ordinated manner, including a PDMP, law enforcement tasks forces to target diverted prescription drugs, and improved regulation and practice standards for pain physicians, clinics and pharmacies. This intervention led to a dramatic reduction of benzodiazepine-related deaths, and while the majority of deaths were attributable to alprazolam, the next largest contributor, diazepam, similarly showed a marked reduction, with a one-third reduction in the year following the introduction of the PDMP(18) (see Figure 7.2.1). No other Australian Schedule 4 benzodiazepines were specifically recorded in this cohort as they were aggregated under ‘other benzodiazepines’, but they were regulated by the PDMP during this time and there is no mitigating reason why they would demonstrate an alternative trend, especially since similar cohorts have shown concordant reductions in prescribing within class for benzodiazepines(19). Data from the latest PDMP annual report from Florida has shown this trend to be a durable one (see Figure 7.2.2), although it should be noted full benefit was not

realised until at least two years after. In addition, deaths attributable to prescription drugs decreased without an increase in illicit drug or ethanol-related deaths that might suggest a substitution effect(20) (also see Figure 7.2.3). These successes correlate with overall improvements in other measures for this PDMP, including the multiple provider episode rate (i.e. 'doctor shopping' rate) (Figure 7.2.4). It should be noted that these improvements were from a precipitously poor baseline and there may be some element of regression to the mean, but conversely enacting change in this particularly challenging environment represented a substantial achievement. In addition, cuts to substance use disorder treatment services and the second worst funding for mental health of the fifty states has allowed for a later escalation in heroin and fentanyl deaths in 2015, although it remains one of only five states to have seen a reduction in overall drug (licit and illicit) drug-related deaths between 2010 and 2015(21). It is notable that all five of these states have active PDMP programs. Florida therefore provides a good example as to possible successes that might be realised over two to three years with a PDMP as part of a co-ordinated response despite a hostile pharmacotherapy environment.

It is worth contrasting this with another relevant experience from the United States. Investigators reviewed rates of emergency department presentations in eleven metropolitan areas in a number of states in the time after implementation, and did not find any improvement in the first three years, and in fact a mild but statistically significant detriment in the first year(22), and a similar phenomenon was noted with opioids by the same group(23). There are a number of reasons the authors cited why no effect might have been seen, but primary amongst them would be the limitations of the related PDMPs, including poor uptake in voluntary systems given the focus on opioids, the absence of real-time monitoring and the absence of effective feedback to prescribers. These differing experiences emphasise the need for an empowered PDMP with a co-ordinated, multifaceted approach.

[redacted from public release]

Figure 7.2.1. Mortality rates (deaths/100,000 population) for selected sedatives in Florida, before and after the 2011 implementation. It is notable that alprazolam, diazepam and benzodiazepines as a whole reduced after the implementation. Published in Lee et al.(18)

[redacted on public release]

Figure 7.2.2. Mortality rates for selected drugs (deaths/100,000 population) in Florida, before and after the 2011 implementation of a PDMP as part of a co-ordinated response (which included law enforcement targeting diversion, and improved regulation of pain clinics). There was a sharp escalation from under 2.0 deaths per 100,000 population in 2005 to above 8.0 in 2010, after which there was a decline in mortality down to less than 3.0 in 2015. Published in the E-FORSCE 2015-2016 PDMP Annual Report(24).

[redacted on public release]

Figure 7.2.3. Mortality rates (deaths/100,000 population) aggregated for prescription drugs, illicit drugs and ethanol, before and after the 2011 implementation. Prescription drug-related death decreased without increases in illicit drugs or ethanol. Published in Lee et al.(18)

[redacted on public release]

Figure 7.2.4. Rates of ‘doctor shopping’ in Florida since the implementation of its PDMP in September 2011 have progressively decreased. In the population aged 35-54, the multiple provider episodes per 100,000 population have decreased from over 18 in Q4 2011 to less than 3 in Q2 2016. Published in the E-FORSCE 2015-2016 PDMP Annual Report(24).

Two provinces in Canada have also published work regarding regulation of benzodiazepines. The rollout of a real-time prescription monitoring service in 1995 in British Columbia led to a near halving in inappropriate prescribing in patients receiving social assistance (see Figure 7.2.5) and in senior residents(25), both groups chosen because of the availability of data preceding the intervention but both groups also at risk of harm from inappropriate prescribing. Data from Ontario between 2007 and 2013 captured both legislative change and the introduction of a PDMP in quick succession (see Figure 7.2.6), and was also able to demonstrate a halving of inappropriate prescribing when publicly funded prescriptions were examined(26). Both of these studies showed a more pronounced effect for benzodiazepines than opioids and this may well reflect the ease of effectiveness in regulating this group as a class.

In summary, prominent examples of integrated solutions targeting benzodiazepine inappropriate prescribing, with prescription monitoring as a key component, have been shown to be effective but full effect may take time to realise and comprehensive support appears necessary to realise benefit.

[redacted from public release]

Figure 7.2.5. Rates of potentially inappropriate prescriptions in British Columbia as influenced by a multifaceted approach including a PDMP. Opioids, having been stable prior to the introduction of PharmaNet in 1995, dropped from over 3.5% of prescriptions down to 2.0% of prescriptions soon after. Similarly benzodiazepines had consistently made up over 1% of prescriptions prior to the introduction of PharmaNet and dropped to less than 0.5% soon after. This dramatic change was maintained over the following 24 moths. Published in Dormuth et al.(25)

[redacted from public release]

Figure 7.2.5. Rates of potentially inappropriate prescriptions in Ontario as influenced by a multifaceted approach including a PDMP. Opioid and stimulant use dropped dramatically after changes to legislation and the introduction of a monitoring system. Published in Gomes et al(26).

7.3. Monitoring opioids

Monitoring opioids has proven more problematic, and a number of reasons might contribute to that. Opioids vary in regulatory controls, spanning different schedules of the Controlled Substances Act in the United States, and are subject to greater pressure from diversion due to the pharmacological proximity of illicit opioids. As detailed in chapter 5, prescription opioids have been subject to increasing non-prescription abuse but oxycodone and now fentanyl in particular have become an emerging problem(27). In addition, the rise in opioid abuse in North America has been greater than that of benzodiazepines, and this escalation has proved challenging to manage from a public health perspective. Many data exist in this domain however few directly deal with Australian schedule 4 opioids. Propoxyphene has been removed from the US market, and codeine and tramadol are less utilised (see Figure 7.3.1.) in the face of alternatives such as hydrocodone (codeine is in fact one of the few opioids to have shown reduction over time in the US market prior to widespread PDMP rollout(28)). This report will address broad trends in this area but data may be less applicable to answering the research question underlying this report than that for benzodiazepines.

[redacted from public release]

Figure 7.3.1. Commonly prescribed controlled opioids and utilisation in New York state. The New York state PDMP real-time registry, I-STOP, took effect in February 2013 at the same time as up-scheduling of hydrocodone on the background of a multifaceted management program for opioid abuse. Tramadol was upscheduled and first monitored from this point forward. In the first two years of real-time monitoring, the number of doctor shoppers has dropped 82%. Overdose deaths are not yet available from this time period. Published in the New York State Opioid Poisoning, Overdose and Prevention 2015 Report(29).

The use of PDMPs in the United States has primarily focussed on opioids, and this has shown direct results. The implementation of any PDMP has led to fewer prescription opioid related admissions(28, 30), fewer poisons information calls about intentional poisoning(30), reductions in total opioid dispensing(6, 31) and reductions in multiple prescribers episodes without increasing heroin use or diverted prescription medicine use(32). Of note with the data supporting these benefits is that the magnitude is often relatively modest when analysed as a whole. While discussions about reductions in opioid-related deaths in specific circumstances occur(33), the mere presence of a PDMP in general is insufficient. It should be noted that the mere presence of legal restrictions is insufficient too(34, 35).

What appears to be the case is that the design of the PDMP impacts on its success. Overly burdensome programs lead to worse outcomes, as has been well documented with the dedicated authority prescriptions that California, New York and Texas had previously required(36-38), and the chilling effect can occur(39). At the same time, if and when programs are robust in terms of breadth, identifying suspicious prescribing, access to appropriate stakeholders and mandatory use, they are able to reduce opioid-related deaths(7, 40). Where provider review of the system was made mandatory, there was a 12% reduction in prescription opioid deaths(35) (see Figure 7.3.1), and in many ways this is unsurprising as when not mandatory, as in Maine, uptake is poor with only 56% of pharmacists self-reporting using the system(41). PDMPs should be targeted to realise benefit(42) and, if appropriately designed, need not lead to the chilling effect(43). Simple measures can go a long way – when emergency department providers were shown a chronic pain patient's PDMP data, 41% of the time they changed management(44) and they had increased confidence in prescribing appropriately(45) although such programs need to be supported by appropriate measures such as education(46), otherwise prescribing practice moves to suboptimal options just to circumvent difficulties(47). It also takes time for a PDMP to reach full effect(48). In short, just having a PDMP is not enough, but well-designed and well-supported PDMPs which are targeted, mandatory and are useful to clinicians can reduce opioid-related deaths.

[redacted from public release]

Figure 7.3.1. Changes in opioid prescribing and prescription opioid-related deaths in states with mandatory review requirements (where programs were largely introduced between end 2009 and mid 2012) vs comparison states. Both opioid prescribing rates and opioid related deaths reduced in states with both mandatory PDMP review and pain clinic laws implemented, but there was no change in comparison states. Published in Dowell et al.(35)

[redacted from public release]

Figure 7.3.2. Drug overdose deaths involving pharmaceutical opioids, Kentucky versus national US data. Kentucky introduced a PDMP in 2012. Prior to this, deaths had steadily climbed from 1.8 deaths/100,000 people in 2000 to 13.2 deaths/100,000 people in 2011. Following the PDMP introduction, deaths declined to 10.1 deaths/100,000 people in 2013. National US figures showed little change in the years before and after the introduction of a PDMP. Published in Data-Driven Multidisciplinary Approaches to Reduce Prescription Drug Abuse in Kentucky: Second Action Team Meeting Data Update(8).

The Florida experience once again illustrates the fine balance that needs to be struck. Florida's problem opioid at the time PDMPs were initiated was oxycodone(49), and this became the focus of their action. The number of prescriptions for and volume of opioids reduced(50), as did diversion(51). Mortality benefits were realised(52), probably by disproportionately affecting the high-risk prescribers(53), but possibly by the nature of this focus on high-risk prescribers, the reductions were only realised with oxycodone-related deaths and not with deaths associated with aggregated other prescription opioids(54). Overall the benefits were more modest in comparison to benzodiazepines(18), and may not have been solely the realisation of the PDMP.

In Canada, the benefits for monitoring opioids were similarly less than had been seen for benzodiazepines in British Columbia(25) (see Figure 7.2.5) and Ontario(26) (see Figure 7.2.6), although benefit was definite in both cases on a whole population basis. Despite this benefit in general populations, at risk populations such as street drug users and First Nations people failed to benefit as clearly, and opioid-related driving risks and neonatal morbidity remained a problem(55). Clearly a PDMP for opioids is insufficient in isolation and needs to be appropriately supported by programs, particularly relevant to at-risk subgroups whose benefit may not be synchronous with the overall population.

7.4. Discussion and conclusions from this chapter

While the depth of experience of PDMPs in North America is extensive, context is crucial and makes translation of results to the Victorian context challenging, and while few data from assessments of these programs have specifically examined Australian Schedule 4 medications, overall useful trends are evident. The most effective programs have been able to derive significant reductions in benzodiazepine-related overdose deaths without displacing harm elsewhere; these jurisdictions combined PDMPs with other programs to reduce drug harm, made appropriate adjustments regularly and were implemented with strong legislative backing and good logistic design. Programs without these factors, and without factors to anticipate substitution or chilling effects, have actually been associated with increased deaths, although causality is unclear. While there have been some successes for opioids demonstrated, context is particularly important and such programs must be carefully implemented.

Although there are many positive precedents for benzodiazepine control, and to a lesser extent with opioids, there are many other reasons why not all PDMPs have been successful and PDMPs have not demonstrated as convincing success with opioids or other prescription drugs. Assessments are rarely controlled and have fought an overall trend of escalating prescription drug abuse. PDMPs have previously usually only been very successful when a central part of an integrated multifaceted approach, and global endpoints in some assessments such as overdose deaths might not have recognised the benefit of a single intervention like a PDMP in isolation. Success for individual drugs in assessments may be lost in the overall context of harm, particularly when overall classes are being monitored. It should be noted that successful public health interventions less commonly have evidence of precedent in being introduced; the absence of evidence is not the evidence of absence, particularly when a jurisdiction faces challenges unique to it, and it is evident from the US experience that inaction is an active choice.

Chapter 8. Findings and discussion

While superficially it might appear to be a straightforward task, there are multiple intricacies surrounding collecting and interpreting information that might aid a truly informed decision as to what medications should be monitored on a real-time prescription monitoring system. Even if we determine that a RTPM system is in place primarily to reduce prescription medication-related morbidity and mortality, rather than monitoring trends or preventing diversion, how can we quantify and compare harm from the past to determine what tomorrow's threats will be? Given that overdose deaths are a coarse endpoint which can be affected by multiple factors, are slow to increase to emerging threats and can be hard to attribute causality to, but preventing them is the ultimate end goal, how do we measure previous harm? How can we determine the danger a drug poses when its data is collected as a class, or causes harm in combination (or is thought to), or is more or less commonly used than other drugs by higher or lower risk individuals? How can we learn lessons from other jurisdictions when their implementation and aims may be completely different, and their context inside and out of the health system is dramatically so? How do we anticipate the effect of one action on the whole system, to ensure the best decision might be made?

The answers, of course, are neither clear nor straightforward, but this report has attempted to address each intricacy in turn, and more than that, to provide the best quality information for a decision to be made. To do this, the authors have tried to furnish this report with the facts that might lead to appreciation of the process. For the prescription medication biologically plausible to cause harm, how do we separate its threat and its need to be monitored from any affective or observational bias? A threat to harm may follow a trajectory of evolution of harm: it might start as a trending threat elsewhere before those threats (or their related drugs) are episodically noted locally, and progress to cause increased ambulance callouts and increased poisons information centre calls before resulting in overdose deaths. This report has pursued the information relating to each of these steps, both information published and that kept in database repositories, in order to fairly illustrate the burden of harm from each drug, and the patterns that might continue into the future. Information is kept by multiple groups in multiple ways, and this report has tried to interpret the implications of the context of each dataset in order to relevantly explain the data. This report has corrected each dataset for supply, to best determine the given risk from any prescription medication. As best as possible has made this correction on a per prescription basis, because that represents not only the existing way our prescription medications are regulated but also the triggers for monitoring and moderating their use. Using these tools, we have built a profile of how we can understand the dangers each prescription medication poses.

Of course, this process is far from existing in a vacuum, and confounders can affect the results, but this report acknowledges them where possible. Even coroners focusing on a single case must make assumptions in interpreting the information they are presented with; even when forensic pharmacology is relevant, a drug may not be detected or misattributed on autopsy, and often contextually the cause is hard to determine as causal agents might look like 'innocent bystanders'. Furthermore, a death due to a medication may partially represent not just what that medication is, and how it is used, but the type of consumer that

is using it and their risk profile. This report has tried to determine where the limits of estimation might sit, to exclude the contribution of such situations, and where this is not possible, has discussed the ramifications.

The precedents overseas have served to highlight that each PDMP by nature should be different in order to address the threats that its setting faces. It has been instructive not only to look at the successes, the medications which they have benefited and the circumstances in which they have achieved that success, but also the failures and why that occurred, so that when we see failures, we do not dismiss a RTPM system for a medication on the basis of poor implementation elsewhere. In this, two related effects have proved important. The chilling effect occurs where prescribers avoid prescribing and sometimes make suboptimal changes in order to avoid or in response to increased regulation and surrounding scrutiny or a new perception of concern from a medication. The substitution effect (or 'squeezed balloon' effect) occurs if medications are regulated in an uncoordinated manner and harm is displaced to related medications. Clear examples exist, both with other PDMPs and with other local regulation, of how these effects can cause increased systemic harm. Both can be direct products of changes in regulation, their impact is partially predictable and understanding them is crucial to understanding why a medication should or shouldn't be regulated.

Benzodiazepines have been affected by this in the recent past in Australia. The rescheduling of alprazolam merely shifted use and harm to other benzodiazepines, and there is no pharmacological or practical reason to think this would not occur again in the future. While alprazolam was thought to be the most dangerous benzodiazepine, and demonstrates consistently high metrics of harm across the local databases and peer reviewed literature, it is not the only dangerous benzodiazepine. The impact of clonazepam has been well recognised overseas as a target of abuse, and perhaps has come to less attention here due to low levels of supply, but it has extremely high normalised metrics of harm across the local databases. Diazepam, oxazepam, nitrazepam, and lorazepam have all shown high normalised metrics of harm, harm that exists without combination with opioids, and there is no reason to think that a model of increased regulation of these benzodiazepines but not others, would not displace high-risk users and medication misuse and abuse to these other benzodiazepines, whose metrics have been hard to quantify. Temazepam has shown stable metrics of harm similar to other metrics but not only might these metrics be diluted due to prescribers using it as a first-line choice for low-risk users, but also there is no reason to think it might not be susceptible to the substitution (or 'squeezed balloon') effect, and that that might not deliver real harm. Furthermore, well implemented monitoring of benzodiazepines overseas, in combination with a multifaceted approach, has encouragingly led to marked improvements in overdose deaths. It therefore stands that the benzodiazepines either all have significant harm associated with them and warrant regulation of themselves, or are likely to cause harm if other benzodiazepines are regulated but they are not.

The z-drugs, while not having the popularity that they once looked like they might have, or have had internationally, appear culpable for a significant burden of harm. While private supply for zopiclone is at risk of being underestimated, in many datasets its rate of harm is

over ten times that of comparable drugs, meaning that its supply might need to be ten times underestimated in order to be reduced to a comparable rate of harm. Only zopiclone's supply has been able to be estimated, but there is no pharmacological or practical reason why zolpidem should be any different and the numerical values for both drugs are similar, not to mention that if zopiclone was regulated and zolpidem was not, it would be subject to the substitution (or 'squeezed balloon') effect, just as the z-drugs might also be if benzodiazepines are regulated. It therefore stands that the z-drugs as a class do confer significant harm as well as being likely to cause even further harm if alternatives are regulated but z-drugs are not.

There may be multiple factors involved in driving quetiapine-related harm, which has evolved over recent years and which seems to clearly exceed that of other antipsychotics like olanzapine and risperidone. This may well relate to its increased off-label use, or its pharmacological properties which mean it is preferred for abuse, the patterns of which are seen both locally and internationally. What it seems less likely to relate to is co-existence as an 'innocent bystander' with, or even putatively mitigating, fatal heroin or methamphetamine, as seen in with our data from mortality cohorts where the majority of quetiapine-related deaths do not involve heroin or methamphetamine. The harm from quetiapine is real, and while it has taken time to evolve in recent years, appears to be established, durable and an appropriate target of monitoring. Olanzapine and risperidone are distinct enough, both pharmacologically and in terms of impact from current harm, to be less susceptible to the substitution (or 'squeezed balloon') effect, although that it cannot be absolutely excluded to evolve in the future.

The assessment for the relevant harm of what currently represents Australian Schedule 4 codeine in its current regulatory context is far from simple, and in many ways it acts as a key example of the difficulties in estimating its harm, as illustrated in the text in Table 4.2.1. It is a commonly used drug, a commonly misused drug, and a reasonable total burden of harm exists as a consequence, particularly in the local peer-reviewed literature, although contextually codeine has not caused the same problems in North America, probably due to the presence of other more efficacious opioids with greater abuse potential, although results from the monitoring of opioids in North America have been less impressive than the results from the monitoring of benzodiazepines. It is likely that current regulatory mechanisms in Australia of Schedule 4 codeine, in particular pack size, help limit its normalised rates of harm, and it is in that context that codeine is examined by this report. Estimations of its harm proportionate to use are prone to multiple confounders, but there are factors which could both increase or decrease these estimations. This report's primary model represents what the authors feel are the best estimations of its harm, and on this basis its harm from the data examined seems no higher than that of the antidepressants examined in this study, although the authors would emphasise the limitations of this estimation. It also cannot be excluded that monitoring of Schedule 8 opioids might lead to the chilling effect and this might accentuate any substitution (or 'squeezed balloon') effect seen with codeine, but there are few data to support this.

Tramadol, the other commonly used Schedule 4 opioid, is one which clinicians have had an increased preference for in recent years. Estimations of its serotonin toxicity risk appear to

be overstated, and there is little in the international or local trends or the peer-reviewed literature to suggest that it is a drug of significant potential for harm. There is very little in the evidence from local databases to suggest otherwise, with low, steady normalised rates of harm across all metrics. An important question remains – is tramadol a drug which truly has low abuse potential, or is it spared because there is currently easier access to other opioids of high abuse potential, a situation which might change with monitoring of Schedule 8 opioids in an accentuation of the substitution (or 'squeezed balloon') effect? It is hard to truly determine this but not only does it seem pharmacologically plausible that it has low abuse potential, its very low current rates would suggest that harm would have to very dramatically increase in order to become concerning. Furthermore, amongst similar medications, it seems to be the least concerning, and it may in fact be a desirable outcome for use to be displaced to it. It therefore stands that there is little to support a need to monitor tramadol.

Purely by observing trends of total harm, it would be easy to assume that pregabalin poses a significant emerging threat. Ambulance calls have increased from an annualised rate of 14/year in 2011 to 336/year in 2016, poisons information calls have increased from 5 in 2009 to 204 in 2016, and while pregabalin was not routinely tested on autopsy until 2013, deaths caused by it doubled between 2013 and 2015. What is important is that supply over this time dramatically increased, with our estimations for Victorian overall supply going from 27,124 prescriptions in 2009 and 37,866 prescriptions in 2011 to 814,572 prescriptions in 2016, a clear consequence of inclusion on the PBS. On this basis, pregabalin has maintained stably low metrics of harm normalised for supply across the whole study period, across databases. Gabapentin, likely more popular in the United States than pregabalin due to cost and the absence of controlled substance scheduling, has been an emerging threat of concern in the US and had had slightly higher normalised rates of harm in the poisons information centre data, and an emerging but still low level risk in mortality databases. It still remains at low normalised rates of harm and there is no clear reason to suspect a dramatic escalation from here, although it remains of possible concern for the future.

In summary, benzodiazepines and z-drugs confer a significant burden of harm and, without a co-ordinated response, would be a significant risk to merely displace harm to other drugs within these groups rather than to dispel it. Quetiapine appears to represent a true and sustained source of harm markedly in excess of other antipsychotics and antidepressants. The harm from Schedule 4 codeine in the current regulatory environment seems to be somewhat mitigated although its estimation is subject to confounders. Other prescription medications examined did not demonstrate a large current direct threat to prescription medication-related harm. The precedents from North America suggest that, with effective implementation, a prescription monitoring program could reduce the harm that some of these Australian Schedule 4 medications pose and, while not sufficient to control overdose deaths by itself, is likely to be an important innovation if supported by a suite of related measures.

References

Chapter 1 references

1. Islam MM, McRae IS. An inevitable wave of prescription drug monitoring programs in the context of prescription opioids: pros, cons and tensions. BMC Pharmacol Toxicol. 2014;15:46.
2. Scheduling Policy Framework for Medicines and Chemicals. 2015.

Chapter 2 references

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Chapter 3 references

1. Scheduling Policy Framework for Medicines and Chemicals. 2015.
2. Schaffer AL, Buckley NA, Cairns R, Pearson SA. Interrupted time series analysis of the effect of rescheduling alprazolam in Australia: Taking control of prescription drug use. JAMA Intern Med. 2016;176(8):1223-5.
3. Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC Res Notes. 2015;8:634.
4. Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry. 2010;196(5):354-8.
5. Reith DM, Fountain J, McDowell R, Tilyard M. Comparison of the fatal toxicity index of zopiclone with benzodiazepines. J Toxicol Clin Toxicol. 2003;41(7):975-80.
6. Henry JA. A fatal toxicity index for antidepressant poisoning. Acta Psychiatr Scand Suppl. 1989;354:37-45.

Chapter 4 references

1. Buckley NA, Whyte IM, Dawson AH, Isbister GK. A prospective cohort study of trends in selfpoisoning, newcastle, Australia, 1987-2012: Plus ca change, plus c'est la meme chose. Med J Aust. 2015;202(8):438-43.
2. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. Br J Clin Pharmacol. 2014;78(5):1159-66.
3. Berecki-Gisolf J, Hassani-Mahmooei B, Clapperton A, McClure R. Prescription opioid dispensing and prescription opioid poisoning: Population data from Victoria, Australia 2006 to 2013. Aust N Z J Public Health. 2017;41(1):85-91.
4. Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, Nielsen S, et al. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. Med J Aust. 2015;203(7):299.e1-.e7.
5. Darke S, Torok M, Duflou J. Circumstances and toxicology of sudden or unnatural deaths involving alprazolam. Drug and Alcohol Dependence. 2014;138(1):61-6.
6. Degenhardt L, Bruno R, Ali R, Lintzeris N, Farrell M, Larance B. The introduction of a potentially abuse deterrent oxycodone formulation: Early findings from the Australian National Opioid Medications Abuse Deterrence (NOMAD) study. Drug and Alcohol Dependence. 2015;151:56-67.
7. Peacock A, Bruno R, Cama E, Kihas I, Larance B, Lintzeris N, et al. Jurisdictional differences in opioid use, other licit and illicit drug use, and harms associated with substance use among people who tamper with pharmaceutical opioids. Drug and alcohol review. 2015;34(6):611-22.
8. Nielsen S, Bruno R, Lintzeris N, Fischer J, Carruthers S, Stoove M. Pharmaceutical opioid analgesic and heroin dependence: How do treatment-seeking clients differ in Australia? Drug and Alcohol Review. 2011;30(3):291-9.
9. Nielsen S, Roxburgh A, Bruno R, Lintzeris N, Jefferson A, Degenhardt L. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002 to 2011. Drug Alcohol Depend. 2015;149:212-9.
10. Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clinical Toxicology. 2015;53(6):545-50.
11. Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving serotonergic drugs. Forensic Sci Int. 2010;198(1-3):110-7.
12. Garret PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesthesia and Intensive Care. 2004;32(4):575-7.

13. Nielsen S, Dietze P, Lee N, Dunlop A, Taylor D. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. Addiction (Abingdon, England). 2007;102(4):616-22.
14. Afshari R, Maxwell S, Dawson A, Bateman DN. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. Clinical Toxicology. 2005;43(4):255-9.
15. Afshari R, Good AM, Maxwell SR, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol. 2005;60(4):444-7.
16. FDA Drug Safety Communication: FDA recommends against the continued use of propoxyphene [press release]. US Food and Drug Administration, 19/11/2010 2010.
17. Anonymous. UK withdrawal of co-proxamol delivers poisoning mortality reduction. Australian Journal of Pharmacy. 2009;90(1074):78.
18. Buckley NA, Faunce TA. Trials and tribulations in the removal of dextropropoxyphene from the Australian register of therapeutic goods. Med J Aust. 2013;199(4):257-60.
19. Guidance for *Di-Gesic* and *Doloxene* dispensing: Pharmaceutical Society of Australia; 2014 [Available from: http://www.psa.org.au/downloads/ent/uploads/filebase/guidelines/member-only-guidelines/guidance-di-gesic%20and%20doloxene.pdf.
20. Lloyd BK, McElwee PR. Trends over time in characteristics of pharmaceutical drug-related ambulance attendances in Melbourne. Drug Alcohol Rev. 2011;30(3):271-80.
21. Hutton J, Dent A, Buykx P, Burgess S, Flander L, Dietze P. The characteristics of acute non-fatal medication-related events attended by ambulance services in the Melbourne Metropolitan Area 1998-2002. Drug Alcohol Rev. 2010;29(1):53-8.
22. Buykx P, Loxley W, Dietze P, Ritter A. Medications used in overdose and how they are acquired - an investigation of cases attending an inner Melbourne emergency department. Aust N Z J Public Health. 2010;34(4):401-4.
23. Rahman A, Martin C, Graudins A, Chapman R. Deliberate self-poisoning presenting to an emergency medicine network in South-East melbourne: a descriptive study. emerg. 2014;2014:461841.
24. Ch'ng CW, Fitzgerald M, Gerostamoulos J, Cameron P, Bui D, Drummer OH, et al. Drug use in motor vehicle drivers presenting to an Australian, adult major trauma centre. EMA - Emergency Medicine Australasia. 2007;19(4):359-65.
25. Lintzeris N, Rivas C, Monds LA, Leung S, Withall A, Draper B. Substance use, health status and service utilisation of older clients attending specialist drug and alcohol services. Drug Alcohol Rev. 2016;35(2):223-31.
26. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiology and Drug Safety. 2009;18(2):93-103.
27. Pillans P, Page CB, Ilango S, Kashchuk A, Isbister GK. Self-poisoning by older Australians: a cohort study. MJA. 2017;206(4):164-69.
28. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. Bmj. 2017;356:j760.
29. Monheit B, Pietrzak D, Hocking S. Prescription drug abuse - A timely update. Aust Fam Physician. 2016;45(12):862-6.
30. Dietze P, Jolley D, Fry C, Bammer G. Transient changes in behaviour lead to heroin overdose: Results from a case-crossover study of non-fatal overdose. Addiction (Abingdon, England). 2005;100(5):636-42.
31. Darke S, Ross J, Mills K, Teesson M, Williamson A, Havard A. Benzodiazepine use among heroin users: Baseline use, current use and clinical outcome. Drug and Alcohol Review. 2010;29(3):250-5.
32. Green JL, Besharat AC, Goodman EM, Bucher-Bartelson B, Wood DM, Dargan PI. Non-medical use of benzodiazepines and opioids: An online national survey in the United Kingdom. Pharmacoepidemiology and Drug Safety. 2015;24:377-8.
33. Winter R, Stoove M, Degenhardt L, Hellard M, Spelman T, Jenkinson R, et al. Incidence and predictors of non-fatal drug overdose after release from prison among people who inject drugs in Queensland, Australia. Drug and Alcohol Dependence. 2015;153:43-9.
34. Reynolds M, Fulde G, Hendry T. Trends in benzodiazepine abuse: 2007-2011. EMA - Emergency Medicine Australasia. 2013;25(2):199-200.
35. Schaffer A, Isometsa ET, Tondo L, Moreno DH, Sinyor M, Lars Vedel K, et al. Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Australian and New Zealand Journal of Psychiatry. 2015;49(9):785-802.
36. Lloyd B, Dwyer J, Bugeja L, Jamieson A. Alprazolam in fatal overdose following regulatory rescheduling: A response to Deacon et al. Int J Drug Policy. 2017;39:138-9.
37. Gunja N. The Clinical and Forensic Toxicology of Z-drugs. Journal of Medical Toxicology. 2013;9(2):155-62.
38. Olson LG. Hypnotic hazards: Adverse effects of zolpidem and other z-drugs. Australian Prescriber. 2008;31(6):146-9.
39. Darke S, Deady M, Duflou J. Toxicology and Characteristics of Deaths Involving Zolpidem in New South Wales, Australia 2001-2010. Journal of Forensic Sciences. 2012;57(5):1259-62.
40. Nasti JJ, Brakoulias V. Chronic baclofen abuse and withdrawal delirium. Australian and New Zealand Journal of Psychiatry. 2011;45(1):86-7.
41. Leung NY, Whyte IM, Isbister GK. Baclofen overdose: Defining the spectrum of toxicity. EMA - Emergency Medicine Australasia. 2006;18(1):77-82.
42. Isbister GK, Heppell SP, Page CB, Ryan NM. Adult clonidine overdose: prolonged bradycardia and central nervous system depression, but not severe toxicity. Clinical Toxicology. 2017;55(3):187-92.
43. Berling I, Buckley NA, Isbister GK. The antipsychotic story: Changes in prescriptions and overdose without better safety. British Journal of Clinical Pharmacology. 2016.
44. Hollingworth SA, Siskind DJ, Nissen LM, Robinson M, Hall WD. Patterns of antipsychotic medication use in Australia 2002-2007. Aust N Z J Psychiatry. 2010;44(4):372-7.

45. Heilbronn C, Lloyd B, McElwee P, Eade A, Lubman DI. Trends in quetiapine use and non-fatal quetiapine-related ambulance attendances. Drug and Alcohol Review. 2013;32(4):405-11.
46. Isbister GK, Duffull SB. Quetiapine overdose: predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal. Int Clin Psychopharmacol. 2009;24(4):174-80.
47. Garg V, Farah N. Quetiapine overdose. Australian and New Zealand Journal of Psychiatry. 2010;44(12):1144.
48. Alexander J. Delirium as a symptom of quetiapine poisoning. Aust N Z J Psychiatry. 2009;43(8):781.
49. Pilgrim JL, Drummer OH. The toxicology and comorbidities of fatal cases involving quetiapine. Forensic Sci Med Pathol. 2013;9(2):170-6.
50. Heilbronn CE, Lloyd B, McElwee P, Eade A, Lubman DI. Quetiapine-related harms are on the rise. Australian and New Zealand Journal of Psychiatry. 2012;46(3):279-80.
51. Reddel SE, Bruno R, Burns L, Kirwan A, Lokuge K, Dietze P. Prevalence and associations of quetiapine fumarate misuse among an Australian national city sample of people who regularly inject drugs. Addiction (Abingdon, England). 2014;109(2):295-302.
52. O'Connor N, Hunt GE, O'Hara-Aarons M, Hall A, Snars J, Storm V, et al. The Sydney mental health client mortality audit: What does it tell us and what are we to do? Australasian Psychiatry. 2014;22(2):154-9.
53. Spence D. Bad medicine: gabapentin and pregabalin. Bmj. 2013;347:f6747.
54. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017:1-24.
55. Darke S, Torok M, Duflou J. Contributory and incidental blood concentrations in deaths involving citalopram. Journal of forensic sciences. 2013;58(2):432-5.
56. Dudley M, Hadzi-Pavlovic D, Andrews D, Perich T. New-generation antidepressants, suicide and depressed adolescents: How should clinicians respond to changing evidence? Australian and New Zealand Journal of Psychiatry. 2008;42(6):456-66.
57. Gordon MS, Melvin GA. Do antidepressants make children and adolescents suicidal? Journal of Paediatrics and Child Health. 2014;50(11):847-54.
58. Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. Australasian Psychiatry. 2010;18(3):242-5.
59. Friedman RA. Antidepressants' black-box warning--10 years later. N Engl J Med. 2014;371(18):1666-8.
60. Wong A, Taylor DM, Ashby K, Robinson J. Changing epidemiology of intentional antidepressant drug overdose in Victoria, Australia. Australian and New Zealand Journal of Psychiatry. 2010;44(8):759-64.
61. Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry. 2010;196(5):354-8.
62. Hiremath M, Craig S, Graudins A. Adolescent deliberate self-poisoning in South-East Melbourne. EMA - Emergency Medicine Australasia. 2016;28(6):704-10.
63. Copeland J, Dillon P, Gascoigne M. Ecstasy and the concomitant use of pharmaceuticals. Addictive Behaviors. 2006;31(2):367-70.
64. van Gorp F, Whyte IM, Isbister GK. Clinical and ECG Effects of Escitalopram Overdose. Annals of emergency medicine. 2009;54(3):404-8.
65. Chan AN, Gunja N, Ryan CJ. A Comparison of Venlafaxine and SSRIs in Deliberate Self-poisoning. Journal of Medical Toxicology. 2010:1-6.
66. Pilgrim JL, Gerostamoulos D, Drummer OH. The prevalence of duloxetine in medico-legal death investigations in Victoria, Australia (2009-2012). Forensic Sci Int. 2014;234:165-73.
67. Cooper JM, Brown JA, Cairns R, Isbister GK. Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects. Clinical Toxicology. 2017;55(1):18-24.
68. Berling I, Isbister GK. Mirtazapine overdose is unlikely to cause major toxicity. Clin Toxicol (Phila). 2014;52(1):20-4.
69. Gillman PK. A systematic review of the serotonergic effects of Mirtazapine in humans: Implications for its dual action status. Hum. 2006;21(2):117-25.
70. Baird-Gunning J, Lea-Henry T, Hoegberg LC, Gosselin S, Roberts DM. Lithium Poisoning. J Intensive Care Med. 2016;11:11.
71. Downes MA, Whyte IM, Isbister GK. QTc abnormalities in deliberate self-poisoning with moclobemide. Internal Medicine Journal. 2005;35(7):388-91.
72. Gisev N, Nielsen S, Cama E, Larance B, Bruno R, Degenhardt L. An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia. Eur J Clin Pharmacol. 2016;72(4):469-94.
73. Lee SC, Klein-Schwartz W, Doyon S, Welsh C. Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. Drug and Alcohol Dependence. 2014;138:118-23.
74. Goldberger BA, Maxwell JC, Campbell A, Wilford BB. Uniform standards and case definitions for classifying opioid-related deaths: recommendations by a SAMHSA consensus panel. J Addict Dis. 2013;32(3):231-43.
75. Dwyer J. Coroners Prevention Unit Data Summary, Attachment to the Coroners finding into the death of Frank Edward Frood (2012 4080). Coroners Court of Victoria; 2016 16/03/2016.
76. Dwyer J, Ogeil RP, Bugeja L, Heilbronn C, Lloyd B. Victorian Overdose Deaths: The Role of Pharmaceutical Drugs and Drug Combinations. Turning Point; 2016.

Chapter 5 references

1. Licata SC, Rowlett JK. Abuse and dependence liability of benzodiazepine-type drugs: GABA A receptor modulation and beyond. Pharmacology Biochemistry and Behavior. 2008;90(1):74-89.
2. Reynolds M, Fulde G, Hendry T. Trends in benzodiazepine abuse: 2007-2011. EMA - Emergency Medicine Australasia. 2013;25(2):199-200.
3. Buykx P, Loxley W, Dietze P, Ritter A. Medications used in overdose and how they are acquired - an investigation of cases attending an inner Melbourne emergency department. Aust N Z J Public Health. 2010;34(4):401-4.
4. Best D, Wilson A, Reed M, Lloyd B, Eade A, Lubman DI. Alprazolam and wider benzodiazepine misuse in Australia -- sources of supply and evidence of harms. Aust N Z J Psychiatry. 2013;47(1):94-5.
5. Nielsen S, Bruno R, Degenhardt L, Stoove MA, Fischer JA, Carruthers SJ, et al. The sources of pharmaceuticals for problematic users of benzodiazepines and prescription opioids. Med J Aust. 2013;199(10):696-9.
6. Chu M, Gerostamoulos D, Beyer J, Rodda L, Boorman M, Drummer OH. The incidence of drugs of impairment in oral fluid from random roadside testing. Forensic Sci Int. 2012;215(1-3):28-31.
7. Darke S, Ross J, Mills K, Teesson M, Williamson A, Havard A. Benzodiazepine use among heroin users: Baseline use, current use and clinical outcome. Drug and Alcohol Review. 2010;29(3):250-5.
8. Darke S, Torok M, Duflou J. Circumstances and toxicology of sudden or unnatural deaths involving alprazolam. Drug and Alcohol Dependence. 2014;138:61-6.
9. Albrecht B, Staiger PK, Best D, Hall K, Nielsen S, Lubman DI, et al. Benzodiazepine use of community-based violent offenders: a preliminary investigation. Journal of Substance Use. 2016:1-9.
10. Rosas-Gutierrez I, Simon-Arceo K, Mercado F. Cellular and molecular mechanism of the benzodiazepines addiction. Salud Mental. 2013;36(4):325-9.
11. Marienfeld CB, Tek E, Diaz E, Schottenfeld R, Chawarski M. Psychiatrist decision-making towards prescribing benzodiazepines: The dilemma with substance abusers. Psychiatric Quarterly. 2012;83(4):521-9.
12. Green JL, Besharat AC, Goodman EM, Bucher-Bartelson B, Wood DM, Dargan PI. Non-medical use of benzodiazepines and opioids: An online national survey in the United Kingdom. Pharmacoepidemiology and Drug Safety. 2015;24:377-8.
13. Pauly V, Pradel V, Pourcel L, Nordmann S, Frauger E, Lapeyre-Mestre M, et al. Estimated magnitude of diversion and abuse of opioids relative to benzodiazepines in France. Drug and Alcohol Dependence. 2012;126(1-2):13-20.
14. Sundstrom M, Pelander A, Simojoki K, Ojanpera I. Patterns of drug abuse among drug users with regular and irregular attendance for treatment as detected by comprehensive UHPLC-HR-TOF-MS. Drug Testing and Analysis. 2016;8(1):39-46.
15. Weaver MF. Prescription sedative misuse and abuse. Yale Journal of Biology and Medicine. 2015;88(3):247-56.
16. Okumura Y, Shimizu S, Matsumoto T. Prevalence, prescribed quantities, and trajectory of multiple prescriber episodes for benzodiazepines: A 2-year cohort study. Drug and Alcohol Dependence. 2016;158:118-25.
17. Joe KH, Seo JS. The problems of prescription drug abuse in Korea and taking actions to overcome. Alcohol and Alcoholism. 2014;49:i3.
18. Flovig JC, Vaaler AE, Morken G. Substance use at admission to an acute psychiatric department. Nord J Psychiatry. 2009;63(2):113-9.
19. Kurtz SP, Buttram ME, Surratt HL. Benzodiazepine Dependence among Young Adult Participants in the Club Scene Who Use Drugs. J Psychoactive Drugs. 2016:1-8.
20. Kurtz SP, Surratt HL, Levi-Minzi MA, Mooss A. Benzodiazepine dependence among multidrug users in the club scene. Drug and Alcohol Dependence. 2011;119(1-2):99-105.
21. Murphy KD, Byrne S, McCarthy S, Lambert S, Sahm LJ. Benzodiazepine use among young attendees of an Irish substance treatment center. J Addict Med. 2014;8(3):199-204.
22. O'Brien C P. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry. 2005;66 Suppl 2:28-33.
23. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine Use, Misuse, and Harm at the Population Level in Canada: A Comprehensive Narrative Review of Data and Developments Since 1995. Clinical Drug Investigation. 2016;36(7):519-30.
24. Hidalgo RB, Sheehan DV. Benzodiazepines risk, abuse, and dependence: A tsunami in a tea cup. Psychiatry. 2009;6(12):13-4.
25. Bharadwaj RS. The complex clinical picture of benzodiazepine misuse. Gen Hosp Psychiatry. 2014;36(4):e5-e6.
26. Hay G, Gannon M. Capture-recapture estimates of the local and national prevalence of problem drug use in Scotland. International Journal of Drug Policy. 2006;17(3):203-10.
27. Boeuf O, Lapeyre-Mestre M, French Network of Centers for E, Information P. Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. Drug Safety. 2007;30(3):265-76.
28. Konopka A, Pelka-Wysiecka J, Grzywacz A, Samochowiec J. Psychosocial characteristics of benzodiazepine addicts compared to not addicted benzodiazepine users. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2013;40(1):229-35.
29. Guina J, Nahhas RW, Goldberg AJ, Farnsworth S. PTSD symptom severities, interpersonal traumas, and benzodiazepines are associated with substance-related problems in trauma patients. Journal of Clinical Medicine. 2016;5(8).
30. Schneider R, Jr., Ottoni GL, de Carvalho HW, Elisabetsky E, Lara DR. Temperament and character traits associated with the use of alcohol, cannabis, cocaine, benzodiazepines, and hallucinogens: Evidence from a large Brazilian web survey. Revista Brasileira de Psiquiatria. 2015;37(1):31-9.
31. McCabe SE, West BT. Medical and nonmedical use of prescription benzodiazepine anxiolytics among U.S. high school seniors. Addictive Behaviors. 2014;39(5):959-64.
32. McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: Results from a national survey of U.S. college students. Drug and Alcohol Dependence. 2005;79(1):53-62.
33. Rigg KK, Ford JA. The misuse of benzodiazepines among adolescents: Psychosocial risk factors in a national sample. Drug and Alcohol Dependence. 2014;137:137-42.
34. Khanal P, Ghimire RH, Gautam B, Dhungana SK, Parajuli P, Jaiswal AK, et al. Substance use among medical students in Kathmandu valley. Jnm. 2010;50(180):267-72.

35. Murphy K, Sahm L, McCarthy S, Lambert S, Byrne S. Substance use in young persons in Ireland, a systematic review. Addictive Behaviors. 2013;38(8):2392-401.
36. Stone AM, Merlo LJ. Attitudes of college students toward mental illness stigma and the misuse of psychiatric medications. J Clin Psychiatry. 2011;72(2):134-9.
37. Paredes NP, Miasso AI, Tirapelli CR. Consumption of benzodiazepines without prescription among first-year nursing students at the University of Guayaquil, school of nursing, Ecuador. Revista Latino-Americana de Enfermagem. 2008;16 Spec No:634-9.
38. Raitasalo K, Holmila M, Autti-Ramo I, Martikainen JE, Sorvala V-M, Makela P. Benzodiazepine use among mothers of small children: A register-based cohort study. Addiction (Abingdon, England). 2015;110(4):636-43.
39. Lovett A. The emerging problem of prescription drugs and the pregnant woman. Journal of Paediatrics and Child Health. 2012;48:6.
40. Woo BK, Chen W. Substance misuse among older patients in psychiatric emergency service. Gen Hosp Psychiatry. 2010;32(1):99-101.
41. Maree RD, Marcum ZA, Saghafi E, Weiner DK, Karp JF. A Systematic Review of Opioid and Benzodiazepine Misuse in Older Adults. American Journal of Geriatric Psychiatry. 2016;24(11):949-63.
42. Landreat MG, Vigneau CV, Hardouin JB, Bronnec MG, Marais M, Venisse JL, et al. Can we say that seniors are addicted to benzodiazepines? Substance Use & Misuse. 2010;45(12):1988-99.
43. Heberlein A, Buchl R, Groschl M, Kornhuber J, Bleich S, Hillemacher T, et al. Alterations in pain perception during benzodiazepine withdrawal: A case series. J Clin Psychopharmacol. 2010;30(6):743-5.
44. Lader M. Benzodiazepine harm: how can it be reduced? Br J Clin Pharmacol. 2014;77(2):295-301.
45. McConnell JG. Benzodiazepine tolerance, dependency, and withdrawal syndromes and interactions with fluoroquinolone antimicrobials. British Journal of General Practice. 2008;58(550):365-6.
46. Lader M. Benzodiazepines revisited--will we ever learn? Addiction (Abingdon, England). 2011;106(12):2086-109.
47. Manthey L, Lohbeck M, Giltay EJ, van Veena T, Zitman FG, Penninx BW. Correlates of benzodiazepine dependence in the Netherlands study of depression and anxiety. Addiction (Abingdon, England). 2012;107(12):2173-82.
48. Alvarenga JM, Loyola Filho AI, Firmo JO, Lima-Costa MF, Uchoa E. Prevalence and sociodemographic characteristics associated with benzodiazepines use among community dwelling older adults: the Bambui Health and Aging Study (BHAS). Revista Brasileira de Psiquiatria. 2008;30(1):7-11.
49. Willems IA, Gorgels WJ, Voshaar RC, Mulder J, Lucassen PL. Tolerance to benzodiazepines among long-term users in primary care. Family Practice. 2013;30(4):404-10.
50. Matsumoto T, Ozaki S, Kobayashi O, Wada K. Current situation and clinical characteristics of sedative-related disorder patients in Japan: Comparison with methamphetamine-related disorder patients. Activitas Nervosa Superior. 2015;57(1):12-28.
51. Ashton H. The diagnosis and management of benzodiazepine dependence. Current Opinion in Psychiatry. 2005;18(3):249-55.
52. Murakoshi A, Takausu Y, Komada Y, Ishikawa J, Inoue Y. Factors associated with development of benzodiazepine dependence. Sleep Medicine. 2013;14:e216.
53. Liebrenz M, Gehring M-T, Buadze A, Caflisch C. High-dose benzodiazepine dependence: A qualitative study of patients' perception on cessation and withdrawal. BMC Psychiatry Vol 15 2015, ArtID 116. 2015;15.
54. Liebrenz M, Schneider M, Buadze A, Gehring MT, Dube A, Caflisch C. High-Dose Benzodiazepine Dependence: A Qualitative Study of Patients' Perceptions on Initiation, Reasons for Use, and Obtainment. PLoS ONE. 2015;10(11):e0142057.
55. Gopalan P, Glance JB, Azzam PN. Managing benzodiazepine withdrawal during pregnancy: Case-based guidelines. Archives of Women's Mental Health. 2014;17(2):167-70.
56. Murakoshi A, Takaesu Y, Komada Y, Ishikawa J, Inoue Y. Prevalence and associated factors of hypnotics dependence among Japanese outpatients with psychiatric disorders. Psychiatry Research. 2015;230(3):958-63.
57. Schallemberger JB, Colet CF. Assessment of dependence and anxiety among benzodiazepine users in a provincial municipality in Rio Grande do sul, Brazil. Trends in Psychiatry and Psychotherapy. 2016;38(2):63-70.
58. Dong Y, Winslow M, Chan YH, Subramaniam M, Whelan G. Benzodiazepine dependence in Singapore. Substance Use & Misuse. 2007;42(8):1345-52.
59. Mehdi T. Benzodiazepines revisited. British Journal of Medical Practitioners. 2012;5(1).
60. Ribeiro CS, Azevedo RCS, da Silva VF, Botega NJ. Chronic use of diazepam in primary healthcare centers: User profile and usage pattern. Sao Paulo Medical Journal. 2007;125(5):270-4.
61. Janhsen K, Roser P, Hoffmann K. The problems of long-term treatment with benzodiazepines and related substances. Dtsch. 2015;112(1-2):1-7.
62. Kurko TA, Saastamoinen LK, Tahkapaa S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - a systematic review of register-based studies. Eur Psychiatry. 2015;30(8):1037-47.
63. Morel A, Grall-Bronnec M, Bulteau S, Chauvin-Grelier P, Gailledrat L, Pinot ML, et al. Benzodiazepine dependence in subjects with alcohol use disorders: what prevalence? Expert Opin Drug Saf. 2016;15(10):1313-9.
64. Gerardin M, Victorri-Vigneau C, Guerlais M, Guillou-Landreat M, Grall-Bronnec M, Jolliet P. Benzodiazepines consumption: Does dependence vary with age? Substance Use & Misuse. 2014;49(11):1417-25.
65. Fresan A, Minaya O, Cortes-Lopez JL, Ugalde O. Demographic and clinical features related to benzodiazepine dependence in psychiatric patients. Salud Mental. 2011;34(2):103-9.
66. Fujii K, Uchida H, Suzuki T, Mimura M. Dependence on benzodiazepines in patients with panic disorder: A cross-sectional study. Psychiatry and Clinical Neurosciences. 2015;69(2):93-9.
67. Guerlais M, Grall-Bronnec M, Feuillet F, Gerardin M, Jolliet P, Victorri-Vigneau C. Dependence on prescription benzodiazepines and z-drugs among young to middle-aged patients in France. Substance Use & Misuse. 2015;50(3):320-7.

68. Sobow T, Kisiela E, Kloszewska I. Depression in the elderly and benzodiazepines abuse and dependence. Psychogeriatria Polska. 2006;3(4):183-90.
69. Hartz I, Tverdal A, Skille E, Skurtveit S. Disability pension as predictor of later use of benzodiazepines among benzodiazepine users. Social Science & Medicine. 2010;70(6):921-5.
70. Voyer P, Preeville M, Martin LS, Roussel M-E, Beeland S-G, Berbiche D. Factors associated with self-rated benzodiazepine addiction among community-dwelling seniors. Journal of Addictions Nursing. 2011;22(1-2):46-56.
71. Voyer P, Preville M, Roussel M-E, Berbiche D, Beland S-G. Factors associated with benzodiazepine dependence among community-dwelling seniors. Journal of Community Health Nursing. 2009;26(3):101-13.
72. Kan CC. Identifying risk factors for benzodiazepine dependence. Directions in Psychiatry. 2008;28(4):305-14.
73. Voyer P, Preville M. Insomnia and benzodiazepine dependency among older adults. Geriatrics and Aging. 2007;10(6):369-75.
74. Mueller TI, Pagano ME, Rodriguez BF, Bruce SE, Stout RL, Keller MB. Long-Term Use of Benzodiazepines in Participants with Comorbid Anxiety and Alcohol Use Disorders. Alcoholism: Clinical and Experimental Research. 2005;29(8):1411-8.
75. Hermos JA, Young MM, Lawler EV, Rosenbloom D, Fiore LD. Long-term, high-dose benzodiazepine prescriptions in veteran patients with PTSD: Influence of preexisting alcoholism and drug-abuse diagnoses. Journal of Traumatic Stress. 2007;20(5):909-14.
76. Voyer P, Cappeliez P, Perodeau G, Preville M. Mental health for older adults and Benzodiazepine use. Journal of Community Health Nursing. 2005;22(4):213-29.
77. Johannessen A. Older peoples' narratives of use and misuse of alcohol and psychotropic drugs among older people. International Psychogeriatrics. 2015;27:S24.
78. Canham SL, Gallo J, Simoni-Wastila L. Perceptions of benzodiazepine dependence among women age 65 and older. Journal of Gerontological Social Work. 2014;57(8):872-88.
79. Fang SY, Chen CY, Chang IS, Wu ECH, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: A population-based study. Drug and Alcohol Dependence. 2009;104(1-2):140-6.
80. Culberson JW, Ticker RL, Burnett J, Marcus MT, Pickens SL, Dyer CB. Prescription medication use among self neglecting elderly. Journal of Addictions Nursing. 2011;22(1-2):63-8.
81. Chandler A, Whittaker A, Williams N, McGorm K, Cunningham-Burley S, Mathews G. Mother's little helper? Contrasting accounts of benzodiazepine and methadone use among drug-dependent parents in the UK. Drugs: Education, Prevention & Policy. 2014;21(6):470-5.
82. Aguilera P, Garrido M, Lessard E, Swanson J, Mallon WK, Saldias F, et al. Medication Overdoses at a Public Emergency Department in Santiago, Chile. West J Emerg Med. 2016;17(1):75-80.
83. Reis AD, Figlie NB, Laranjeira R. Prevalence of substance use among trauma patients treated in a Brazilian emergency room. Revista Brasileira de Psiquiatria. 2006;28(3):191-5.
84. Shih HI, Lin MC, Lin CC, Hsu HC, Lee HL, Chi CH, et al. Benzodiazepine therapy in psychiatric outpatients is associated with deliberate self-poisoning events at emergency departments-a population-based nested case-control study. Psychopharmacology (Berl). 2013;229(4):665-71.
85. Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes. Drug and Alcohol Dependence. 2013;132(3):580-6.
86. Price JW. Benzodiazepines and workplace safety: An examination of postaccident urine drug tests. J Addict Med. 2014;8(5):333-7.
87. Price JW. Comparison of random and postaccident urine drug tests in Southern Indiana coal miners. J Addict Med. 2012;6(4):253-7.
88. Chan YC, Tse ML, Lau FL. Hong kong poison information centre: Annual report 2009. Hong Kong Journal of Emergency Medicine. 2011;18(4):221-31.
89. Chan YC, Tse ML, Lau FL. Hong Kong Poison Information Centre: Annual report 2013. Hong Kong Journal of Emergency Medicine. 2014;21(4):249-59.
90. Coutinho D, Vieira DN, Teixeira HM. Driving under the influence of benzodiazepines and antidepressants prescription and abuse. Acta Medica Portuguesa. 2011;24(3):431-8.
91. Rapoport MJ, Lanctot KL, Streiner DL, Bedard M, Vingilis E, Murray B, et al. Benzodiazepine use and driving: a meta-analysis. J Clin Psychiatry. 2009;70(5):663-73.
92. Breitenbach TC, Pechansky F, Benzano D, De Boni R. High rates of injured motorcycle drivers in emergency rooms and the association with substance use in Porto Alegre, Brazil. Emerg Med J. 2012;29(3):205-7.
93. Chowaniec C, Rygol K, Kobek M, Albert M. Medicines and psychoactive agents in traffic users - The medico-legal problem in Poland. Forensic Sci Int. 2005;147(SUPPL.):S53-S5.
94. Mravcik V, Vorel F, Zabransky T. Drugs and fatal traffic accidents in the Czech Republic. Cent Eur J Public Health. 2007;15(4):158-62.
95. Senna MC, Augsburger M, Aebi B, Briellmann TA, Donze N, Dubugnon JL, et al. First nationwide study on driving under the influence of drugs in Switzerland. Forensic Sci Int. 2010;198(1-3):11-6.
96. Webster M, Staton-Tindall M, Leukefeld C, Havens JR, Oser CB, Harp KLH. Impaired driving histories among rural female drug-involved offenders. Drug and Alcohol Dependence. 2015;146:e18.
97. Holmgren A, Holmgren P, Kugelberg FC, Jones AW, Ahlner J. Predominance of illicit drugs and poly-drug use among drug-impaired drivers in Sweden. Traffic Injury Prevention. 2007;8(4):361-7.
98. Karjalainen K, Lintonen T, Impinen A, Lillsunde P, Makela P, Rahkonen O, et al. Socio-economic determinants of drugged driving--a register-based study. Addiction (Abingdon, England). 2011;106(8):1448-59.
99. Impinen A, Rahkonen O, Karjalainen K, Lintonen T, Lillsunde P, Ostamo A. Substance use as a predictor of driving under the influence (DUI) rearrests. a 15-year retrospective study. Traffic Injury Prevention. 2009;10(3):220-6.
100. Scherer M, Harrell P, Romano E. Marijuana and Other Substance Use Among Motor Vehicle Operators: A Latent Class Analysis. J Stud Alcohol. 2015;76(6):916-23.

101. Hojsted J, Ekholm O, Kurita GP, Juel K, Sjogren P. Addictive behaviors related to opioid use for chronic pain: A population-based study. Pain. 2013;154(12):2677-83.
102. Mazer-Amirshahi M, Dorazio J, Mullins P, Van Den Anker J, Perrone J, Nelson L. Concomitant use of opioid analgesics and benzodiazepines in U.S. Ambulatory clinics and emergency departments. Clinical Toxicology. 2014;52 (7):704.
103. Jones AW, Holmgren A, Ahlner J. Heroin poisoning deaths with 6-acetylmorphine in blood: Demographics of the victims, previous drug-related offences, polydrug use, and free morphine concentrations in femoral blood. Forensic Toxicology. 2012;30(1):19-24.
104. Stein MD, Kanabar M, Anderson BJ, Lembke A, Bailey GL. Reasons for Benzodiazepine use Among Persons Seeking Opioid Detoxification. J Subst Abuse Treat. 2016;68:57-61.
105. Fatseas M, Lavie E, Denis C, Auriacombe M. Self-perceived motivation for benzodiazepine use and behavior related to benzodiazepine use among opiate-dependent patients. J Subst Abuse Treat. 2009;37(4):407-11.
106. Vogel M, Knopfli B, Schmid O, Prica M, Strasser J, Prieto L, et al. Treatment or "high": benzodiazepine use in patients on injectable heroin or oral opioids. Addictive Behaviors. 2013;38(10):2477-84.
107. Sun EC, Dixit A, Humphreys K, Darnell B D, Baker L C, Redlich S M. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. Bmj. 2017;356:760.
108. Park TW, Nelson K, Xuan Z, Lasser KE, Liebschutz JM, Saitz R. The association between benzodiazepine prescription and aberrant drug behaviors in primary care patients receiving chronic opioid therapy. Drug and Alcohol Dependence. 2015;146:e61-e2.
109. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. Bmj. 2015;350:h2698.
110. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. Journal of Pharmacy Practice. 2014;27(1):5-16.
111. Petrushevska T, Jakovski Z, Poposka V, Stefanovska VV. Drug-related deaths between 2002 and 2013 with accent to methadone and benzodiazepines. Journal of Forensic and Legal Medicine. 2015;31:12-8.
112. Jones CM, McAninch JK. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. American Journal of Preventive Medicine. 2015;49(4):493-501.
113. Hull MJ, Juhascik M, Mazur F, Flomenbaum MA, Behonick GS. Fatalities associated with fentanyl and co-administered cocaine or opiates. Journal of Forensic Sciences. 2007;52(6):1383-8.
114. Camenga DR, Gaither JR, Leventhal J, Ryan S. Increasing incidence of hospital admissions for opioid poisonings in adolescents and young adults: 2000-2009. Drug and Alcohol Dependence. 2015;146:e237.
115. Wolf BC, Lavezzi WA, Sullivan LM, Flannagan LM. One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. Journal of Forensic Sciences. 2005;50(1):192-5.
116. Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. The American Journal on Addictions. 2009;18(1):5-14.
117. Dilokthornsakul P, Moore G, Campbell JD, Lodge R, Traugott C, Zerzan J, et al. Risk factors of prescription opioid overdose among Colorado medicaid beneficiaries. Journal of Pain. 2016;17(4):436-43.
118. Bradvik L, Hulenvik P, Frank A, Medvedeo A, Berglund M. Self-reported and observed heroin overdoses in Malmoe. Journal of Substance Use. 2007;12(2):119-26.
119. Cannon R, Bozeman M, Miller KR, Smith JW, Harbrecht B, Franklin G, et al. The prevalence and impact of prescription controlled substance use among injured patients at a Level I trauma center. Journal of Trauma and Acute Care Surgery. 2014;76(1):172-5.
120. Lavie E, Fatseas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: Correlates of use, abuse and dependence. Drug and Alcohol Dependence. 2009;99(1-3):338-44.
121. Chen KW, Berger CC, Forde DP, D'Adamo C, Weintraub E, Gandhi D. Benzodiazepine use and misuse among patients in a methadone program. BMC Psychiatry Vol 11 2011, ArtID 90. 2011;11.
122. Backmund M, Meyer K, Henkel C, Soyka M, Reimer J, Schutz CG. Co-consumption of benzodiazepines in heroin users, methadone-substituted and codeine-substituted patients. Journal of Addictive Diseases. 2005;24(4):17-29.
123. Lee SC, Klein-Schwartz W, Doyon S, Welsh C. Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. Drug and Alcohol Dependence. 2014;138:118-23.
124. Musshoff F, Trafkowski J, Lichtermann D, Madea B. Comparison of urine results concerning co-consumption of illicit heroin and other drugs in heroin and methadone maintenance programs. International journal of legal medicine. 2010;124(5):499-503.
125. Peles E, Schreiber S, Adelson M. Deleterious effects of benzodiazepine abuse among methadone maintenance treatment patients. Heroin Addiction and Related Clinical Problems. 2014;16(4):63-70.
126. Lintzeris N, Mitchell TB, Bond A, Nestor L, Strang J. Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. J Clin Psychopharmacol. 2006;26(3):274-83.
127. Giacomuzzi SM, Ertl M, Pavlic M, Libiseller K, Riemer Y, Kemmler G, et al. Maintenance treatment of opioid dependence and patterns of non-prescribed drug use: Results of a 4-year trial. Letters in Drug Design and Discovery. 2006;3(10):731-40.
128. Mijatovic V, Dickov A, Petkovic S, Popov T, Samojlik I. Safety assessment of low doses of methadone in combination with benzodiazepines in real occasions during methadone maintenance treatment-a pilot study. Clinical Therapeutics. 2013;1):e30.
129. Moitra E, Anderson BJ, Stein MD. Perceived stress and substance use in methadone-maintained smokers. Drug Alcohol Depend. 2013;133(2):785-8.
130. Apantaku-Olajide T, Ducray K, Byrne P, Smyth BP. Perception of unmet needs and association with benzodiazepine misuse among patients on a methadone maintenance treatment programme. Psychiatrist. 2012;36(5):169-74.
131. Vogel M, Dursteler-MacFarland KM, Walter M, Strasser J, Fehr S, Prieto L, et al. Prolonged use of benzodiazepines is associated with childhood trauma in opioid-maintained patients. Drug and Alcohol Dependence. 2011;119(1-2):93-8.

132. Peles E, Schreiber S, Adelson M. Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. European Neuropsychopharmacology. 2009;19(8):581-8.
133. Specka M, Bonnet U, Heilmann M, Schifano F, Scherbaum N. Longitudinal patterns of benzodiazepine consumption in a German cohort of methadone maintenance treatment patients. Human Psychopharmacology: Clinical and Experimental. 2011;26(6):404-11.
134. Walton GRT, Hayashi K, Bach P, Dong H, Kerr T, Ahamad K, et al. The impact of benzodiazepine use on mortality among polysubstance users in Vancouver, Canada. Public Health Rep. 2016;131(3):491-9.
135. Narongchai P, Narongchai S, Thampituk S. The incidence of drug abuse in unnatural deaths in Northern Thailand. Journal of the Medical Association of Thailand. 2007;90(1):137-42.
136. Yen CF, Yang YH, Ko CH, Yen JY. Substance initiation sequences among Taiwanese adolescents using methamphetamine. Psychiatry Clin Neurosci. 2005;59(6):683-9.
137. Bogstrand ST, Middelkoop G, Christophersen AS. Trends in amphetamine and benzodiazepine use among drivers arrested for drug impaired driving in Norway 2000-2009. Norsk Epidemiologi. 2011;21(1):61-6.
138. Jones CM, Paulozzi LJ, Mack KA, Centers for Disease C, Prevention. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths - United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(40):881-5.
139. Eizadi-Mood N, Sabzghabaee AM, Saghaei M, Gheshlaghi F, Mohammad-Ebrahimi B. Benzodiazepines co-ingestion in reducing tricyclic antidepressant toxicity. Med Arh. 2012;66(1):49-52.
140. Peles E, Schreiber S, Adelson M. Tricyclic antidepressants abuse, with or without benzodiazepines abuse, in former heroin addicts currently in methadone maintenance treatment (MMT). European Neuropsychopharmacology. 2008;18(3):188-93.
141. Scherer M, Voas RB, Furr-Holden D. Marijuana as a predictor of concurrent substance use among motor vehicle operators. J Psychoactive Drugs. 2013;45(3):211-7.
142. McAuley A, Hecht G, Barnsdale L, Thomson CS, Graham L, Priyadarshi S, et al. Mortality related to novel psychoactive substances in Scotland, 2012: An exploratory study. International Journal of Drug Policy. 2015;26(5):461-7.
143. Bernstein MH, McSheffrey SN, van den Berg JJ, Vela JE, Stein LAR, Roberts MB, et al. The association between impulsivity and alcohol/drug use among prison inmates. Addictive Behaviors. 2015;42:140-3.
144. Crane CA, Schlauch RC, Devine S, Easton CJ. Comorbid substance use diagnoses and partner violence among offenders receiving pharmacotherapy for opioid dependence. Journal of Addictive Diseases. 2016;35(3):205-11.
145. Rouve N, Bagheri H, Telmon N, Pathak A, Franchitto N, Schmitt L, et al. Prescribed drugs and violence: A case/noncase study in the French PharmacoVigilance Database. Eur J Clin Pharmacol. 2011;67(11):1189-98.
146. Ickowicz S, Hayashi K, Dong H, Milloy MJ, Kerr T, Montaner JSG, et al. Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting. Drug and Alcohol Dependence. 2015;155:190-4.
147. Partanen TA, Vikatmaa P, Tukiainen E, Lepantalo M, Vuola J. Outcome after Injections of Crushed Tablets in Intravenous Drug Abusers in the Helsinki University Central Hospital. European Journal of Vascular and Endovascular Surgery. 2009;37(6):704-11.
148. Tucker D, Hayashi K, Milloy MJ, Nolan S, Dong H, Kerr T, et al. Risk factors associated with benzodiazepine use among people who inject drugs in an urban Canadian setting. Addictive Behaviors. 2016;52:103-7.
149. Federico A, Tamburin S, Maier A, Faccini M, Casari R, Morbioli L, et al. Multifocal cognitive dysfunction in high-dose benzodiazepine users: a cross-sectional study. Neurological Sciences. 2016:1-6.
150. Mazza M, Losurdo A, Testani E, Marano G, Di Nicola M, Dittoni S, et al. Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. J Clin Sleep Med. 2014;10(1):35-42.
151. Lund IO, Skurtveit S, Engeland A, Furu K, Ravndal E, Handal M. Prescription drug use among pregnant women in opioid Maintenance Treatment. Addiction (Abingdon, England). 2013;108(2):367-76.
152. Lugoboni F, Mirijello A, Faccini M, Casari R, Cossari A, Musi G, et al. Quality of life in a cohort of high-dose benzodiazepine dependent patients. Drug Alcohol Depend. 2014;142:105-9.
153. Tamburin S, Federico A, Faccini M, Casari R, Morbioli L, Sartore V, et al. Determinants of quality of life in high-dose benzodiazepine misusers. International Journal of Environmental Research and Public Health. 2017;14 (1) (no pagination)(38).
154. Turner BJ, Liang Y. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. Journal of General Internal Medicine. 2015;30(8):1081-96.
155. Okumura Y, Tachimori H, Matsumoto T, Nishi D. Exposure to psychotropic medications prior to overdose: A case-control study. Psychopharmacology (Berl). 2015;232(16):3101-9.
156. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. Am J Public Health. 2016;106(4):686-8.
157. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. J Clin Psychiatry. 2010;71(4):491-6.
158. Tjagvad C, Skurtveit S, Bramness JG, Gjersing L, Gossop M, Clausen T. Misuse of prescription drugs and overdose deaths. Journal of Substance Use. 2016;21(5):515-20.
159. Sgarlato A, deRoux SJ. Prescription opioid related deaths in New York City: a 2 year retrospective analysis prior to the introduction of the New York State I-STOP law. Forensic science, medicine, and pathology. 2015;11(3):388-94.
160. Chan GM, Stajic M, Marker EK, Hoffman RS, Nelson LS. Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: analysis of medical examiner data. Acad Emerg Med. 2006;13(5):543-7.
161. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiology and Drug Safety. 2009;18(2):93-103.
162. Bertol E, Mari F, Boscolo Berto R, Mannaioni G, Vaiano F, Favretto D. A mixed MDPV and benzodiazepine intoxication in a chronic drug abuser: determination of MDPV metabolites by LC-HRMS and discussion of the case. Forensic Sci Int. 2014;243:149-55.

163. Lee D, Delcher C, Maldonado-Molina MM, Bazydlo LAL, Thogmartin JR, Goldberger BA. Trends in licit and illicit drug-related deaths in Florida from 2001 to 2012. Forensic Sci Int. 2014;245:178-86.
164. Pillans P, Page CB, Ilango S, Kashchuk A, Isbister GK. Self-poisoning by older Australians: a cohort study. MJA. 2017;206(4):164-69.
165. Riley E, Hahn JA, Evans JL, Briceno A, Davidson PJ, Lum PJ, et al. The longitudinal influence of multiple depressant use on nonfatal overdose among young people who inject drugs. Drug and Alcohol Dependence. 2015;156:e190.
166. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, et al. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug Alcohol Depend. 2007;87(1):39-45.
167. Verwey B, Muntendam A, Ensing K, Essink G, Pasker-de Jong PC, Willekens FL, et al. Clinically relevant anterograde amnesia and its relationship with blood levels of benzodiazepines in suicide attempters who took an overdose. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(1):47-53.
168. Baranchuk A, Simpson CS, Methot M, Gibson K, Strum D. Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines. Can J Cardiol. 2008;24(7):e38-40.
169. Lam SM, Lau AC, Yan WW. Over 8 years experience on severe acute poisoning requiring intensive care in Hong Kong, China. Hum Exp Toxicol. 2010;29(9):757-65.
170. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: A conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry. 2005;66(SUPPL. 9):31-41.
171. Tarasoff G, Osti K. Black-market value of antipsychotics, antidepressants, and hypnotics in Las Vegas, Nevada. The American Journal of Psychiatry. 2007;164(2):350.
172. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor shopping' as an indicator. CNS Drugs. 2010;24(7):611-20.
173. Frauger E, Amaslidou D, Giocanti A, Braunstein D, Boucherie Q, Thirion X, et al. Which psychoactive prescription drugs are illegally obtained and through which ways of acquisition? Main trends since 2008 through the national program OPPIDUM. Fundamental and Clinical Pharmacology. 2015;29:28.
174. Kapil V, Green J, Le Lait C, Wood D, Dargan P. Misuse of benzodiazepines and Z-drugs in the UK. The British Journal of Psychiatry. 2014;205(5):407-8.
175. Chan WL, Wood DM, Dargan PI. Misuse of prescription and over-the-counter medicines in South London nightclubs. Journal of Substance Use. 2016;21(5):495-500.
176. Babakhanian M, Sadeghi M, Mansoori N, Mehrjerdi ZA, Tabatabai M. Nonmedical abuse of benzodiazepines in opiate-dependent patients in Tehran, Iran. Iranian Journal of Psychiatry and Behavioral Sciences. 2012;6(1):62-7.
177. Frauger E, Moracchini C, Albertini F, Thirion X, Micallef J. French specific surveillance system for drug abuse. International Journal of Mental Health. 2014;43(3):49-62.
178. Kanyoni M, Gishoma D, Ndahindwa V. Prevalence of psychoactive substance use among youth in Rwanda. BMC Res Notes. 2015;8:190.
179. Labat L, Fontaine B, Delzenne C, Doublet A, Marek MC, Tellier D, et al. Prevalence of psychoactive substances in truck drivers in the Nord-Pas-de-Calais region (France). Forensic Sci Int. 2008;174(2-3):90-4.
180. Naqvi H, Hussan S, Dossa F. Benzodiazepine: Slow sand of addiction. Journal of the Pakistan Medical Association. 2009;59(6):415-7.
181. Ojha SP, Sigdel S, Meyer-Thompson H-G, Oechsler H, Verthein U. 'South Asian cocktail'-The concurrent use of opioids, benzodiazepines and antihistamines among injecting drug users in Nepal and associations with HIV risk behaviour. Harm Reduction Journal Vol 11 2014, ArtID 17. 2014;11.
182. Fields MD, Abate MA, Hu L, Long DL, Blommel ML, Haikal NA, et al. Parent and Metabolite Opioid Drug Concentrations in Unintentional Deaths Involving Opioid and Benzodiazepine Combinations. Journal of Forensic Sciences. 2015;60(4):950-6.
183. Lai SH, Yao YJ, Lo DST. A survey of buprenorphine related deaths in Singapore. Forensic Sci Int. 2006;162(1-3):80-6.
184. Mijatovic V, Samojlik I, Ajdukovic N, Durendic-Brenesel M, Petkovic S. Methadone-related deaths-Epidemiological, pathohistological, and toxicological traits in 10-year retrospective study in Vojvodina, Serbia. Journal of Forensic Sciences. 2014;59(5):1280-5.
185. Black DL, Cawthon B, Robert T, Moser F, Caplan YH, Cone EJ. Multiple drug ingestion by ecstasy abusers in the United States. J Anal Toxicol. 2009;33(3):143-7.
186. Kurtz SP, Inciardi JA, Surratt HL, Cottler L. Prescription drug abuse among ecstasy users in Miami. Journal of Addictive Diseases. 2005;24(4):1-16.
187. Blencowe T, Raaska K, Lillsunde P. Benzodiazepines and sedative-hypnotics in blood of drivers under the influence and their association with other common illegal drug use and national sales figures. Ther Drug Monit. 2011;33(1):64-71.
188. Augsburger M, Donze N, Menetrey A, Brossard C, Sporkert F, Giroud C, et al. Concentration of drugs in blood of suspected impaired drivers. Forensic Sci Int. 2005;153(1):11-5.
189. Burch HJ, Clarke EJ, Hubbard AM, Scott-Ham M. Concentrations of drugs determined in blood samples collected from suspected drugged drivers in England and Wales. Journal of Forensic and Legal Medicine. 2013;20(4):278-89.
190. Kim E, Choe S, Lee J, Jang M, Choi H, Chung H. Detection of drugs in 275 alcohol-positive blood samples of Korean drivers. Forensic Sci Int. 2016;265:186-92.
191. Jones AW. Driving under the influence of drugs in Sweden with zero concentration limits in blood for controlled substances. Traffic Injury Prevention. 2005;6(4):317-22.
192. Christophersen AS, Morland J. Frequent detection of benzodiazepines in drugged drivers in Norway. Traffic Injury Prevention. 2008;9(2):98-104.
193. Tjaderborn M, Jonsson AK, Sandstrom TZ, Ahlner J, Hagg S. Non-prescribed use of psychoactive prescription drugs among drug-impaired drivers in Sweden. Drug and Alcohol Dependence. 2016;161:77-85.
194. Gjerde H, Christophersen AS, Normann PT, Assum T, Oiestad EL, Morland J. Norwegian roadside survey of alcohol and drug use by drivers (2008-2009). Traffic Injury Prevention. 2013;14(5):443-52.

195. Schwilke EW, Sampaio dos Santos MI, Logan BK. Changing patterns of drug and alcohol use in fatally injured drivers in Washington State. Journal of Forensic Sciences. 2006;51(5):1191-8.
196. Ahlner J, Holmgren A, Jones AW. Demographics and post-mortem toxicology findings in deaths among people arrested multiple times for use of illicit drugs and/or impaired driving. Forensic Sci Int. 2016;265:138-43.
197. Hall AJ, Bixler D, Helmkamp JC, Kraner JC, Kaplan JA. Fatal all-terrain vehicle crashes: injury types and alcohol use. American Journal of Preventive Medicine. 2009;36(4):311-6.
198. Wiese Simonsen K, Steentoft A, Bernhoft IM, Hels T, Rasmussen BS, Linnet K. Psychoactive substances in seriously injured drivers in Denmark. Forensic Sci Int. 2013;224(1-3):44-50.
199. Kim E, Park Y, Ha H, Chung H. Patterns of drugs & poisons in southern area of South Korea in 2014. Forensic Sci Int. 2016;269:50-5.
200. Jones AW, Holmgren A, Ahlner J. Toxicology findings in suicides: Concentrations of ethanol and other drugs in femoral blood in victims of hanging and poisoning in relation to age and gender of the deceased. Journal of Forensic and Legal Medicine. 2013;20(7):842-7.
201. Vukcevic NP, Ercegovic GV, Segrt Z, Djordjevic S, Stosic JJ. Benzodiazepine poisoning in elderly. Vojnosanit Pregl. 2016;73(3):234-8.
202. Rupasinghe J, Jasinarachchi M. Progressive encephalopathy with cerebral oedema and infarctions associated with valproate and diazepam overdose. Journal of Clinical Neuroscience. 2011;18(5):710-1.
203. Peranantham S, Manigandan G, Tamilselvi V, Shanmugam K. Fatal case of diazepam and paraquat poisoning - A case report. Medico-Legal Update. 2015;15(1):6-8.
204. Bird SM, Robertson J. Toxicology of Scotland's drugs-related deaths in 2000-2007: Presence of heroin, methadone, diazepam and alcohol by sex, age-group and era. Addiction Research & Theory. 2011;19(2):170-8.
205. Jones KA, Nielsen S, Bruno R, Frei M, Lubman DI. Benzodiazepines - Their role in aggression and why GPs should prescribe with caution. Aust Fam Physician. 2011;40(11):862-5.
206. Forsyth AJM, Khan F, McKinlay B. Diazepam, alcohol use and violence among male young offenders: 'The devil's mixture'. Drugs: Education, Prevention & Policy. 2011;18(6):468-76.
207. Neale G, Smith AJ. Self-harm and suicide associated with benzodiazepine usage. British Journal of General Practice. 2007;57(538):407-8.
208. Scott-Ham M, Burton FC. Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. Journal of Clinical Forensic Medicine. 2005;12(4):175-86.
209. Hagemann CT, Helland A, Spigset O, Espnes KA, Ormstad K, Schei B. Ethanol and drug findings in women consulting a Sexual Assault Center--associations with clinical characteristics and suspicions of drug-facilitated sexual assault. J Forensic Leg Med. 2013;20(6):777-84.
210. Martin M, Vanichseni S, Suntharasamai P, Mock PA, van Griensven F, Pitisuttithum P, et al. Drug use and the risk of HIV infection amongst injection drug users participating in an HIV vaccine trial in Bangkok, 1999-2003. International Journal of Drug Policy. 2010;21(4):296-301.
211. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir study, Thailand. PLoS ONE. 2011;6 (9) (no pagination)(e25127).
212. Werb D, Hayashi K, Fairbairn N, Kaplan K, Suwannawong P, Lai C, et al. Drug use patterns among Thai illicit drug injectors amidst increased police presence. Substance abuse treatment, prevention, and policy. 2009;4:16.
213. Fairbairn N, Hayashi K, Kaplan K, Suwannawong P, Qi J, Wood E, et al. Factors associated with methadone treatment among injection drug users in Bangkok, Thailand. J Subst Abuse Treat. 2012;43(1):108-13.
214. Ti L, Hayashi K, Kaplan K, Suwannawong P, Wood E, Kerr T. Groin injecting among a community-recruited sample of people who inject drugs in Thailand. Substance Abuse Treatment, Prevention, and Policy Vol 9 2014, ArtID 4. 2014;9.
215. Vanichseni S, Martin M, Suntharasamai P, Sangkum U, Mock PA, Gvetadze RJ, et al. High Mortality Among Non-HIV-Infected People Who Inject Drugs in Bangkok, Thailand, 2005-2012. Am J Public Health. 2015;105(6):1136-41.
216. Kerr T, Kiatying-Angsulee N, Fairbairn N, Hayashi K, Suwannawong P, Kaplan K, et al. High rates of midazolam injection among drug users in Bangkok, Thailand. Harm Reduction Journal Vol 7 2010, ArtID 7. 2010;7.
217. Hayashi K, Suwannawong P, Ti L, Kaplan K, Wood E, Kerr T. High rates of midazolam injection and associated harms in Bangkok, Thailand. Addiction (Abingdon, England). 2013;108(5):944-52.
218. Lefrancois E, Esseiva P, Gervasoni JP, Lucia S, Zobel F, Augsburger M. Analysis of residual content of used syringes collected from low threshold facilities in Lausanne, Switzerland. Forensic Sci Int. 2016;266:534-40.
219. Braun IM, Tavares H, de Nucci G, Bernik M. Abuse liability of intra-nasal midazolam in inhaled-cocaine abusers. European Neuropsychopharmacology. 2008;18(10):723-8.
220. Colucci AP, Gagliano-Candela R, Aventaggiato L, De Donno A, Leonardi S, Strisciullo G, et al. Suicide by Self-Administration of a Drug Mixture (Propofol, Midazolam, and Zolpidem) in an Anesthesiologist: The First Case Report in Italy. Journal of Forensic Sciences. 2013;58(3):837-41.
221. Bruce RD, Govindasamy S, Sylla L, Haddad MS, Kamarulzaman A, Altice FL. Case series of buprenorphine injectors in Kuala Lumpur, Malaysia. American Journal of Drug and Alcohol Abuse. 2008;34(4):511-7.
222. Ng WL, Mythily S, Song G, Chan YH, Winslow M. Concomitant use of midazolam and buprenorphine and its implications among drug users in Singapore. Annals of the Academy of Medicine Singapore. 2007;36(9):774-7.
223. Prybylski D, Manopaiboon C, Visavakum P, Yongvanitjit K, Aramrattana A, Manomaipiboon P, et al. Diverse HIV epidemics among people who inject drugs in Thailand: Evidence from respondent-driven sampling surveys in Bangkok and Chiang Mai. Drug and Alcohol Dependence. 2015;148:126-35.
224. Voon P, Hayashi K, Ti L, Kaplan K, Suwannawong P, Wood E, et al. High prevalence of syringe lending among HIV-positive people who inject drugs in Bangkok, Thailand. Harm Reduction Journal. 2015;12 (1) (no pagination)(16).
225. Frauger E, Moracchini C, Le Boisselier R, Braunstein D, Thirion X, Micallef J, et al. OPPIDUM surveillance program: 20 years of information on drug abuse in France. Fundam Clin Pharmacol. 2013;27(6):672-82.
226. Hoiseth G, Middelkoop G, Morland J, Gjerde H. Has previous abuse of flunitrazepam been replaced by clonazepam? Eur Addict Res. 2015;21(4):217-21.

227. Rasson S, Mete D. Clonazepam abuse and anxiety disorder. Comparative study in young Creole prisoners in Reunion island in 2011. Alcoologie et Addictologie. 2015;37(2):115-23.
228. Rasson S, Mete D, Simon N. Clonazepam misuse does not impact upon penal issues: A comparative study in adult male Creole convicts on Reunion Island in 2011. Alcoologie et Addictologie. 2013;35(1):7-15.
229. Frauger E, Pauly V, Thirion X, Natali F, Pradel V, Reggio P, et al. Estimation of clonazepam abuse liability: A new method using a reimbursed drug database. Int Clin Psychopharmacol. 2009;24(6):318-24.
230. England R, Dholakia N, Tukmachi E, Murphy De Souza T, Moss B, Ovaisi S. Replace clonazepam with an alternative antiepileptic drug to reduce drug misuse. Bmj. 2012;345:e7809.
231. Frauger E, Pauly V, Pradel V, Rouby F, Arditti J, Thirion X, et al. Evidence of clonazepam abuse liability: results of the tools developed by the French Centers for Evaluation and Information on Pharmacodependence (CEIP) network. Fundam Clin Pharmacol. 2011;25(5):633-41.
232. Pauly V, Frauger E, Pradel V, Nordmann S, Pourcel L, Natali F, et al. Monitoring of benzodiazepine diversion using a multi-indicator approach. Int Clin Psychopharmacol. 2011;26(5):268-77.
233. Chen CY, Shiah IS, Lee WK, Kuo SC, Huang CC, Wang TY. Dependence on quetiapine in combination with zolpidem and clonazepam in bipolar depression. Psychiatry and Clinical Neurosciences. 2009;63(3):427-8.
234. Mowla A, Firoozabadi A, Haghighi AB, Sahraian A. Megadose clonazepam dependence: A case report [20]. J Clin Psychopharmacol. 2007;27(5):542-3.
235. Arroyo Plasencia AM, Ballentine LM, Mowry JB, Kao LW. Benzodiazepine-associated atrioventricular block. American Journal of Therapeutics. 2012;19(1):e48-e52.
236. Huston B, Mills K, Froloff V, McGee M. Bladder rupture after intentional medication overdose. Am J Forensic Med Pathol. 2012;33(2):184-5.
237. Rajkumar AP, Jebaraj P, Tharyan P. Multi-drug overdose risperidone, ziprasidone, valproate, trihexyphenidyl, and clonazepam. J Assoc Physicians India. 2007;55:146-8.
238. Menchetti M, Gozzi BF, Saracino MA, Mercolini L, Petio C, Raggi MA. Non-fatal overdose of duloxetine in combination with other antidepressants and benzodiazepines. World J Biol Psychiatry. 2009;10(4 Pt 2):385-9.
239. Schindler EAD, Tirado-Morales DJ, Kushon D. Clonidine abuse in a methadone-maintained, clonazepam-abusing patient. J Addict Med. 2013;7(3):218-9.
240. Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. Am J Addict. 2015;24(2):173-7.
241. Bogstrand ST, Gjerde H. Which drugs are associated with highest risk for being arrested for driving under the influence? A case-control study. Forensic Sci Int. 2014;240:21-8.
242. Fride Tvete I, Bjorner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. Scand J Prim Health Care. 2015;33(4):252-9.
243. Howland RH. Safety and abuse liability of oxazepam: Is this benzodiazepine drug underutilized? Journal of Psychosocial Nursing and Mental Health Services. 2016;54(4):22-5.
244. Uzun S, Kozumplik O. Reinforcement of irritability during therapy with benzodiazepines. Psychiatria Danubina. 2011;23(1):129-30.
245. Filter ER, Gorczynski L, Fernandes JR. Fatal intoxication with a selective serotonin reuptake inhibitor, lorazepam, and codeine. Am J Forensic Med Pathol. 2007;28(4):361-3.
246. Palmentier JPFP, Warren R, Gorczynski LY. Alcohol and drugs in suspected impaired drivers in Ontario from 2001 to 2005. Journal of Forensic and Legal Medicine. 2009;16(8):444-8.
247. Dwyer R. Privileging pleasure: Temazepam injection in a heroin marketplace. International Journal of Drug Policy. 2008;19(5):367-74.
248. Uhlmann C, Froscher W. Low risk of development of substance dependence for barbiturates and clobazam prescribed as antiepileptic drugs: Results from a questionnaire study. CNS Neuroscience & Therapeutics. 2009;15(1):24-31.
249. Pelissier-Alicot AL, Piercecchi-Marti MD, Bartoli C, Kuhlmann E, Coiffait PE, Sanvoisin A, et al. Abusive prescription of psychostimulants: A study of two cases. Journal of Forensic Sciences. 2006;51(2):407-10.
250. Wainstein L, Victorri-Vigneau C, Sebille V, Hardouin JB, Feuillet F, Pivette J, et al. Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis. Int Clin Psychopharmacol. 2011;26(1):54-62.
251. Lapeyre-Mestre M, Gony M, Carvajal A, Macias D, Conforti A, D'Incau P, et al. A European community pharmacy-based survey to investigate patterns of prescription fraud through identification of falsified prescriptions. Eur Addict Res. 2014;20(4):9.
252. Quaglio G, Pattaro C, Gerra G, Mathewson S, Verbanck P, Des Jarlais DC, et al. High dose benzodiazepine dependence: Description of 29 patients treated with flumazenil infusion and stabilised with clonazepam. Psychiatry Research. 2012;198(3):457-62.
253. Bastide A, De Codt A, Monhonval P, Bongaerts X, Tecco JM. Megadose bromazepam dependence. Psychiatria Danubina. 2016;28:154-8.
254. Lakhal K, Pallancher S, Mathieu-Daude JC, Harry P, Capdevila X. Protracted deep coma after bromazepam poisoning. Int J Clin Pharmacol Ther. 2010;48(1):79-83.
255. Heilbronn C, Lloyd B, McElwee P, Eade A, Lubman DI. Trends in quetiapine use and non-fatal quetiapine-related ambulance attendances. Drug and Alcohol Review. 2013;32(4):405-11.
256. Reddel SE, Bruno R, Burns L, Kirwan A, Lokuge K, Dietze P. Prevalence and associations of quetiapine fumarate misuse among an Australian national city sample of people who regularly inject drugs. Addiction (Abingdon, England). 2014;109(2):295-302.
257. Erdogan S. Quetiapine in substance use disorders, abuse and dependence possibility: A review. Turk Psikiyatri Derg. 2010;21(2):167-75.
258. Fischer BA, Boggs DL. The role of antihistaminic effects in the misuse of quetiapine: A case report and review of the literature. Neuroscience and Biobehavioral Reviews. 2010;34(4):555-8.
259. George M, Haasz M, Coronado A, Salhanick S, Korbel L, Kitzmiller JP. Acute dyskinesia, myoclonus, and akathisa in an adolescent male abusing quetiapine via nasal insufflation: a case study. BMC Pediatr. 2013;13:187.
260. Haridas A, Kushon D, Gurmu S, Oluwabusi O. Smoking quetiapine: A "maq ball"? Primary Psychiatry. 2010;17(9):38-9.

261. Hussain MZ, Waheed W, Hussain S. Intravenous quetiapine abuse [2]. Am J Psychiatry. 2005;162(9):1755-6.
262. Morin AK. Possible intranasal quetiapine misuse. Am J Health-Syst Pharm. 2007;64(7):723-5.
263. Waters BM, Joshi KG. Intravenous quetiapine-cocaine use ("Q-ball") [8]. Am J Psychiatry. 2007;164(1):173-4.
264. Reccoppa L. Less abuse potential with XR formulation of quetiapine? Am J Addict. 2011;20(2):178.
265. Sansone RA, Sansone LA. Is seroquel developing and illicit reputation for misuse/abuse? Innovations in Clinical Neuroscience. 2010;7(1):13-6.
266. Chen CY, Shiah IS, Lee WK, Kuo SC, Huang CC, Wang TY. Dependence on quetiapine in combination with zolpidem and clonazepam in bipolar depression. Psychiatry Clin Neurosci. 2009;63(3):427-8.
267. Cubala WJ, Springer J. Quetiapine abuse and dependence in psychiatric patients: A systematic review of 25 case reports in the literature. Journal of Substance Use. 2014;19(5):388-93.
268. Keltner NL, Vance DE. Biological perspectives: Incarcerated care and quetiapine abuse. Perspect Psychiatr Care. 2008;44(3):202-6.
269. Murphy D, Bailey K, Stone M, Wirshing WC. Addictive potential of quetiapine. Am J Psychiatry. 2008;165(7):918.
270. Paparrigopoulos T, Karaiskos D, Liappas J. Quetiapine: Another drug with potential for misuse? A case report. J Clin Psychiatry. 2008;69(1):162-3.
271. Reeves RR, Brister JC. Additional evidence of the abuse potential of quetiapine. South Med J. 2007;100(8):834-6.
272. Klein-Schwartz W, Schwartz EK, Anderson BD. Evaluation of quetiapine abuse and misuse reported to poison centers. J Addict Med. 2014;8(3):195-8.
273. Tcheremissine OV. Is quetiapine a drug of abuse? Reexamining the issue of addiction. Expert Opin Drug Saf. 2008;7(6):739-48.
274. Pinta ER, Taylor RE. Quetiapine addiction? [9]. Am J Psychiatry. 2007;164(1):174-5.
275. Tamburello AC, Lieberman JA, Baum RM, Reeves R. Successful removal of quetiapine from a correctional formulary. J Am Acad Psychiatry Law. 2012;40(4):502-8.
276. Kolli V, Mary H, Garcia-Delgar B, Coffey BJ. Quetiapine Addiction in an Adolescent. J Child Adolesc Psychopharmacol. 2016;26(2):174-6.
277. Srivastava A, Patil V, Da Silva Pereira Y. A case series of quetiapine addiction/dependence. German Journal of Psychiatry. 2013;16(4):152-5.
278. Teran A, Majadas S, Galan J. Quetiapine in the treatment of sleep disturbances associated with addictive conditions: a retrospective study. Substance Use & Misuse. 2008;43(14):2169-71.
279. Yargic I, Caferov C. Quetiapine dependence and withdrawal: a case report. Subst Abus. 2011;32(3):168-9.
280. McLarnon ME, Fulton HG, MacIsaac C, Barrett SP. Characteristics of quetiapine misuse among clients of a community-based methadone maintenance program. J Clin Psychopharmacol. 2012;32(5):721-3.
281. Malekshahi T, Tioleco N, Ahmed N, Campbell AN, Haller D. Misuse of atypical antipsychotics in conjunction with alcohol and other drugs of abuse. J Subst Abuse Treat. 2015;48(1):8-12.
282. Reeves RR, Ladner ME. Potentiation of the effect of buprenorphine/naloxone with gabapentin or quetiapine. Am J Psychiatry. 2014;171(6):691.
283. Pilgrim JL, Drummer OH. The toxicology and comorbidities of fatal cases involving quetiapine. Forensic Sci Med Pathol. 2013;9(2):170-6.
284. Alexander J. Delirium as a symptom of quetiapine poisoning. Aust N Z J Psychiatry. 2009;43(8):781.
285. Antia SX, Sholevar EH, Baron DA. Overdoses and ingestions of second-generation antipsychotics in children and adolescents. J Child Adolesc Psychopharmacol. 2005;15(6):970-85.
286. Arslan ED, Demir A, Yilmaz F, Kavalci C, Karakilic E, Celikel E. Treatment of quetiapine overdose with intravenous lipid emulsion. Keio J Med. 2013;62(2):53-7.
287. Bartos M, Knudsen K. Use of intravenous lipid emulsion in the resuscitation of a patient with cardiovascular collapse after a severe overdose of quetiapine. Clin Toxicol (Phila). 2013;51(6):501-4.
288. Bodmer M, Burkard T, Kummer O, Beyrau R, Krahenbuhl S, Haschke M. Pharmacokinetics and pharmacodynamics of quetiapine in a patient with a massive overdose. Ther Drug Monit. 2008;30(4):553-6.
289. Brown S, Sweeney R. Overdose and treatment of quetiapine ingestions. J Emerg Nurs. 2007;33(6):582-4.
290. Capuano A, Ruggiero S, Vestini F, Ianniello B, Rafaniello C, Rossi F, et al. Survival from coma induced by an intentional 36-g overdose of extended-release quetiapine. Drug Chem Toxicol. 2011;34(4):475-7.
291. Cole JB, Stellpflug SJ, Ellsworth H, Harris CR. Reversal of quetiapine-induced altered mental status with physostigmine: a case series. Am J Emerg Med. 2012;30(6):950-3.
292. Dickmann JR, Dickmann LM. An uncommonly recognized cause of rhabdomyolysis after quetiapine intoxication. Am J Emerg Med. 2010;28(9):1060.e1-2.
293. Eyer F, Pfab R, Felgenhauer N, Strubel T, Saugel B, Zilker T. Clinical and analytical features of severe suicidal quetiapine overdoses--a retrospective cohort study. Clin Toxicol (Phila). 2011;49(9):846-53.
294. Finn SD, Uncles DR, Willers J, Sable N. Early treatment of a quetiapine and sertraline overdose with Intralipid. Anaesthesia. 2009;64(2):191-4.
295. Flammia DD, Valouch T, Venuti S. Tissue distribution of quetiapine in 20 cases in Virginia. J Anal Toxicol. 2006;30(4):287-92.
296. Garg V, Farah N. Quetiapine overdose. Aust N Z J Psychiatry. 2010;44(12):1144.
297. Grace RF, Newell SD. Paradoxical and severe hypotension in response to adrenaline infusions in massive quetiapine overdose: the case for lipid rescue. Crit Care Resusc. 2009;11(2):162.
298. Hantson P, Di Fazio V, Wallemacq P. Toxicokinetic interaction between quetiapine and antiretroviral therapy following quetiapine overdose. Drug Metab Lett. 2010;4(1):7-8.
299. Hawkins DJ, Unwin P. Paradoxical and severe hypotension in response to adrenaline infusions in massive quetiapine overdose. Crit Care Resusc. 2008;10(4):320-2.
300. Hunfeld NG, Westerman EM, Boswijk DJ, de Haas JA, van Putten MJ, Touw DJ. Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. Ther Drug Monit. 2006;28(2):185-9.

301. Isbister GK, Duffull SB. Quetiapine overdose: predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal. Int Clin Psychopharmacol. 2009;24(4):174-80.
302. Isbister GK, Friberg LE, Hackett LP, Duffull SB. Pharmacokinetics of quetiapine in overdose and the effect of activated charcoal. Clin Pharmacol Ther. 2007;81(6):821-7.
303. Khan KH, Tham TC. Neuroleptic malignant syndrome induced by quetiapine overdose. Br J Hosp Med (Lond). 2008;69(3):171.
304. Lannemyr L, Knudsen K. Severe overdose of quetiapine treated successfully with extracorporeal life support. Clin Toxicol (Phila). 2012;50(4):258-61.
305. Malik AR, Wolf PK, Ravasia S. Hypokalemia from risperidone and quetiapine overdose. Can J Psychiatry. 2005;50(1):76.
306. Martin CA, Chapman R, Rahman A, Graudins A. A retrospective descriptive study of the characteristics of deliberate self-poisoning patients with single or repeat presentations to an Australian emergency medicine network in a one year period. BMC emerg. 2014;14:21.
307. Maclaren G, Butt W, Cameron P, Preovolos A, McEgan R, Marasco S. Treatment of polypharmacy overdose with multimodality extracorporeal life support. Anaesth Intensive Care. 2005;33(1):120-3.
308. Nielsen AS, Damek DM. Window of opportunity: flexion myelopathy after drug overdose. J Emerg Med. 2012;42(1):36-9.
309. Papazisis G, Mastrogianni O, Chatzinikolaou F, Vasiliadis N, Raikos N. Sudden cardiac death due to quetiapine overdose. Psychiatry Clin Neurosci. 2012;66(6):535.
310. Precourt A, Dunewicz M, Gregoire G, Williamson DR. Multiple complications and withdrawal syndrome associated with quetiapine/venlafaxine intoxication. Ann Pharmacother. 2005;39(1):153-6.
311. Rauber-Luthy C, Hofer KE, Bodmer M, Kullak-Ublick GA, Kupferschmidt H, Ceschi A. Gastric pharmacobezoars in quetiapine extended-release overdose: a case series. Clin Toxicol (Phila). 2013;51(10):937-40.
312. Reichert C, Reichert P, Monnet-Tschudi F, Kupferschmidt H, Ceschi A, Rauber-Luthy C. Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin Toxicol (Phila). 2014;52(6):629-34.
313. Silversides JA, Scott KC. Diabetes insipidus following overdose of baclofen and quetiapine. Anaesth Intensive Care. 2009;37(2):319-20.
314. Strachan PM, Benoff BA. Mental status change, myoclonus, electrocardiographic changes, and acute respiratory distress syndrome induced by quetiapine overdose. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2006;26(4):578-82.
315. Tan HH, Hoppe J, Heard K. A systematic review of cardiovascular effects after atypical antipsychotic medication overdose. Am J Emerg Med. 2009;27(5):607-16.
316. Young AC, Kleinschmidt KC, Wax PM. Late-onset seizures associated with quetiapine poisoning. J Med Toxicol. 2009;5(1):24-6.
317. Ngo A, Ciranni M, Olson KR. Acute quetiapine overdose in adults: a 5-year retrospective case series. Annals of emergency medicine. 2008;52(5):541-7.
318. Kumsar NA, Erol A. Olanzapine abuse. Subst Abus. 2013;34(1):73-4.
319. Lai CH. Olanzapine abuse was relieved after switching to aripiprazole in a patient with psychotic depression. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(7):1363-4.
320. Reeves RR. Abuse of Olanzapine by substance abusers. J Psychoactive Drugs. 2007;39(3):297-9.
321. Valeriani G, Corazza O, Bersani FS, Melcore C, Metastasio A, Bersani G, et al. Olanzapine as the ideal "trip terminator"? Analysis of online reports relating to antipsychotics' use and misuse following occurrence of novel psychoactive substance-related psychotic symptoms. Hum. 2015;30(4):249-54.
322. Arora M, Praharaj SK. Nonfatal suicidal olanzapine overdose: a case report. Clin Neuropharmacol. 2006;29(4):190-1.
323. Austin AE, van den Heuvel C, Byard RW. Physician suicide. Journal of Forensic Sciences. 2013;58 Suppl 1:S91-3.
324. Ballesteros S, Martinez MA, Ballesteros MA, de la Torre CS, Rodriguez-Borregan JC. A severe case of olanzapine overdose with analytical data. Clin Toxicol (Phila). 2007;45(4):412-5.
325. Bhanji NH, Chouinard G, Hoffman L, Margolese HC. Seizures, coma, and coagulopathy following olanzapine overdose. Can J Psychiatry. 2005;50(2):126-7.
326. Broyd C, McGuinness A. Pontine haemorrhage mimicked by an olanzapine overdose. Emerg Med J. 2006;23(4):e29.
327. Davis LE, Becher MW, Tlomak W, Benson BE, Lee RR, Fisher EC. Persistent choreoathetosis in a fatal olanzapine overdose: drug kinetics, neuroimaging, and neuropathology. Am J Psychiatry. 2005;162(1):28-33.
328. Horak EL, Jenkins AJ. Postmortem tissue distribution of olanzapine and citalopram in a drug intoxication. Journal of Forensic Sciences. 2005;50(3):679-81.
329. Kocer E, Alcelik A, Canan F. Olanzapine intoxication-related transient diabetes insipidus. Ren Fail. 2011;33(8):842-3.
330. Lennestal R, Asplund C, Nilsson M, Lakso HA, Mjorndal T, Hagg S. Serum levels of olanzapine in a non-fatal overdose. J Anal Toxicol. 2007;31(2):119-21.
331. Lung DD, Wu AH, Gerona RR. Cardiotoxicity in a citalopram and olanzapine overdose. J Emerg Med. 2013;45(4):554-8.
332. Morgan M, Hackett LP, Isbister GK. Olanzapine overdose: a series of analytically confirmed cases. Int Clin Psychopharmacol. 2007;22(3):183-6.
333. Morris E, Green D, Graudins A. Neuroleptic malignant syndrome developing after acute overdose with olanzapine and chlorpromazine. J Med Toxicol. 2009;5(1):27-31.
334. Pons S, Gonzva J, Prunet B, Gaillard T, Brisou P, Vest P, et al. Acute overdose of enteric-coated valproic acid and olanzapine: unusual presentation and delayed toxicity. Clin Toxicol (Phila). 2012;50(4):268.
335. Singh LK, Praharaj SK, Sahu M. Nonfatal suicidal overdose of olanzapine in an adolescent. Curr Drug Saf. 2012;7(4):328-9.
336. Tanoshima R, Chandranipapongse W, Colantonio D, Stefan C, Nulman I. Acute olanzapine overdose in a toddler: a case report. Ther Drug Monit. 2013;35(5):557-9.
337. Theisen FM, Grabarkiewicz J, Fegbeutel C, Hubner A, Mehler-Wex C, Remschmidt H. Olanzapine overdose in children and adolescents: two case reports and a review of the literature. J Child Adolesc Psychopharmacol. 2005;15(6):986-95.

338. Tse GH, Warner MH, Waring WS. Prolonged toxicity after massive olanzapine overdose: two cases with confirmatory laboratory data. J Toxicol Sci. 2008;33(3):363-5.
339. Tylutki Z, Jawien W, Ciszowski K, Wilimowska J, Anand JS. Abnormal olanzapine toxicokinetic profiles--population pharmacokinetic analysis. Toxicol. 2015;25(1):1-12.
340. Waring WS, Wrate J, Bateman DN. Olanzapine overdose is associated with acute muscle toxicity. Hum Exp Toxicol. 2006;25(12):735-40.
341. Yaylaci S, Tamer A, Kocayigit I, Gunduz H. Atrial fibrillation due to olanzapine overdose. Clin Toxicol (Phila). 2011;49(5):440.
342. Yurtlu BS, Hanci V, Gur A, Turan IO. Intravenous lipid infusion restores consciousness associated with olanzapine overdose. Anesth Analg. 2012;114(4):914-5.
343. Minns AB, Clark RF. Toxicology and overdose of atypical antipsychotics. J Emerg Med. 2012;43(5):906-13.
344. Akyol A, Senel AC, Ulusoy H, Karip F, Erciyes N. Delayed respiratory depression after risperidone overdose. Anesth Analg. 2005;101(5):1490-1.
345. Hitosugi M, Tsukada C, Yamauchi S, Nagai T. A case of fatal risperidone poisoning alerts physicians. J Clin Psychopharmacol. 2014;34(2):268-9.
346. Hsu YC, Yeh YW. Multidrug overdose-induced myoclonus complicated by rhabdomyolysis: possible role and mechanism of muscle toxicity of risperidone. J Clin Pharm Ther. 2014;39(6):698-700.
347. Page CB, Calver LA, Isbister GK. Risperidone overdose causes extrapyramidal effects but not cardiac toxicity. J Clin Psychopharmacol. 2010;30(4):387-90.
348. Isbister GK, Balit CR, Macleod D, Duffull SB. Amisulpride overdose is frequently associated with QT prolongation and torsades de pointes. J Clin Psychopharmacol. 2010;30(4):391-5.
349. Isbister GK, Murray L, John S, Hackett LP, Haider T, O'Mullane P, et al. Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. Med J Aust. 2006;184(7):354-6.
350. Joy JP, Coulter CV, Duffull SB, Isbister GK. Prediction of torsade de pointes from the QT interval: analysis of a case series of amisulpride overdoses. Clin Pharmacol Ther. 2011;90(2):243-5.
351. Stevenson RJ. Amisulpride overdose: suggested management of prolonged QTc. Emerg Med J. 2010;27(7):565.
352. Carstairs SD, Williams SR. Overdose of aripiprazole, a new type of antipsychotic. J Emerg Med. 2005;28(3):311-3.
353. Lo B, Pizon A. Delayed presentation of an aripiprazole overdose. Clin Toxicol (Phila). 2008;46(4):348-9.
354. Lofton AL, Klein-Schwartz W. Atypical experience: a case series of pediatric aripiprazole exposures. Clin Toxicol (Phila). 2005;43(3):151-3.
355. Prakash R, Munda S, Pattojoshi A, Choudhary PP. Benign clinical picture after ingestion of 780 milligrams of aripiprazole and 1050 milligrams of amitriptyline. Indian J Med Sci. 2009;63(2):77-80.
356. Seifert SA, Schwartz MD, Thomas JD. Aripiprazole (abilify) overdose in a child. Clin Toxicol (Phila). 2005;43(3):193-5.
357. Matsumoto H, Ohnishi M, Takegawa R, Hirose T, Hattori Y, Shimazu T. Effect of lipid emulsion during resuscitation of a patient with cardiac arrest after overdose of chlorpromazine and mirtazapine. Am J Emerg Med. 2015;33(10):1541.e1-2.
358. Takase I, Yamamoto Y, Nakagawa T, Nishi K. A fatal case of potential chronic overdoses of prescribed and proprietary remedies. Hum Exp Toxicol. 2010;29(8):695-9.
359. Tanaka N, Kinoshita H, Kuse A, Takatsu M, Jamal M, Kumihashi M, et al. Forensic toxicological implications of pleural effusion; an autopsy case of drug overdose. Soud Lek. 2012;57(3):48-50.
360. Tournier M, Grolleau A, Cougnard A, Verdoux H, Molimard M. The prognostic impact of psychotropic drugs in intentional drug overdose. Pharmacopsychiatry. 2009;42(2):51-6.
361. Flanagan RJ, Spencer EP, Morgan PE, Barnes TR, Dunk L. Suspected clozapine poisoning in the UK/Eire, 1992-2003. Forensic Sci Int. 2005;155(2-3):91-9.
362. Rotella JA, Zarei F, Frauman AG, Greene SL. Refractory hypotension treated with vasopressin after intentional clozapine overdose. Eur J Emerg Med. 2014;21(4):319-20.
363. West S, Jeffery-Smith A, Brownlee W, Kenedi C. Covert clozapine overdose: Clozapine toxicity in a naive patient. Aust N Z J Psychiatry. 2013;47(12):1208-9.
364. Bhatia MS, Gupta R, Dhawan J. Myocarditis after overdose of conventional antipsychotics. World J Biol Psychiatry. 2009;10(4 Pt 2):606-8.
365. Molnar GP, Grimsich LC, Catalano G, Catalano MC. Acute lurasidone overdose. J Clin Psychopharmacol. 2014;34(6):768-70.
366. Lapid MI, Cunningham JL, Hugo Z, Kung S. Acute dystonia associated with paliperidone overdose. Psychosomatics. 2011;52(3):291-4.
367. Levine M, Lovecchio F, Tafoya P, Graham R. Paliperidone overdose with delayed onset of toxicity. Annals of emergency medicine. 2011;58(1):80-2.
368. Liang CS, Bai YM, Liou YJ, Chou YH. Acute renal failure after paliperidone overdose: a case report. J Clin Psychopharmacol. 2012;32(1):128.
369. Gill JS, Pillai SK, Koh OH, Jambunathan S. [Non-fatal paliperidone overdose: a case report]. Turk Psikiyatri Derg. 2010;21(4):331-4.
370. Alipour A, Cruz R, Lott RS. Torsade de pointes after ziprasidone overdose with coingestants. J Clin Psychopharmacol. 2010;30(1):76-7.
371. Arbuck DM. 12,800-mg ziprasidone overdose without significant ECG changes. Gen Hosp Psychiatry. 2005;27(3):222-3.
372. Berling I, Isbister GK, Calver L, Clunas S. Digital Holter measurement of QT prolongation in ziprasidone overdose. Clin Toxicol (Phila). 2011;49(7):694-6.
373. Gomez-Criado MS, Bernardo M, Florez T, Gutierrez JR, Gandia R, Ayani I. Ziprasidone overdose: cases recorded in the database of Pfizer-Spain and literature review. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2005;25(11):1660-5.
374. Klein-Schwartz W, Lofton AL, Benson BE, Spiller HA, Crouch BI. Prospective observational multi-poison center study of ziprasidone exposures. Clin Toxicol (Phila). 2007;45(7):782-6.
375. LoVecchio F, Watts D, Eckholdt P. Three-year experience with ziprasidone exposures. Am J Emerg Med. 2005;23(4):586-7.
376. MacVane CZ, Baumann MR. Unintentional ingestion of ziprasidone in a 22-month-old. Pediatr Emerg Care. 2009;25(7):460-2.

377. Manini AF, Raspberry D, Hoffman RS, Nelson LS. QT prolongation and Torsades de Pointes following overdose of ziprasidone and amantadine. J Med Toxicol. 2007;3(4):178-81.
378. Prieto T, Benabarre A, Bernardo M. The highest intentional ziprasidone overdose was not fatal. Acta Psychiatr Scand. 2005;112(1):79-80; author reply
379. Chakraborty R, Chatterjee A, Chaudhury S. Withdrawal symptoms of trifluoperazine. The Journal of Neuropsychiatry and Clinical Neurosciences. 2008;20(4):495-6.
380. Gunja N. The clinical and forensic toxicology of Z-drugs. J Med Toxicol. 2013;9(2):155-62.
381. Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European union: A systematic review of the literature. Eur Addict Res. 2012;18(5):228-45.
382. Bogstrand ST, Gjerde H, Normann PT, Rossow I, Ekeberg O. Alcohol, psychoactive substances and non-fatal road traffic accidents--a case-control study. BMC Public Health. 2012;12:734.
383. Gjerde H, Strand MC, Morland J. Driving Under the Influence of Non-Alcohol Drugs--An Update Part I: Epidemiological Studies. Forensic sci. 2015;27(2):89-113.
384. Ahlner J, Holmgren A, Jones AW. Prevalence of alcohol and other drugs and the concentrations in blood of drivers killed in road traffic crashes in Sweden. Scandinavian Journal of Public Health. 2014;42(2):177-83.
385. Legrand SA, Houwing S, Hagenzieker M, Verstraete AG. Prevalence of alcohol and other psychoactive substances in injured drivers: comparison between Belgium and The Netherlands. Forensic Sci Int. 2012;220(1-3):224-31.
386. Hels T, Lyckegaard A, Simonsen KW, Steentoft A, Bernhoft IM. Risk of severe driver injury by driving with psychoactive substances. Accid Anal Prev. 2013;59:346-56.
387. Kapil V, Green JL, Le Lait C, Wood DM, Dargan PI. Misuse of benzodiazepines and Z-drugs in the UK. Br J Psychiatry. 2014;205(5):407-8.
388. Schepis TS. Age cohort differences in the nonmedical use of prescription zolpidem: Findings from a nationally representative sample. Addictive Behaviors. 2014;39(9):1311-7.
389. Cruz HG, Hoever P, Chakraborty B, Schoedel K, Sellers EM, Dingemanse J. Assessment of the abuse liability of a dual orexin receptor antagonist: A crossover study of almorexant and zolpidem in recreational drug users. CNS Drugs. 2014;28(4):361-72.
390. Schoedel KA, Sun H, Sellers EM, Faulknor J, Levy-Cooperman N, Li X, et al. Assessment of the abuse potential of the orexin receptor antagonist, suvorexant, compared with zolpidem in a randomized crossover study. J Clin Psychopharmacol. 2016;36(4):314-23.
391. Beyraghi N, Shamsi A, Farrokhian A. Detoxification of high-dose zolpidem using phenobarbital and gabapentin: Two case reports. Archives of Psychiatry and Psychotherapy. 2016;18(4):16-9.
392. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: Results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. Br J Clin Pharmacol. 2007;64(2):198-209.
393. Whitty M, Connor JO. Intra-arterial injection of zolpidem and substance misusers. Irish Journal of Psychological Medicine. 2007;24(4):161.
394. Benyamina A, Dublanchet O, Karila L, Blecha L, Reynaud M. Intravenous zolpidem abuse: A case for serotonin depletion. Am J Addict. 2007;16(6):534.
395. Hsu WY, Chiu NY. Intravenous zolpidem injection in a zolpidem abuser. Pharmacopsychiatry. 2013;46(3):121.
396. Licata SC, Mashhoon Y, MacLean RR, Lukas SE. Modest abuse-related subjective effects of zolpidem in drug-naive volunteers. Behavioural Pharmacology. 2011;22(2):160-6.
397. Victorri-Vigneau C, Feuillet F, Wainstein L, Grall-Bronnec M, Pivette J, Chaslerie A, et al. Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. Eur J Clin Pharmacol. 2013;69(11):1965-72.
398. Brunelle E, Rotily M, Lancon C, Goisset P, Piquet JM, Lagadec G, et al. Zolpidem: Intravenous misuse in drug abusers [8]. Addiction (Abingdon, England). 2005;100(9):1377-8.
399. Kummer L, Rzewuska M, Sienkiewicz-Jarosz H, Mierzejewski P, Bienkowski P, Samochowiec J. Zolpidem misuse in two women with no psychiatric history: A crucial role of pleasant visual hallucinations. Journal of Neuropsychiatry and Clinical Neurosciences. 2012;24(2):E32.
400. Heydari M, Isfeedvajani MS. Zolpidem dependence, abuse and withdrawal: A case report. Journal of Research in Medical Sciences. 2013;18(11):1006-7.
401. Victorri-Vigneau C, Gerardin M, Rousselet M, Guerlais M, Grall-Bronnec M, Jolliet P. An update on zolpidem abuse and dependence. Journal of Addictive Diseases. 2014;33(1):15-23.
402. Pourshams M, Malakouti SK. Zolpidem abuse and dependency in an elderly patient with major depressive disorder: A case report. DARU, Journal of Pharmaceutical Sciences. 2014;22 (1) (no pagination)(54).
403. Cubala WJ, Landowski J, Wichowicz HM. Zolpidem abuse, dependence and withdrawal syndrome: Sex as susceptibility factor for adverse effects. Br J Clin Pharmacol. 2008;65(3):444-5.
404. Askew JP. Zolpidem addiction in a pregnant woman with a history of second-trimester bleeding. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2007;27(2):306-8.
405. Sethi PK, Khandelwal DC. Zolpidem at supratherapeutic doses can cause drug abuse, dependence and withdrawal seizure. J Assoc Physicians India. 2005;53:139-40.
406. MacFarlane J, Morin CM, Montplaisir J. Hypnotics in insomnia: The experience of zolpidem. Clinical Therapeutics. 2014;36(11):1676-701.
407. Fernandes W, Da Silva Pereira Y, O'Tereza S. A case of Zolpidem dependence successfully detoxified with gabapentin. Indian Journal of Psychiatry. 2013;55(3):290-2.
408. Keuroghlian AS, Barry AS, Weiss RD. Circadian dysregulation, zolpidem dependence, and withdrawal seizure in a resident physician performing shift work. Am J Addict. 2012;21(6):576-7.
409. Yen C-F, Yen C-N, Ko C-H, Hwang T-J, Chen C-S, Chen T-T, et al. Correlates of dependence and beliefs about the use of hypnotics among zolpidem and zopiclone users. Substance Use & Misuse. 2015;50(3):350-7.
410. Huang MC, Lin HY, Chen CH. Dependence on zolpidem. Psychiatry Clin Neurosci. 2007;61(2):207-8.

411. Quaglio G, Lugoboni F, Fornasiero A, Lechi A, Gerra G, Mezzelani P. Dependence on zolpidem: Two case reports of detoxification with flumazenil infusion. Int Clin Psychopharmacol. 2005;20(5):285-7.
412. Sharan P, Bharadwaj RS, Grover S, Padhy SK, Kumar V, Singh J. Dependence syndrome and intoxication delirium associated with zolpidem. National Medical Journal of India. 2007;20(4):180-1.
413. Yen CF, Ko CH, Chang YP, Yu CY, Huang MF, Yeh YC, et al. Dependence, misuse, and beliefs regarding use of hypnotics by elderly psychiatric patients taking zolpidem, estazolam, or flunitrazepam. Asia-Pacific Psychiatry. 2015;7(3):298-305.
414. Svitek J, Heberlein A, Bleich S, Wiltfang J, Kornhuber J, Hillemacher T. Extensive craving in high dose zolpidem dependency. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008;32(2):591-2.
415. Krueger TH, Kropp S, Huber TJ. High-dose zolpidem dependence in a patient with chronic facial pain. Ann Pharmacother. 2005;39(4):773-4.
416. Bhatia MS, Kohli GS. Iatrogenic zolpidem dependence. Journal of Neuropsychiatry and Clinical Neurosciences. 2014;26(2):E38.
417. Quaglio G, Faccini M, Vigneau CV, Casari R, Mathewson S, Licata M, et al. Megadose bromazepam and zolpidem dependence: two case reports of treatment with flumazenil and valproate. Subst Abus. 2012;33(2):195-8.
418. Haasen C, Mueller-Thomsen T, Fink T, Bussopulos A, Reimer J. Zopiclone dependence after insomnia related to torticollis [3]. International Journal of Neuropsychopharmacology. 2005;8(2):309-10.
419. Aggarwal A, Sharma DD. Zolpidem withdrawal delirium: A case report. Journal of Neuropsychiatry and Clinical Neurosciences. 2010;22(4):E27-E8.
420. Chien C-C, Huanga H-T, Lung F-W, Lin C-H. Zolpidem withdrawal delirium, seizure, and acute psychosis: Case reports and literature review. Journal of Substance Use. 2011;16(4):330-8.
421. Yeh YW, Chang HA, Chen CL. Zolpidem dependence, withdrawal seizure and comorbidity following different outcomes: Two case reports and a review of the literature. Journal of Medical Sciences. 2008;28(6):263-7.
422. Oulis P, Nakkas G, Masdrakis VG. Pregabalin in zolpidem dependence and withdrawal. Clin Neuropharmacol. 2011;34(2):90-1.
423. Mariani JJ, Levin FR. Quetiapine treatment of zolpidem dependence. The American Journal on Addictions. 2007;16(5):426.
424. Cubala WJ, Landowski J. Seizure following sudden zolpidem withdrawal. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(2):539-40.
425. Damm J, Eser D, Moeller HJ, Rupprecht R. Severe dependency on zolpidem in a patient with multiple sclerosis suffering from paraspasticity. World J Biol Psychiatry. 2010;11(2 Pt 2):516-8.
426. Lu SH, Tzeng NS, Chou HW. Using benzodiazepine detoxification and cognitive behavioral psychotherapy in the treatment of a patient with generalized anxiety disorder comorbid with high-dose zolpidem dependence. Journal of Medical Sciences (Taiwan). 2016;36(5):194-6.
427. Cubala WJ, Wichowicz HM. Dependence on zolpidem: Is pharmacokinetics important? [2]. Psychiatry and Clinical Neurosciences. 2008;62(1):127.
428. Rao Ravindra V, Sameer M. Zolpidem dependence. Indian Journal of Pharmacology. 2005;37(6):412-3.
429. Wang LJ, Ree SC, Chu CL, Juang YY. Zolpidem dependence and withdrawal seizure--report of two cases. Psychiatria Danubina. 2011;23(1):76-8.
430. Styliani S, Ioannis D, Jannis N, Apostolos I, Georgios K. Zolpidem dependence in a geriatric patient: A case report. Journal of the American Geriatrics Society. 2009;57(10):1962-3.
431. Roehrs T, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not produce withdrawal symptoms on drug discontinuation: A prospective placebo controlled study. Sleep. 2011;34:A178.
432. Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to dose escalation: A prospective placebo-controlled study. Sleep. 2011;34(2):207-12.
433. Lu TH, Lee YY, Lee HC, Lin YM. Doctor Shopping Behavior for Zolpidem Among Insomnia Patients in Taiwan: A Nationwide Population-Based Study. Sleep. 2015;38(7):1039-44.
434. Jouanjus E, Cisse A, Lapeyre-Mestre M. What does continuous survey of falsified prescriptions tell us? Lessons from the OSIAP survey. Fundamental and Clinical Pharmacology. 2013;27:102.
435. Kintz P, Villain M, Dumestre-Toulet V, Ludes B. Drug-facilitated sexual assault and analytical toxicology: The role of LC-MS/MS. A case involving zolpidem. Journal of Clinical Forensic Medicine. 2005;12(1):36-41.
436. Boucher A, Assaad S, Pariset C, Descotes J. Digital ischemia following injection of a crushed tablet of zolpidem: Tardive improvement with iloprost. [French]. Therapie. 2008;63(6):463-7.
437. Sharma A, Sayeed N, Khess CRJ, Akhtar S. High dose zolpidem induced fetal neural tube defects. Curr Drug Saf. 2011;6(2):128-9.
438. Kriikku P, Hurme H, Wilhelm L, Rintatalo J, Hurme J, Kramer J, et al. Sedative-hypnotics are widely abused by drivers apprehended for driving under the influence of drugs. Ther Drug Monit. 2015;37(3):339-46.
439. Jones AW, Holmgren A, Kugelberg FC. Concentrations of scheduled prescription drugs in blood of impaired drivers: considerations for interpreting the results. Ther Drug Monit. 2007;29(2):248-60.
440. Zosel A, Osterberg EC, Mycyk MB. Zolpidem misuse with other medications or alcohol frequently results in intensive care unit admission. American Journal of Therapeutics. 2011;18(4):305-8.
441. Sano R, Takahashi K, Kominato Y, Araki T, Yamamoto K, Takei H, et al. A case of fatal drug intoxication showing a high-density duodenal content by postmortem computed tomography. Leg Med (Tokyo). 2011;13(1):39-40.
442. Kuzniar TJ, Balagani R, Radigan KA, Factor P, Mutlu GM. Coma with absent brainstem reflexes resulting from zolpidem overdose. American Journal of Therapeutics. 2010;17(5):e172-4.
443. Manfredi G, Kotzalidis GD, Lazanio S, Savoja V, Talamo A, Koukopoulos AE, et al. Command hallucinations with self-stabbing associated with zolpidem overdose. The Journal of Clinical Psychiatry. 2010;71(1):92-3.
444. Chou S, Ayabe S, Sekine N. Myocardial Injury without Electrocardiographic Changes after a Suicide Attempt by an Overdose of Glimepiride and Zolpidem: A Case Report and Literature Review. Intern Med. 2015;54(21):2727-33.

445. Thornton SL, Negus E, Carstairs SD. Pediatric zolpidem ingestion demonstrating zero-order kinetics treated with flumazenil. Pediatr Emerg Care. 2013;29(11):1204-6.
446. Mortaz Hejri S, Faizi M, Babaeian M. Zolpidem-induced suicide attempt: A case report. DARU, Journal of Pharmaceutical Sciences. 2013;21 (1) (no pagination)(77).
447. Bannan N, Rooney S, O'Connor J. Zopiclone misuse: An update from Dublin. Drug and Alcohol Review. 2007;26(1):83-5.
448. Curreen M, Lidmila J. Zopiclone: Is there cause for concern in addiction services and general practice? International Journal of Risk and Safety in Medicine. 2014;26(4):183-9.
449. Cimolai N. Zopiclone: Is it a pharmacologic agent for abuse? Canadian Family Physician. 2007;53(12):2124-9.
450. Flynn A, Cox D. Dependence on Zopiclone. Addiction (Abingdon, England). 2006;101(6):898.
451. Wong CP, Chiu PKC, Chu LW. Zopiclone withdrawal: An unusual cause of delirium in the elderly. Age and Ageing. 2005;34(5):526-7.
452. Bogstrand ST, Normann PT, Rossow I, Larsen M, Morland J, Ekeberg O. Prevalence of alcohol and other substances of abuse among injured patients in a Norwegian emergency department. Drug and Alcohol Dependence. 2011;117(2-3):132-8.
453. Elvik R. Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. Accid Anal Prev. 2013;60:254-67.
454. Elliott SP, Burgess V. Clinical urinalysis of drugs and alcohol in instances of suspected surreptitious administration ("spiked drinks"). Sci Justice. 2005;45(3):129-34.
455. Bjornaas MA, Teige B, Hovda KE, Ekeberg O, Heyerdahl F, Jacobsen D. Fatal poisonings in Oslo: A one-year observational study. BMC emerg. 2009;10 (no pagination)(13).
456. Fung HT, Lai CH, Wong OF, Lam SK, Lam KK. Hemolytic anemia after zopiclone overdose. Clin Toxicol (Phila). 2009;47(9):902-3.
457. chan YC, Tse ML, Lau FL. Hong Kong Poison Information Centre: Annual report 2015. Hong Kong Journal of Emergency Medicine. 2016;23(6).
458. Hillyard SG, Barrera-Groba C, Tighe R. Intralipid reverses coma associated with zopiclone and venlafaxine overdose. European Journal of Anaesthesiology. 2010;27(6):582-3.
459. Fung HT, Lai CH, Wong OF, Lam KK, Kam CW. Two cases of methemoglobinemia following zopiclone ingestion. Clin Toxicol (Phila). 2008;46(2):167-70.
460. Chan TY. Zopiclone induced methemoglobinemia and hemolytic anemia. Int J Clin Pharmacol Ther. 2014;52(5):402-6.
461. Lloyd BK, McElwee PR. Trends over time in characteristics of pharmaceutical drug-related ambulance attendances in Melbourne. Drug Alcohol Rev. 2011;30(3):271-80.
462. Ablooshi H, Hulse GK, Kashef AE, Hashmi HA, Shawky M, Al Ghaferi H, et al. The pattern of substance use disorder in the United Arab Emirates in 2015: Results of a National Rehabilitation Centre cohort study. Substance Abuse Treatment, Prevention, and Policy Vol 11 2016, ArtID 19. 2016;11.
463. Ashwini S, Amit DR, Ivan NS, Alka PV. Pregabalin dependence with pregabalin induced intentional self-harm behavior: A case report. Indian Journal of Psychiatry. 2015;57(1):110-1.
464. Caster O, Edwards IR, Noren GN, Lindquist M. Earlier discovery of pregabalin's dependence potential might have been possible. Eur J Clin Pharmacol. 2011;67(3):319-20.
465. Carrus D, Schifano F. Pregabalin misuse-related issues; intake of large dosages, drug-smoking allegations, and possible association with myositis: Two case reports. J Clin Psychopharmacol. 2012;32(6):839-40.
466. Chan WL, Wood DM, Wood T, Vermette AE, Dargan PI. Misuse of pregabalin, gabapentin and baclofen in UK men who have sex with men clubbers. Journal of Medical Toxicology. 2014;10 (1):75-6.
467. Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS Drugs. 2016;30(7):647-54.
468. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017:1-24.
469. Filipetto FA, Zipp CP, Coren JS. Potential for pregabalin abuse or diversion after past drug-seeking behavior. J Am Osteopath Assoc. 2010;110(10):605-7.
470. Gahr M, Freudenmann RW, Hiemke C, Kolle MA, Schonfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: Results from a database query. Eur J Clin Pharmacol. 2013;69(6):1335-42.
471. Gahr M, Franke B, Freudenmann RW, Kolle MA, Schonfeldt-Lecuona C. Concerns about pregabalin: Further experience with its potential of causing addictive behaviors. J Addict Med. 2013;7(2):147-9.
472. Gahr M, Freudenmann RW, Kolle MA, Schonfeldt-Lecuona C. Pregabalin and addiction: Lessons from published cases. Journal of Substance Use. 2014;19(6):448-9.
473. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, et al. Pregabalin abuse, dependence, and withdrawal: A case report. The American Journal of Psychiatry. 2010;167(7):869.
474. Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the gamma-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol. 2014;78(1):190-1.
475. Muquebil Ali Al Shaban Rodriguez OW, Garcia Alvarez G. Pregabalin abuse in an impulsive patient: Treatment with topiramate. Psiquiatria Biologica. 2016;23(2):74-6.
476. Papazisis G, Garyfallos G, Sardeli C, Kouvelas D. Pregabalin abuse after past substance-seeking behavior. Int J Clin Pharmacol Ther. 2013;51(5):441-2.
477. Papazisis G, Tzachanis D. Pregabalin's abuse potential: A mini review focusing on the pharmacological profile. International Journal of Clinical Pharmacology and Therapeutics. 2014;52(8):709-16.
478. Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, et al. Is there a recreational misuse potential for pregabalin? analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychotherapy and Psychosomatics. 2011;80(2):118-22.

479. Schjerning O, Pottegard A, Damkier P, Rosenzweig M, Nielsen J. Use of Pregabalin - A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential. Pharmacopsychiatry. 2016;49(4):155-61.
480. Schjerning O, Rosenzweig M, Pottegard A, Damkier P, Nielsen J. Abuse Potential of Pregabalin: A Systematic Review. CNS Drugs. 2016;30(1):9-25.
481. Skibicka-Stepien I, Lazowska A, Brosch S, Goedecke T, Newbould V, Pinheiro L, et al. The new definition of an adverse drug reaction (ADR) with focus on abuse/misuse: the example of pregabalin. Drug Safety. 2015;38 (10):1027.
482. Sonmez MB. Pregabalin use disorder. Noropsikiyatri Arsivi. 2015;52(4):421-2.
483. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010;66(9):947-53.
484. Spadari M, Frauger E, Drouet G, Ferre M, Pourcel L, Moracchini C, et al. Is pregabalin abused in France? Fundamental and Clinical Pharmacology. 2012;26:71.
485. Stannard C. Misuse of gabapentin and pregabalin: A marker for a more serious malaise? Addiction (Abingdon, England). 2016;111(10):1699-700.
486. Suardi NE, Preve M, Godio M, Bolla E, Colombo RA, Traber R. Misuse of pregabalin: Case series and literature review. European Psychiatry. 2016;33:S312.
487. Wazaify M, Abood E, Tahaineh L, Albsoul-Younes A. Jordanian community pharmacists' experience regarding prescription and nonprescription drug abuse and misuse in Jordan - An update. Journal of Substance Use. 2016:1-6.
488. Wiegand TJ, Gorodetsky RM. Recreational abuse of gabapentin and pregabalin are under-recognized causes of hospitalization related to these prescription drugs. Clinical Toxicology. 2013;51 (4):316.
489. Yazdi K, Hemetsberger U, Baier C. Pregabalin abuse of benzodiazepine and alcohol addicted patient. Psychiatria Danubina. 2015;27(3):278-9.
490. Schifano F. Misuse and abuse of pregabalin and gabapentin: Cause for concern? CNS Drugs. 2014;28(6):491-6.
491. Osman M, Casey P. Pregabalin abuse for enhancing sexual performance: Case discussion and literature review. Irish Journal of Psychological Medicine. 2014;31(4):281-6.
492. Bossard JB, Ponte C, Dupouy J, Lapeyre-Mestre M, Jouanjus E. Disproportionality Analysis for the Assessment of Abuse and Dependence Potential of Pregabalin in the French Pharmacovigilance Database. Clinical Drug Investigation. 2016;36(9):735-42.
493. Gahr M, Freudenmann RW, Kolle MA, Schonfeldt-Lecuona C. From benzodiazepine to pregabalin dependence: Different agents, similar problems. Indian Journal of Psychiatry. 2015;57(1):111-2.
494. Halaby A, Kassm SA, Naja WJ. Pregabalin dependence: A case report. Curr Drug Saf. 2015;10(2):184-6.
495. Baird CRW, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: A survey among substance misusers. Eur Addict Res. 2014;20(3):115-8.
496. Bicknell M. The pain of pregabalin prescribing in prisons. British Journal of General Practice. 2013;63(613):405.
497. Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, et al. Pregabalin abuse among opiate addicted patients. Eur J Clin Pharmacol. 2013;69(12):2021-5.
498. Hakkinen M, Vuori E, Kalso E, Gergov M, Ojanpera I. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. Forensic Sci Int. 2014;241:1-6.
499. Hakkinen M, Vuori E, Kalso E, Gergov M, Ojanpera I. Pregabalin and gabapentin abuse and toxicity as disclosed from postmortem cases. Clinical Toxicology. 2014;52:329.
500. McNamara S, Stokes S, Kilduff R, Shine A. Pregabalin Abuse amongst Opioid Substitution Treatment Patients. Ir Med J. 2015;108(10):309-10.
501. Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. The American Journal on Addictions. 2015;24(2):173-7.
502. Aksakal E, Bakirci EM, Emet M, Uzkeser M. Complete atrioventricular block due to overdose of pregabalin. The American journal of emergency medicine. 2012;30(9):2101.e1-4.
503. Braga AJ, Chidley K. Self-poisoning with lamotrigine and pregabalin. Anaesthesia. 2007;62(5):524-7.
504. Simonsen KW, Edvardsen HME, Thelander G, Ojanpera I, Thordardottir S, Andersen LV, et al. Fatal poisoning in drug addicts in the Nordic countries in 2012. Forensic Sci Int. 2015;248:172-80.
505. Spiller HA, Bratcher R, Griffith JR. Pregabalin overdose with benign outcome. Clin Toxicol (Phila). 2008;46(9):917.
506. Wills B, Reynolds P, Chu E, Murphy C, Cumpston K, Stromberg P, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. J Med Toxicol. 2014;10(3):254-60.
507. Wood DM, Berry DJ, Glover G, Eastwood J, Dargan PI. Significant pregabalin toxicity managed with supportive care alone. J Med Toxicol. 2010;6(4):435-7.
508. Kriikku P, Wilhelm L, Rintatalo J, Hurme J, Kramer J, Ojanpera I. Pregabalin serum levels in apprehended drivers. Forensic Sci Int. 2014;243:112-6.
509. Dunlop AJ. Commentary on Smith et al. (2016): Gabapentin-looks like a drug that can be misused..., probably is a drug that can be misused. Addiction (Abingdon, England). 2016;111(7):1175-6.
510. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother. 2016;50(3):229-33.
511. Piskorska B, Miziak B, Czuczwar SJ, Borowicz KK. Safety issues around misuse of antiepileptics. Expert Opin Drug Saf. 2013;12(5):647-57.
512. Tcheremissine OV, Bestha DP. Gabapentin abuse in a patient with comorbid mood and substance use disorders. Innovations in Clinical Neuroscience. 2016;13(7-8):13-4.
513. Victorri-Vigneau C, Guerlais M, Jolliet P. Abuse, dependency and withdrawal with Gabapentin: A first case report. Pharmacopsychiatry. 2007;40(1):43-4.

514. Pittenger C, Desan PH. Gabapentin abuse, and delirium tremens upon gabapentin withdrawal [1]. J Clin Psychiatry. 2007;68(3):483-4.
515. Smith BH, Higgins C, Baldacchino A, Kidd B, Bannister J. Substance misuse of gabapentin. British Journal of General Practice. 2012;62(601):406-7.
516. Howland RH. Gabapentin: can it be misused? Journal of psychosocial nursing and mental health services. 2014;52(1):12-5.
517. Kruszewski SP, Paczynski RP, Kahn DA. Gabapentin-induced delirium and dependence. Journal of Psychiatric Practice. 2009;15(4):314-9.
518. Bastiaens L, Galus J, Mazur C. Abuse of gabapentin is associated with opioid addiction. Psychiatric Quarterly. 2016;87(4):763-7.
519. Satish R, Kandasamy A, Jayarajan D, Benegal V. Gabapentin dependence in a patient with opioid dependence syndrome. Journal of Neuropsychiatry and Clinical Neurosciences. 2015;27 (1) (no pagination)(e64).
520. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: A systematic review. Addiction (Abingdon, England). 2016;111(7):1160-74.
521. Smith RV, Lofwall MR, Havens JR. Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. Am J Psychiatry. 2015;172(5):487-8.
522. Howland RH. Gabapentin for substance use disorders: Is it safe and appropriate? Journal of Psychosocial Nursing and Mental Health Services. 2014;52(2):13-6.
523. Reeves RR, Burke RS. Abuse of combinations of gabapentin and quetiapine. Primary Care Companion to the Journal of Clinical Psychiatry. 2014;16(5).
524. Hung OL, Shih RD. Antiepileptic drugs: the old and the new. Emerg Med Clin North Am. 2011;29(1):141-50.
525. Middleton O. Suicide by gabapentin overdose. Journal of Forensic Sciences. 2011;56(5):1373-5.
526. Rasimas JJ, Burkhart KK. Cardiac conduction disturbances after an overdose of nefazodone and gabapentin. Am J Emerg Med. 2006;24(7):886-8.
527. Schauer SG, Varney SM. Gabapentin overdose in a military beneficiary. Mil Med. 2013;178(1):e133-5.
528. Sukumaran S, Herbert J, Tracey J, Delanty N. Safety of newer generation anti-epileptic drugs in non-accidental overdose: an Irish population study. Seizure. 2005;14(3):151-6.
529. Awaad Y. Accidental overdosage of levetiracetam in two children caused no side effects. Epilepsy & Behavior. 2007;11(2):247.
530. Bishop-Freeman SC, Kornegay NC, Winecker RE. Postmortem levetiracetam (Keppra) data from North Carolina. J Anal Toxicol. 2012;36(6):422-8.
531. Bodmer M, Monte AA, Kokko J, Yin S. Safety of non-therapeutic levetiracetam ingestions--a poison center based study. Pharmacoepidemiol Drug Saf. 2011;20(4):366-9.
532. Chua-Tuan JL, Cao D, Iwanicki JL, Hoyte CO. Cardiac sodium channel blockade after an intentional ingestion of lacosamide, cyclobenzaprine, and levetiracetam: Case report. Clin Toxicol (Phila). 2015;53(6):565-8.
533. Larkin TM, Cohen-Oram AN, Catalano G, Catalano MC. Overdose with levetiracetam: a case report and review of the literature. J Clin Pharm Ther. 2013;38(1):68-70.
534. Algahtani HA, Aldarmahi AA, Al-Rabia MW, Almalki WH, Bryan Young G. Generalized myoclonus and spasticity induced by lamotrigine toxicity: a case report and literature review. Clin Neuropharmacol. 2014;37(2):52-4.
535. Daana M, Nevo Y, Tenenbaum A, Taustein I, Berger I. Lamotrigine overdose in a child. J Child Neurol. 2007;22(5):642-4.
536. Fleurat M, Smollin C. Case files of the University of California San Francisco Medical Toxicology Fellowship: lamotrigine toxicity. J Med Toxicol. 2012;8(1):52-8.
537. French LK, McKeown NJ, Hendrickson RG. Complete heart block and death following lamotrigine overdose. Clin Toxicol (Phila). 2011;49(4):330-3.
538. Miller MA, Levsky ME. Choreiform dyskinesia following isolated lamotrigine overdose. J Child Neurol. 2008;23(2):243.
539. Nixon AC, Doak MW, Crozier H, Crooks DP, Waring WS. Patterns of antiepileptic drug overdose differ between men and women: admissions to the Edinburgh Poisons Unit, 2000-2007. Qjm. 2009;102(1):51-6.
540. Schwartz MD, Geller RJ. Seizures and altered mental status after lamotrigine overdose. Ther Drug Monit. 2007;29(6):843-4.
541. Vaks YK, Nandu B. A 34-year-old woman with depression, suicidal ideation. Psychiatric Annals. 2011;41(7):367-9.
542. Veerapandiyan A, Gallentine WB, Winchester SA, Baker J, Kansagra SM, Mikati MA. Oculogyric crises secondary to lamotrigine overdosage. Epilepsia. 2011;52(3):e4-6.
543. Venkatraman N, O'Neil D, Hall AP. Life-threatening overdose with lamotrigine, citalopram, and chlorpheniramine. J Postgrad Med. 2008;54(4):316-7.
544. Anand JS, Chodorowski Z, Wisniewski M. Seizures induced by topiramate overdose. Clin Toxicol (Phila). 2007;45(2):197.
545. Brandt C, Elsner H, Furatsch N, Hoppe M, Nieder E, Rambeck B, et al. Topiramate overdose: a case report of a patient with extremely high topiramate serum concentrations and nonconvulsive status epilepticus. Epilepsia. 2010;51(6):1090-3.
546. Lin G, Lawrence R. Pediatric case report of topiramate toxicity. Clin Toxicol (Phila). 2006;44(1):67-9.
547. Lofton AL, Klein-Schwartz W. Evaluation of toxicity of topiramate exposures reported to poison centers. Hum Exp Toxicol. 2005;24(11):591-5.
548. Lynch MJ, Pizon AF, Siam MG, Krasowski MD. Clinical effects and toxicokinetic evaluation following massive topiramate ingestion. J Med Toxicol. 2010;6(2):135-8.
549. Sein Anand J, Chodorowski Z, Zbikowska-Bojko M. Acute suicidal intoxication with topiramate. Przegl Lek. 2005;62(6):519.
550. Wisniewski M, Lukasik-Glebocka M, Anand JS. Acute topiramate overdose--clinical manifestations. Clin Toxicol (Phila). 2009;47(4):317-20.
551. Al Aly Z, Yalamanchili P, Gonzalez E. Extracorporeal management of valproic acid toxicity: a case report and review of the literature. Semin Dial. 2005;18(1):62-6.
552. Camilleri C, Albertson T, Offerman S. Fatal cerebral edema after moderate valproic acid overdose. Annals of emergency medicine. 2005;45(3):337-8.
553. Carran M. Anticonvulsant overdose: can we shorten the coma? Critical Care Medicine. 2009;37(12):3187-8.

554. Chan YC, Tse ML, Lau FL. Two cases of valproic acid poisoning treated with L-carnitine. Hum Exp Toxicol. 2007;26(12):967-9.
555. Davison AS, Milan AM, Roberts NB. The consequences of valproate overdose. Clin Chem. 2011;57(9):1233-7.
556. Dichtwald S, Dahan E, Adi N, Moses A, Sorkine P. Molecular adsorbent recycling system therapy in the treatment of acute valproic acid intoxication. Isr Med Assoc J. 2010;12(5):307-8.
557. Eyer F, Felgenhauer N, Pfab R, Thurmel K, Zilker T. Treatment of severe intravenous phenytoin overdose with hemodialysis and hemoperfusion. Med Sci Monit. 2008;14(12):CS145-8.
558. Hassanian-Moghaddam H, Zarei MR, Kargar M, Sarjami S, Rasouli MR. Factors associated with nonbenzodiazepine antiepileptic drug intoxication: analysis of 9,809 registered cases of drug poisoning. Epilepsia. 2010;51(6):979-83.
559. Hedge MW. Miscellaneous central nervous system intoxicants. Crit Care Clin. 2012;28(4):587-600.
560. Jung J, Eo E, Ahn KO. A case of hemoperfusion and L-carnitine management in valproic acid overdose. Am J Emerg Med. 2008;26(3):388.e3-4.
561. Kazim S, Mohindra R, Gosselin S, Larocque A. QTc prolongation and valproate toxicity. Clin Toxicol (Phila). 2013;51(3):193.
562. Khan E, Huggan P, Celi L, MacGinley R, Schollum J, Walker R. Sustained low-efficiency dialysis with filtration (SLEDD-f) in the management of acute sodium valproate intoxication. Hemodialysis International. 2008;12(2):211-4.
563. Lheureux PE, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity - what is the evidence? Crit Care. 2005;9(5):431-40.
564. Licari E, Calzavacca P, Warrillow SJ, Bellomo R. Life-threatening sodium valproate overdose: a comparison of two approaches to treatment. Critical Care Medicine. 2009;37(12):3161-4.
565. Lin WC, Tsao JH, Tsai SJ. Delayed thrombocytopenia after valproic acid overdose. Gen Hosp Psychiatry. 2008;30(5):489-90.
566. Marusic S, Obreli Neto PR, Vuletic V, Kirin M. Peripheral mononeuropathy associated with valproic acid poisoning in an adult patient. Int J Clin Pharmacol Ther. 2014;52(9):802-4.
567. Meyer S, Kuhlmann MK, Peters FT, Limbach HG, Lindinger A. Severe valproic acid intoxication is associated with atrial tachycardia: secondary detoxication by hemoperfusion. Klin Padiatr. 2005;217(2):82-5.
568. Min YG, Tse ML. Image in toxicology: Pseudo-subarachnoid hemorrhage in a case of severe valproic acid poisoning. Clin Toxicol (Phila). 2011;49(7):699-700.
569. Moinho R, Dias A, Estanqueiro P, Farela Neves J. Overdose with antiepileptic drugs: the efficacy of extracorporeal removal techniques. BMJ Case Rep. 2014;24:24.
570. Ray S, Skellett S. Valproate toxicity in a child: two novel observations. Clin Toxicol (Phila). 2013;51(1):60.
571. Robinson P, Abbott C. Severe hypothermia in association with sodium valproate overdose. New Zealand Medical Journal. 2005;118(1223):U1681.
572. Sikma MA, Mier JC, Meulenbelt J. Massive valproic acid overdose, a misleading case. Am J Emerg Med. 2008;26(1):110.e3-6.
573. Thanacoody RH. Extracorporeal elimination in acute valproic acid poisoning. Clin Toxicol (Phila). 2009;47(7):609-16.
574. Unal E, Kaya U, Aydin K. Fatal valproate overdose in a newborn baby. Hum Exp Toxicol. 2007;26(5):453-6.
575. Vannaprasaht S, Tiamkao S, Sirivongs D, Piyavhatkul N. Acute valproic acid overdose: enhance elimination with multiple-doses activated charcoal. Journal of the Medical Association of Thailand. 2009;92(8):1113-5.
576. Weiner D, Nir V, Klein-Kremer A, Kassem E. Chronic valproic acid intoxication. Pediatr Emerg Care. 2013;29(6):756-7.
577. Wilimowska J, Klys M, Jawien W. Analysis of variability of concentrations of valproic acid (VPA) and its selected metabolites in the blood serum of patients treated with VPA and patients hospitalized because of VPA poisoning. Arch Med Sadowej Kryminol. 2014;64(4):212-29.
578. Hosseini SH, Ahmadi A. Abuse potential of carbamazepine for euphorigenic effects. Drug Res (Stuttg). 2015;65(4):223-4.
579. Bek K, Kocak S, Ozkaya O, Yilmaz Y, Aydin OF, Tasdoven CS. Carbamazepine poisoning managed with haemodialysis and haemoperfusion in three adolescents. Nephrology. 2007;12(1):33-5.
580. Brahmi N, Kouraichi N, Abderrazek H, Thabet H, Amamou M. Clinical experience with carbamazepine overdose: relationship between serum concentration and neurological severity. J Clin Psychopharmacol. 2008;28(2):241-3.
581. Chung YK, Chang KY, Park HS, Kim MH, Lee KM, Lim TS, et al. Severe carbamazepine intoxication unresponsive to albumin-enhanced continuous venovenous hemodiafiltration with low dialysate flow. Hemodialysis International. 2014;18(2):551-5.
582. Fuh L, Hays H, Brown N, Shirk MB. Characterization of drug overdoses in an Ohio incarcerated population. Clin Toxicol (Phila). 2016;54(3):266-70.
583. Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo TH, Coogan A, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2014;52(10):993-1004.
584. Goktas U, Kati I, Yuce HH. Management of a severe carbamazepine overdose with continuous venovenous hemodiafiltration. Am J Emerg Med. 2010;28(2):260.e1-2.
585. Jha A, Abhilash KP, Bandhyopadhyay R, Victor PJ. Hypoglycemia - a rare complication of carbamazepine overdose. Indian Journal of Pharmacology. 2014;46(6):651-2.
586. Lurie Y, Bentur Y, Levy Y, Baum E, Krivoy N. Limited efficacy of gastrointestinal decontamination in severe slow-release carbamazepine overdose. Ann Pharmacother. 2007;41(9):1539-43.
587. Mise S, Jukic I, Tonkic A, Titlic M, Mise S. Multidose activated charcoal in the treatment of carbamazepine overdose with seizures: a case report. Arh Hig Rada Toksikol. 2005;56(4):333-8.
588. Mittag N, Meister S, Berg AM, Walther UI. A Case Report of a Carbamazepine Overdose With Focus on Pharmacokinetic Aspects. Pharmacopsychiatry. 2016;49(2):76-8.
589. Narayan R, Rizzo M, Cole M. Successful treatment of severe carbamazepine toxicity with 5% albumin-enhanced continuous venovenous hemodialysis. J Artif Organs. 2014;17(2):206-9.

590. Ozhasenekler A, Gokhan S, Guloglu C, Orak M, Ustundag M. Benefit of hemodialysis in carbamazepine intoxications with neurological complications. Eur Rev Med Pharmacol Sci. 2012;16 Suppl 1:43-7.
591. Patel VH, Schindlbeck MA, Bryant SM. Delayed elevation in carbamazepine concentrations after overdose: a retrospective poison center study. American Journal of Therapeutics. 2013;20(6):602-6.
592. Perez A, Wiley JF. Pediatric carbamazepine suspension overdose-clinical manifestations and toxicokinetics. Pediatr Emerg Care. 2005;21(4):252-4.
593. Pilapil M, Petersen J. Efficacy of hemodialysis and charcoal hemoperfusion in carbamazepine overdose. Clin Toxicol (Phila). 2008;46(4):342-3.
594. Shah S, Tomlin M, Sparkes D. Lack of effect of high-volume continuous veno-venous haemofiltration with dialysis in massive carbamazepine overdose. BMJ Case Rep. 2012;12:12.
595. Soderstrom J, Murray L, Little M, Daly FF. Toxicology case of the month: Carbamazepine overdose. Emerg Med J. 2006;23(11):869-71.
596. Takamiya M, Aoki Y, Niitsu H, Saigusa K. A case of carbamazepine overdose with focal myocarditis. Leg Med (Tokyo). 2006;8(4):243-7.
597. Unei H, Ikeda H, Murakami T, Tanigawa K, Kihira K. Detoxication treatment for carbamazepine and lithium overdose. Yakugaku Zasshi. 2008;128(1):165-70.
598. Yildiz TS, Toprak DG, Arisoy ES, Solak M, Toker K. Continuous venovenous hemodiafiltration to treat controlled-release carbamazepine overdose in a pediatric patient. Paediatr Anaesth. 2006;16(11):1176-8.
599. Hofer KE, Trachsel C, Rauber-Luthy C, Kupferschmidt H, Kullak-Ublick GA, Ceschi A. Moderate toxic effects following acute zonisamide overdose. Epilepsy & Behavior. 2011;21(1):91-3.
600. Wightman RS, Zell-Kanter M, Van Roo J, Leikin JB. Zonisamide toxicity in a patient with an intentional overdose. Ann Pharmacother. 2011;45(4):547.
601. Fulton JA, Hoffman RS, Nelson LS. Tiagabine overdose: a case of status epilepticus in a non-epileptic patient. Clin Toxicol (Phila). 2005;43(7):869-71.
602. Kazzi ZN, Jones CC, Morgan BW. Seizures in a pediatric patient with a tiagabine overdose. J Med Toxicol. 2006;2(4):160-2.
603. Spiller HA, Wiles D, Russell JL, Casavant MJ. Review of toxicity and trends in the use of tiagabine as reported to US poison centers from 2000 to 2012. Hum Exp Toxicol. 2016;35(2):109-13.
604. Spiller HA, Winter ML, Ryan M, Krenzelok EP, Anderson DL, Thompson M, et al. Retrospective evaluation of tiagabine overdose. Clin Toxicol (Phila). 2005;43(7):855-9.
605. Furlanut M, Franceschi L, Poz D, Silvestri L, Pecorari M. Acute oxcarbazepine, benazepril, and hydrochlorothiazide overdose with alcohol. Ther Drug Monit. 2006;28(2):267-8.
606. Pedrini M, Noguera A, Vinent J, Torra M, Jimenez R. Acute oxcarbazepine overdose in an autistic boy. Br J Clin Pharmacol. 2009;67(5):579-81.
607. Malissin I, Baud FJ, Deveaux M, Champion S, Deye N, Megarbane B. Fatal lacosamide poisoning in relation to cardiac conduction impairment and cardiovascular failure. Clin Toxicol (Phila). 2013;51(4):381-2.
608. Garg A, Agarwal A, Jiloha RC. Phenytoin dependence syndrome: A case report. Journal of Neuropsychiatry and Clinical Neurosciences. 2010;22(4):E30-E1.
609. Craig S. Phenytoin poisoning. Neurocrit Care. 2005;3(2):161-70.
610. Gaies E, Charfi R, Trabelsi S, Salouage I, Lakahl M, Klouz A. Acute phenytoin intoxication: two cases report and literature review. Therapie. 2011;66(5):461-3.
611. Ghannoum M, Troyanov S, Ayoub P, Lavergne V, Hewlett T. Successful hemodialysis in a phenytoin overdose: case report and review of the literature. Clin Nephrol. 2010;74(1):59-64.
612. Kang CK, Kim MK, Kim MJ, Jun KI, Kim KW, Park SH, et al. Acute respiratory failure caused by phenytoin overdose. Korean J Intern Med. 2013;28(6):736-8.
613. Zhang M, Sproule B. Publication trends from 1950 to 2009: Opioids, benzodiazepines, barbiturates, and amphetamines. Drug and Alcohol Dependence. 2015;146:e30-e1.
614. Khalil A, Okasha T, Shawky M, Haroon A, Elhabiby M, Carise D, et al. Characterization of substance abuse patients presenting for treatment at a university psychiatric hospital in Cairo, Egypt. Addictive Disorders & Their Treatment. 2008;7(4):199-209.
615. Syed T, Cruz M. In brief: barbiturate overdosage. Pediatr Rev. 2006;27(12):e81-2.
616. Hall MT, Howard MO, McCabe SE. Prescription drug misuse among antisocial youths. Journal of Studies on Alcohol and Drugs. 2010;71(6):917-24.
617. Cottler LB, Ajinkya S, Goldberger BA, Ghani MA, Martin DM, Hu H, et al. Prevalence of drug and alcohol use in urban Afghanistan: Epidemiological data from the Afghanistan National Urban Drug Use Study (ANUDUS). The Lancet Global Health. 2014;2(10):e592-e600.
618. Ibanez GE, Purcell DW, Stall R, Parsons JT, Gomez CA. Sexual risk, substance use, and psychological distress in HIV-positive gay and bisexual men who also inject drugs. Aids. 2005;19(Suppl1):S49-S55.
619. Nyhlen A, Fridell M, Backstrom M, Hesse M, Krantz P. Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers a prospective longitudinal study 1970 - 2006. BMC Psychiatry Vol 11 2011, ArtID 122. 2011;11.
620. Mohamed HY, Ahmed SA, Fawzi MM. Sociodemographic study of acute barbiturates overdosed egyptian patients admitted to poison control center of AIN shams university hospitals during the year 2009. Indian Journal of Forensic Medicine and Toxicology. 2011;5(1):37-8.
621. Prajapati P, Sheikh MI, Brahmbhatt J. Barbiturate overdose: A case report. Journal of the Indian Medical Association. 2009;107(12):897-900.
622. Kudo K, Ishida T, Hikiji W, Usumoto Y, Umehara T, Nagamatsu K, et al. Pattern of poisoning in Japan: Selection of drugs and poisons for systematic toxicological analysis. Forensic Toxicology. 2010;28(1):25-32.
623. Therapeutic Goods Administration. Scheduling delegates final decision: codeine. 2016.

624. Bardhi F, Sifaneck SJ, Johnson BD, Dunlap E. Pills, thrills and bellyaches: Case studies of prescription pill use and misuse among marijuana/blunt smoking middle class young women. Contemporary Drug Problems: An Interdisciplinary Quarterly. 2007;34(1):53-102.
625. Van Hout MC. Nod and wave: an Internet study of the codeine intoxication phenomenon. International Journal of Drug Policy. 2015;26(1):67-77.
626. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Archives of internal medicine. 2012;172(5):425-30.
627. Fredheim OM, Skurtveit S, Moroz A, Breivik H, Borchgrevink PC. Prescription pattern of codeine for non-malignant pain: a pharmacoepidemiological study from the Norwegian Prescription Database. Acta Anaesthesiol Scand. 2009;53(5):627-33.
628. Setnik B, Roland CL, Goli V, Pixton GC, Levy-Cooperman N, Smith I, et al. Self-reports of prescription opioid abuse and diversion among recreational opioid users in a canadian and a United States city. Journal of Opioid Management. 2015;11(6):463-73.
629. Fischer B, Argento E. Prescription opioid related misuse, harms, diversion and interventions in Canada: a review. Pain physician. 2012;15(3 Suppl):Es191-203.
630. Wang KH, Becker WC, Fiellin DA. Prevalence and correlates for nonmedical use of prescription opioids among urban and rural residents. Drug and Alcohol Dependence. 2013;127(1-3):156-62.
631. Chenaf C, Kabore J-L, Delorme J, Pereira B, Mulliez A, Roche L, et al. Codeine shopping behavior in a retrospective cohort of chronic noncancer pain patients: Incidence and risk factors. The Journal of Pain. 2016;17(12):1291-301.
632. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain. 2011;152(7):1555-61.
633. Cooper RJ. 'I can' t be an addict. I am.' Over-the-counter medicine abuse: A qualitative study. BMJ Open. 2013;3 (6) (no pagination)(e002913).
634. Birt J, Johnston J, Nelson D. Exploration of claims-based utilization measures for detecting potential nonmedical use of prescription drugs. J Manage Care Pharm. 2014;20(6):639-46.
635. Blazer DG, Wu LT. Nonprescription use of pain relievers by middle-aged and elderly community-living adults: National survey on drug use and health: Brief reports. Journal of the American Geriatrics Society. 2009;57(7):1252-7.
636. Brandt SA, Taverna EC, Hallock RM. A survey of nonmedical use of tranquilizers, stimulants, and pain relievers among college students: Patterns of use among users and factors related to abstinence in non-users. Drug and Alcohol Dependence. 2014;143(1):272-6.
637. Spence D. Bad medicine: co-codamol. Bmj. 2013;346:f1821.
638. Turaeva M, Engmann B. A new pattern of drug abuse among injecting drug users in Tashkent city. Journal of Substance Use. 2013;18(1):12-20.
639. Cohen DP, Unoh E, Barry H, O'Connor JJ. Codeine misuse among service users on a methadone treatment programme. Irish Journal of Medical Science. 2010;179(3):465.
640. Blakley BW, Schilling H. Deafness associated with acetaminophen and codeine abuse. Journal of Otolaryngology - Head and Neck Surgery. 2008;37(4):507-9.
641. Castillo MMA, Caufield C, Meza MVG. Drug consumption and occupational violence in working women of Monterrey, N. L., Mexico. Revista Latino-Americana de Enfermagem. 2005;13(SpecIssue):1155-63.
642. Elhammady M, Mobasher M, Moselhy HF. Pattern of risky sexual behaviors in opioid-dependent Egyptian adults. Addictive Disorders & Their Treatment. 2014;13(2):68-74.
643. Ferreiros N, Dresen S, Hermanns-Clausen M, Auwaerter V, Thierauf A, Muller C, et al. Fatal and severe codeine intoxication in 3-year-old twins--interpretation of drug and metabolite concentrations. International Journal of Legal Medicine. 2009;123(5):387-94.
644. Hakkinen M, Launiainen T, Vuori E, Ojanpera I. Comparison of fatal poisonings by prescription opioids. Forensic Sci Int. 2012;222(1-3):327-31.
645. Schifano F, Zamparutti G, Zambello F, Oyefeso A, Deluca P, Balestrieri M, et al. Review of Deaths Related to Analgesic- and Cough Suppressant-opioids; England and Wales 1996-2002. Pharmacopsychiatry. 2006;39(5):185-91.
646. Sutlovic D, Definis-Gojanovic M. Fatal poisoning by alcohol and heroin. Arh Hig Rada Toksikol. 2007;58(3):323-8.
647. Mayor S. Drug experts call for stronger regulation of tramadol to reduce misuse. Bmj. 2013;346:f1264.
648. Zosel A, Bartelson BB, Bailey E, Lowenstein S, Dart R. Characterization of adolescent prescription drug abuse and misuse using the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System. Journal of the American Academy of Child & Adolescent Psychiatry. 2013;52(2):196-204.
649. Torrens M, Green J, Maremmani I, Touzeau D, Walcher S, Deruvo G, et al. Prescription opioids in southern Europe: Spain. Alcohol and Alcoholism. 2014;49:i15.
650. Pollice R, Casacchia M, Bianchini V, Mazza M, Conti CM, Roncone R. Severe tramadol addiction in a 61 year-old woman without a history of substance abuse. International Journal of Immunopathology and Pharmacology. 2008;21(2):475-6.
651. Farhat S, Hussain SS, Rather YH, Hussain SK. Sociodemographic profile and pattern of opioid abuse among patients presenting to a de-addiction centre in tertiary care Hospital of Kashmir. Journal of Basic and Clinical Pharmacy. 2015;6(3):94-7.
652. Ferrari A, Tiraferri I, Palazzoli F, Licata M. Tramadol abuse in a binge pattern in a young depressed woman. Eur Addict Res. 2014;20(2):82-6.
653. Skipper GE, Brase DA. Tramadol Abuse and Dependence Among Physicians. JAMA: Journal of the American Medical Association. 2005;293(16):1977-8.
654. Apert B, Benzerouk F, Rigaud A. Tramadol use disorder in a young adult. Alcoologie et Addictologie. 2015;37(4):327-32.
655. McDiarmid T, Mackler L. What is the addiction risk associated with tramadol? Journal of Family Practice. 2005;54(1):72-3.
656. Babalonis S, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL. Abuse liability and reinforcing efficacy of oral tramadol in humans. Drug and Alcohol Dependence. 2013;129(1-2):116-24.

657. Zacny JP. Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. Drug and Alcohol Dependence. 2005;80(2):273-8.
658. Winstock A, Bell J, Borschmann R. Friends, doctors, and tramadol: We might have a problem. BMJ (Online). 2013;347 (7925) (no pagination)(f5599).
659. Abdel-Hamid IA, Andersson KE, Waldinger MD, Anis TH. Tramadol Abuse and Sexual Function. Sexual Medicine Reviews. 2016;4(3):235-46.
660. Bassiony MM, Youssif UM, Hussein RA, Saeed M. Psychiatric comorbidity among egyptian patients with opioid use disorders attributed to tramadol. J Addict Med. 2015;10(4):262-8.
661. Cicero TJ, Ellis MS, Kasper ZA. Relative preferences in the abuse of immediate-release versus extended-release opioids in a sample of treatment-seeking opioid abusers. Pharmacoepidemiology and Drug Safety. 2017;26(1):56-62.
662. Abood EA, Wazaify M. Abuse and misuse of prescription and nonprescription drugs from community pharmacies in Aden City-Yemen. Substance Use & Misuse. 2016;51(7):942-7.
663. Bassiony MM, Salah El-Deen GM, Yousef U, Raya Y, Abdel-Ghani MM, El-Gohari H, et al. Adolescent tramadol use and abuse in Egypt. American Journal of Drug and Alcohol Abuse. 2015;41(3):206-11.
664. Al-Hemiary NJ, Al-Diwan JK, Hasson AL, Rawson RA. Drug and alcohol use in Iraq: Findings of the inaugural Iraqi Community Epidemiological Workgroup. Substance Use & Misuse. 2014;49(13):1759-63.
665. Karrari P, Mehrpour O, Afshari R, Keyler D. Pattern of illicit drug use in patients referred to addiction treatment centres in Birjand, Eastern Iran. Journal of the Pakistan Medical Association. 2013;63(6):711-6.
666. Zabihi E, Hoseinzaadeh A, Emami M, Mardani M, Mahmoud B, Akbar MA. Potential for tramadol abuse by patients visiting pharmacies in Northern Iran. Substance Abuse: Research and Treatment. 2011;5(1):11-5.
667. Najafi MR, Sonbolestan SA, Sonbolestan F. The prevalence of substance abuse among the epileptic patients of Isfahan. Shiraz E Medical Journal. 2011;12(3):140-3.
668. Amr M, El-Gilany A-H, El-Mogy A, Fathi W. Substance abuse and dependence among patients attending an emergency hospital in eastern Nile delta, Egypt. African Journal of Psychiatry. 2014;17(2):532-7.
669. Loffredo CA, Boulos DN, Saleh DaA, Jillson IA, Garas M, Loza N, et al. Substance use by Egyptian youth: Current patterns and potential avenues for prevention. Substance Use & Misuse. 2015;50(5):609-18.
670. Maiga DD, Seyni H, Sidikou A, Azouma A. Seizure in Tramadol and caffeine abusers: About 8 cases and review of the literature. Pan African Medical Journal. 2012;13(no pagination).
671. Jovanovic-Cupic V, Martinovic Z, Nesic N. Seizures associated with intoxication and abuse of tramadol. Clinical Toxicology. 2006;44(2):143-6.
672. Nayyar N. Serotonin syndrome associated with sertraline, trazodone and tramadol abuse. Indian Journal of Psychiatry. 2009;51(1):68.
673. Epstein DH, Preston KL, Jasinski DR. Abuse liability, behavioral pharmacology, and physical-dependence potential of opioids in humans and laboratory animals: Lessons from tramadol. Biological Psychology. 2006;73(1):90-9.
674. Raffa RB. Basic pharmacology relevant to drug abuse assessment: Tramadol as example. Journal of Clinical Pharmacy and Therapeutics. 2008;33(2):101-8.
675. Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, et al. A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. Journal of Pain and Symptom Management. 2006;31(5):465-76.
676. Schneider DM. Though it may not have high abuse potential, prescribe tramadol cautiously. Journal of Family Practice. 2005;54(1):73.
677. Radbruch L, Glaeske G, Grond S, Munchberg F, Scherbaum N, Storz E, et al. Topical review on the abuse and misuse potential of tramadol and tilidine in Germany. Subst Abus. 2013;34(3):313-20.
678. Thompson A. Review of tramadol use within nhs Scotland following reclassification. Clinical Pharmacist. 2016;8(2).
679. Robinson G, Judson G, Loan R, Bevin T, O'Connor P. Patterns of prescription drug misuse presenting to provincial drug clinics. New Zealand Medical Journal. 1336;124(1336).
680. Vietri J, Joshi AV, Barsdorf AI, Mardekian J. Prescription opioid abuse and tampering in the united states: Results of a self-report survey. Pain Medicine (United States). 2014;15(12):2064-74.
681. Touzeau D, Green JL, Maremmani I, Torrens M, Walcher S, Deruvo G, et al. Prescription opioids in southern Europe: France. Alcohol and Alcoholism. 2014;49:i15.
682. Xu JJ, Zhang C, Hu QH, Chu ZX, Zhang J, Li YZ, et al. Recreational drug use and risks of HIV and sexually transmitted infections among Chinese men who have sex with men: Mediation through multiple sexual partnerships. BMC Infectious Diseases. 2014;14:642.
683. Vorspan F, Ksouda K, Ginisty S, Lepine JP. A case report of tramadol abuse-associated tics. J Clin Psychopharmacol. 2010;30(5):647-8.
684. Dart RC, Dasgupta N, Bailey JE, Spiller HA. Interpreting poison center call volume associated with tramadol. Ann Pharmacother. 2011;45(3):424.
685. Garcia-Orjuela MG, Alarcon-Franco L, Sanchez-Fernandez JC, Agudelo Y, Zuluaga AF. Dependence to legally prescribed opioid analgesics in a university hospital in Medellin-Colombia: An observational study. BMC Pharmacology and Toxicology. 2016;17 (1) (no pagination)(42).
686. Nebhinani N, Singh SM, Gupta G. A patient with Tramadol dependence and predictable provoked epileptic seizures. Indian Journal of Psychiatry. 2013;55(3):293-4.
687. Lanier RK, Lofwall MR, Mintzer MZ, Bigelow GE, Strain EC. Physical dependence potential of daily tramadol dosing in humans. Psychopharmacology (Berl). 2010;211(4):457-66.
688. Stoehr JD, Essary AC, Ou C, Ashby R, Sucher M. The risk of tramadol abuse and dependence: findings in two patients. JAAPA : official journal of the American Academy of Physician Assistants. 2009;22(7):31-2, 4-5.
689. Bhatia MS, Jhanjee A, Oberoi A. Tramadol dependence in a hospital worker: A case report. Journal of Clinical and Diagnostic Research. 2012;6(4 SUPPL. 2):729-30.
690. Ojha R, Bhatia SC. Tramadol dependence in a patient with no previous substance history. Primary Care Companion to the Journal of Clinical Psychiatry. 2010;12(1).

691. Lakhal MH, Moula O, Maamri A, Zalila H. Tramadol dependence in a tunisian patient with no previous substance misuse history. European Psychiatry. 2015;30:1098.
692. Lafta M. Tramadol dependence in the addiction unit of Baghdad: A cross sectional study. European Psychiatry Conference: 20th European Congress of Psychiatry, EPA. 2012;27(no pagination).
693. Prakash J, Saini R. Tramadol dependence: A case report. Medical Journal Armed Forces India. 2010;66(1):93-4.
694. Tjaderborn M, Jonsson AK, Ahlner J, Hagg S. Tramadol dependence: A survey of spontaneously reported cases in Sweden. Pharmacoepidemiology and Drug Safety. 2009;18(12):1192-8.
695. Ritvo JI, Koonce R, Thurstone CC, Causey HL, III. Tramadol Dependence: Treatment with Buprenorphine/Naloxone. The American Journal on Addictions. 2007;16(1):67-8.
696. Bolin BL, Rush CR, Glaser P, Stoops WW. Repeated exposure produces tolerance to some of the abuse-related subjective effects of oral tramadol in humans. Drug and Alcohol Dependence. 2015;146:e225.
697. Inciardi JA, Cicero TJ, Munoz A, Adams EH, Geller A, Senay EC, et al. The Diversion of Ultram, Ultracet, and Generic Tramadol HCL. Journal of Addictive Diseases. 2006;25(2):53-8.
698. Progler Y. Drug addiction in Gaza and the illicit trafficking of Tramadol. Journal of Research in Medical Sciences. 2010;15(3):185-8.
699. McDonald DC, Carlson KE. Estimating the Prevalence of Opioid Diversion by "Doctor Shoppers" in the United States. PLoS ONE. 2013;8 (7) (no pagination)(e69241).
700. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Roche L, et al. Incidence of tramadol shopping behavior in a retrospective cohort of chronic non-cancer pain patients in France. Pharmacoepidemiology and Drug Safety. 2016;25(9):1088-98.
701. Winstock AR, Borschmann R, Bell J. The non-medical use of tramadol in the UK: findings from a large community sample. International Journal of Clinical Practice. 2014;68(9):1147-51.
702. Cicero TJ, Shores CN, Paradis AG, Ellis MS. Source of drugs for prescription opioid analgesic abusers: A role for the internet? Pain Medicine. 2008;9(6):718-23.
703. Nazarzadeh M, Bidel Z, Carson KV. The association between tramadol hydrochloride misuse and other substances use in an adolescent population: Phase I of a prospective survey. Addictive Behaviors. 2014;39(1):333-7.
704. El-Safty IAM, Mohy El-Deen IE, El-Rasheed AH, El-Ashmawy MFM. Renal effects of tramadol addiction and cannabinoid abuse. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015;6(1):1212-8.
705. Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving serotonergic drugs. Forensic Sci Int. 2010;198(1-3):110-7.
706. Rahimi HR, Soltaninejad K, Shadnia S. Acute tramadol poisoning and its clinical and laboratory findings. Journal of Research in Medical Sciences. 2014;19(9):855-9.
707. Perdreau E, Iriart X, Mouton JB, Jalal Z, Thambo JB. Cardiogenic shock due to acute tramadol intoxication. Cardiovasc Toxicol. 2015;15(1):100-3.
708. Tsutaoka BT, Ho RY, Fung SM, Kearney TE. Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System. Ann Pharmacother. 2015;49(12):1311-6.
709. Taghaddosinejad F, Mehrpour O, Afshari R, Seghatoleslami A, Abdollahi M, Dart RC. Factors Related to Seizure in Tramadol Poisoning and Its Blood Concentration. Journal of Medical Toxicology. 2011;7(3):183-8.
710. Michelon H, Bouchand F, Polito A, Clair B, Annane D. Fatal tramadol-induced multiple organ failure. Therapie. 2016;71(4):435-7.
711. Rizk MMM, Kamal AM, Bakheet MAA, Abdelfadeel NAM, Hassan EM, Khafagi ATM. Frequency and factors associated with occurrence of seizures in patients with tramadol abuse: An upper egyptian experience. Addictive Disorders and their Treatment. 2016;15(1):42-8.
712. Nasouhi S, Talaie H, Pajoumand A, Aghapour S, Rahimi M, Khorasani AG, et al. Hypo and hyperglycemia among tramadol overdose patients in Loghman Hakim Hospital, Tehran, Iran. Pak. 2015;28(6):1959-63.
713. Lota AS, Dubrey SW, Wills P. Profound hyponatraemia following a tramadol overdose. Qjm. 2012;105(4):397-8.
714. Cole JB, Sattiraju S, Bilden EF, Asinger RW, Bertog SC. Isolated tramadol overdose associated with Brugada ECG pattern. Pacing Clin Electrophysiol. 2012;35(8):e219-21.
715. Shadnia S, Brent J, Mousavi-Fatemi K, Hafezi P, Soltaninejad K. Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. Basic Clin Pharmacol Toxicol. 2012;111(2):133-6.
716. Daubin C, Quentin C, Goulle JP, Guillotin D, Lehoux P, Lepage O, et al. Refractory shock and asystole related to tramadol overdose. Clin Toxicol (Phila). 2007;45(8):961-4.
717. Reichert C, Reichert P, Monnet-Tschudi F, Kupferschmidt H, Ceschi A, Rauber-Luthy C. Seizures after single-agent overdose with pharmaceutical drugs: Analysis of cases reported to a poison center. Clinical Toxicology. 2014;52(6):629-34.
718. Goodarzi F, Mehrpour O, Eizadi-Mood N. A study to evaluate factors associated with seizure in tramadol poisoning in Iran. Indian Journal of Forensic Medicine and Toxicology. 2011;5(2):66-9.
719. Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. Ann Pharmacother. 2005;39(6):1039-44.
720. Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: A case series. Clinical Toxicology. 2010;48(4):337-41.
721. Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clin Toxicol (Phila). 2015;53(6):545-50.
722. Afshari R, Ghooshkhanehee H. Tramadol overdose induced seizure, dramatic rise of CPK and acute renal failure. JPMA J Pak Med Assoc. 2009;59(3):178.
723. El-Hussuna A, Arnesen RB, Rosenberg J. Tramadol poisoning with hyperamylasemia. BMJ Case Rep. 2010;06:06.
724. Farajidana H, Hassanian-Moghaddam H, Zamani N, Sanaei-Zadeh H. Tramadol-induced seizures and trauma. Eur Rev Med Pharmacol Sci. 2012;16 Suppl 1:34-7.

725. Bond GR, Ho M, Woodward RW. Trends in hepatic injury associated with unintentional overdose of paracetamol (Acetaminophen) in products with and without opioid: An analysis using the national Poison Data System of the American Association of Poison Control Centers, 2000-7. Drug Safety. 2012;35(2):149-57.
726. Hakkinen M, Launiainen T, Vuori E, Ojanpera I. Comparison of fatal poisonings by prescription opioids. Forensic Sci Int. 2012;222(1-3):327-31.
727. Srinivas NR. Differential Consequences of Tramadol in Overdosing: Dilemma of a Polymorphic Cytochrome P450 2D6-Mediated Substrate. J Pain Pall Care Pharmacother. 2015;29(3):272-5.
728. Elkalioubie A, Allorge D, Robriquet L, Wiart JF, Garat A, Broly F, et al. Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer. Eur J Clin Pharmacol. 2011;67(8):855-8.
729. Iravani FS, Akhgari M, Jokar F, Bahmanabadi L. Current trends in tramadol-related fatalities, Tehran, Iran 2005-2008. Substance Use & Misuse. 2010;45(13):2162-71.
730. Hawkes N. Deaths from tramadol and legal highs reach new highs in England and Wales. BMJ (Clinical research ed). 2013;347:f5336.
731. Hashemnejad M, Fatehi R. Epidemiological study of poisoning in patients of Karaj Shariati hospital in 2011 to 2012. International Journal of Medical Toxicology and Forensic Medicine. 2014;4(1):17-22.
732. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. Br J Clin Pharmacol. 2013;76(5):823-4.
733. De Decker K, Cordonnier J, Jacobs W, Coucke V, Schepens P, Jorens PG. Fatal intoxication due to tramadol alone: case report and review of the literature. Forensic Sci Int. 2008;175(1):79-82.
734. Simonsen KW, Christoffersen DJ, Banner J, Linnet K, Andersen LV. Fatal poisoning among patients with drug addiction. Danish Medical Journal. 2015;62(10).
735. Lelong-Boulouard V, Bourgine J, Cesbron A, Coquerel A, Loilier M, Le Boisselier R, et al. Fatal poisoning with cocaine and tramadol in a former professional cyclist. Fundamental and Clinical Pharmacology. 2015;29:56.
736. Mannocchi G, Napoleoni F, Napoletano S, Pantano F, Santoni M, Tittarelli R, et al. Fatal self administration of tramadol and propofol: a case report. J Forensic Leg Med. 2013;20(6):715-9.
737. Tjaderborn M, Jonsson AK, Hagg S, Ahlner J. Fatal unintentional intoxications with tramadol during 1995-2005. Forensic Sci Int. 2007;173(2-3):107-11.
738. Solarino B, Riesselmann B, Buschmann CT, Tsokos M. Multidrug poisoning involving nicotine and tramadol. Forensic Sci Int. 2010;194(1-3):e17-e9.
739. Hakkinen M, Vuori E, Ojanpera I. Prescription opioid abuse based on representative postmortem toxicology. Forensic Sci Int. 2014;245:121-5.
740. De Backer B, Renardy F, Denooz R, Charlier C. Quantification in postmortem blood and identification in urine of tramadol and its two main metabolites in two cases of lethal tramadol intoxication. J Anal Toxicol. 2010;34(9):599-604.
741. Pothiawala S, Ponampalam R. Surviving tramadol overdose despite a lethal blood level. Proceedings of Singapore Healthcare. 2011;20:145.
742. Randall C, Crane J. Tramadol deaths in Northern Ireland: A review of cases from 1996 to 2012. Journal of Forensic and Legal Medicine. 2014;23:32-6.
743. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol. 2008;27(3):201-5.
744. Fass J. Comment: Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. Ann Pharmacother. 2010;44(9):1509.
745. Spiller HA, Scaglione JM, Aleguas A, Foster H, Durback-Morris L, Scharman EJ, et al. Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. Ann Pharmacother. 2010;44(6):1016-21.
746. Simonsen KW, Steentoft A, Hels T, Bernhoft IM, Rasmussen BS, Linnet K. Presence of psychoactive substances in oral fluid from randomly selected drivers in Denmark. Forensic Sci Int. 2012;221(1-3):33-8.
747. Darwish S, Sadek N, Hoda H, Bothaina M, Farag I. The incidence of hepatitis C virus infection among opiate drug users in Mamoura hospital patient in Alexandria, Egypt. European Psychiatry. 2016;33:S295-S6.
748. Australian Government-Department of Health-TGA. Dextropropoxyphene: questions and answers 2014 [Available from: https://www.tga.gov.au/alert/dextropropoxyphene-questions-and-answers.
749. Fudala PJ, Johnson RE. Development of opioid formulations with limited diversion and abuse potential. Drug and Alcohol Dependence. 2006;83(Suppl 1):S40-S7.
750. Al Khaja KA, Al-Haddad MK, Al-Offi AR, Abdulraheem MH, Sequeira RP. Use of dextropropoxyphene + acetaminophen fixed-dose combination in psychiatric hospital in Bahrain: is there a cause for concern? Fundam Clin Pharmacol. 2009;23(2):253-8.
751. Ambekar A, Rao R, Mishra AK, Agrawal A. Type of opioids injected: Does it matter? A multicentric cross-sectional study of people who inject drugs. Drug and Alcohol Review. 2015;34(1):97-104.
752. Basu D, Aggarwal M, Das PP, Mattoo SK, Kulhara P, Varma VK. Changing pattern of substance abuse in patients attending a de-addiction centre in north India (1978-2008). Indian J Med Res. 2012;135(6):830-6.
753. Balhara YPS. Dextropropoxyphene ban in India: Is there a case for reconsideration? Journal of Pharmacology and Pharmacotherapeutics. 2014;5(1):8-11.
754. Wang KH, Becker WC, Fiellin DA. Prevalence and correlates for nonmedical use of prescription opioids among urban and rural residents. Drug Alcohol Depend. 2013;127(1-3):156-62.
755. Dasgupta N, Kramer ED, Zalman MA, Carino S, Jr., Smith MY, Haddox JD, et al. Association between non-medical and prescriptive usage of opioids. Drug Alcohol Depend. 2006;82(2):135-42.
756. Afshari R, Maxwell S, Dawson A, Bateman DN. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. Clin Toxicol (Phila). 2005;43(4):255-9.

757. Basu D, Banerjee A, Harish T, Mattoo SK. Disproportionately high rate of epileptic seizure in patients abusing dextropropoxyphene. The American Journal on Addictions. 2009;18(5):417-21.
758. Mattoo SK, Singh SM, Bhardwaj R, Kumar S, Basu D, Kulhara P. Prevalence and correlates of epileptic seizure in substance-abusing subjects. Psychiatry and Clinical Neurosciences. 2009;63(4):580-2.
759. Staikowsky F, Candella S, Raphael M. Dextropropoxyphene and the cardiovascular system: about two cases of acute poisoning with cardiac conduction abnormalities. Journal of Opioid Management. 2005;1(5):240-3.
760. Afshari R, Good AM, Maxwell SR, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol. 2005;60(4):444-7.
761. Hayes BD, Anderson BD. Twenty five years of poison center experience with propoxyphene overdoses the FDA could not find. Clin Toxicol (Phila). 2009;47(9):905-6.
762. Hawton K, Simkin S, Gunnell D, Sutton L, Bennewith O, Turnbull P, et al. A multicentre study of coproxamol poisoning suicides based on coroners' records in England. Br J Clin Pharmacol. 2005;59(2):207-12.
763. Jang DH, Hoffman RS, Nelson LS, Chu J, Bhanot K, Bagley W. Fatal outcome of a propoxyphene/acetaminophen (Darvocet) overdose: should it still be used in the United States? Annals of emergency medicine. 2011;57(4):421-2.
764. Jones AW, Kugelberg FC, Holmgren A, Ahlner J. Drug poisoning deaths in Sweden show a predominance of ethanol in mono-intoxications, adverse drug-alcohol interactions and poly-drug use. Forensic Sci Int. 2011;206(1-3):43-51.
765. Schifano F, Zamparutti G, Zambello F, Oyefeso A, Deluca P, Balestrieri M, et al. Review of deaths related to analgesic- and cough suppressant-opioids; England and Wales 1996-2002. Pharmacopsychiatry. 2006;39(5):185-91.
766. Simkin S, Hawton K, Sutton L, Gunnell D, Bennewith O, Kapur N. Co-proxamol and suicide: preventing the continuing toll of overdose deaths. Qjm. 2005;98(3):159-70.
767. Price JW. Comparison of random and postaccident urine drug tests in southern Indiana coal miners. J Addict Med. 2012;6(4):253-7.
768. Suohu K, Humtsoe C, Saggurti N, Sabarwal S, Mahapatra B, Kermode M. Understanding the association between injecting and sexual risk behaviors of injecting drug users in Manipur and Nagaland, India. Harm Reduction Journal Vol 9 2012, ArtID 40. 2012;9.
769. Aschenbrenner DS. FDA raises safety issues concerning propoxyphene. Am. 2010;110(1):59-60.
770. Bateman ND, Sandilands EA. European Medicines Evaluation Agency bans dextropropoxyphene: a landmark decision for clinical toxicology? Clin Toxicol (Phila). 2009;47(8):782-3.
771. Corcoran P, Reulbach U, Keeley HS, Perry IJ, Hawton K, Arensman E. Use of analgesics in intentional drug overdose presentations to hospital before and after the withdrawal of distalgesic from the Irish market. BMC Clin Pharml. 2010;10:6.
772. Gaubert S, Vie M, Damase-Michel C, Pathak A, Montastruc JL. Dextropropoxyphene withdrawal from a French university hospital: impact on analgesic drug consumption. Fundam Clin Pharmacol. 2009;23(2):247-52.
773. Hawton K, Bergen H, Simkin S, Wells C, Kapur N, Gunnell D. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: time-series study. PLoS Med. 2012;9(5):e1001213.
774. Hawton K, Bergen H, Waters K, Murphy E, Cooper J, Kapur N. Impact of withdrawal of the analgesic Co-proxamol on nonfatal self-poisoning in the UK. Crisis: Journal of Crisis Intervention & Suicide. 2011;32(2):81-7.
775. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. JAMA Intern Med. 2015;175(6):978-87.
776. Nordentoft M, Qin P, Helweg-Larsen K, Juel K. Restrictions in means for suicide: an effective tool in preventing suicide: the Danish experience. Suicide Life Threat Behav. 2007;37(6):688-97.
777. Reith DM, Fountain JS, Tilyard M. 'Opioid poisoning deaths in New Zealand (2001-2002)' and the UK's recent decision to withdraw the pain killer coproxamol. New Zealand Medical Journal. 2005;118(1209):U1294.
778. Sandilands EA, Bateman DN. Co-proxamol withdrawal has reduced suicide from drugs in Scotland. Br J Clin Pharmacol. 2008;66(2):290-3.
779. Committee on the Safety of Medicines of the UK. Overdose risk prompts UK withdrawal of propoxyphene combination. J Pain Pall Care Pharmacother. 2006;20(4):49-50.
780. Ottewell L, Walker DJ. Co-proxamol: where have all the patients gone? Rheumatology (Oxford). 2008;47(3):375.
781. Nielsen M, Hansen EH, Gotzsche PC. Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did the health authorities react? International Journal of Risk & Safety in Medicine. 2013;25(3):155-68.
782. McKenzie MS, McFarland BH. Trends in antidepressant overdoses. Pharmacoepidemiol Drug Saf. 2007;16(5):513-23.
783. Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry. 2010;196(5):354-8.
784. Naderi-Heiden A, Shadnia S, Salimi AR, Naderi A, Naderi MM, Schmid D, et al. Self-poisonings with tricyclic antidepressants and selective serotonin reuptake inhibitors in Tehran, Iran. World J Biol Psychiatry. 2009;10(4):302-12.
785. Zahl PH, De Leo D, Ekeberg O, Hjelmeland H, Dieserud G. The relationship between sales of SSRI, TCA and suicide rates in the Nordic countries. BMC Psychiatry. 2010;10:62.
786. Acikalin A, Satar S, Avc A, Topal M, Kuvandk G, Sebe A. QTc intervals in drug poisoning patients with tricyclic antidepressants and selective serotonin reuptake inhibitors. American Journal of Therapeutics. 2010;17(1):30-3.
787. Beaune S, Curis E, Casalino E, Juvin P, Megarbane B. Do serotonin reuptake inhibitors worsen outcome of patients referred to the emergency department for deliberate multi-drug exposure? Basic Clin Pharmacol Toxicol. 2015;116(4):372-7.
788. Chan AN, Gunja N, Ryan CJ. A comparison of venlafaxine and SSRIs in deliberate self-poisoning. J Med Toxicol. 2010;6(2):116-21.
789. Fazel S, Grann M, Goodwin GM. Suicide trends in discharged patients with mood disorders: Associations with selective serotonin uptake inhibitors and comorbid substance misuse. Int Clin Psychopharmacol. 2006;21(2):111-5.
790. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry. 2006;163(11):1898-904.

791. Drasch G, Dahlmann F, von Meyer L, Roider G, Eisenmenger W. Frequency of different anti-depressants associated with suicides and drug deaths. International Journal of Legal Medicine. 2008;122(2):115-21.
792. Olmer A, Iancu I, Strous RD. Exposure to antidepressant medications and suicide attempts in adult depressed inpatients. J Nerv Ment Dis. 2012;200(6):531-4.
793. Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. Australasian Psychiatry. 2010;18(3):242-5.
794. White N, Litovitz T, Clancy C. Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. J Med Toxicol. 2008;4(4):238-50.
795. Duncan RA, Armstrong PA, Paterson B. Severe hypoglycaemia in citalopram overdose. Eur J Emerg Med. 2008;15(4):234-5.
796. Waring WS, Gray JA, Graham A. Predictive factors for generalized seizures after deliberate citalopram overdose. Br J Clin Pharmacol. 2008;66(6):861-5.
797. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. Br J Clin Pharmacol. 2006;61(2):177-90.
798. Maddry JK, Breyer K, Cook KM, Heard K. Monomorphic ventricular tachycardia after intentional citalopram overdose. Am J Emerg Med. 2013;31(2):447.e5-8.
799. Bin Salih S, Al Qahtani M, Al Anazi T, Al Hussein M, Al Hayyan H, Al Modaimegh H. Metabolic acidosis and generalized seizures secondary to citalopram overdose: a case report. J Clin Pharm Ther. 2010;35(4):479-82.
800. Manini A, Smith S, Moskovitz J, Nelson L. In response to Isbister et al.: Application of pharmacokinetic-pharmacodynamic modeling in management of QT abnormalities after citalopram overdose. Intensive Care Medicine. 2007;33(4):738; author reply 9.
801. Yilmaz Z, Ceschi A, Rauber-Luthy C, Sauer O, Stedtler U, Prasa D, et al. Escitalopram causes fewer seizures in human overdose than citalopram. Clin Toxicol (Phila). 2010;48(3):207-12.
802. Liotier J, Coudore F. Drug monitoring of a case of citalopram overdosage. Drug Chem Toxicol. 2011;34(4):420-3.
803. Lung D, Yeh K, Kiang C. Delayed, fatal cardiotoxicity associated with bupropion and citalopram overdose. J Clin Psychopharmacol. 2012;32(3):431-4.
804. Hayes BD, Klein-Schwartz W, Clark RF, Muller AA, Miloradovich JE. Comparison of toxicity of acute overdoses with citalopram and escitalopram. J Emerg Med. 2010;39(1):44-8.
805. Jimmink A, Caminada K, Hunfeld NG, Touw DJ. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit. 2008;30(3):365-71.
806. Masullo LN, Miller MA, Baker SD, Bose S, Levsky M. Clinical course and toxicokinetic data following isolated citalopram overdose in an infant. Clin Toxicol (Phila). 2006;44(2):165-8.
807. Tarabar AF, Hoffman RS, Nelson L. Citalopram overdose: late presentation of torsades de pointes (TdP) with cardiac arrest. J Med Toxicol. 2008;4(2):101-5.
808. Kraai EP, Seifert SA. Citalopram Overdose: a Fatal Case. J Med Toxicol. 2015;11(2):232-6.
809. Isbister GK, Friberg LE, Stokes B, Buckley NA, Lee C, Gunja N, et al. Activated charcoal decreases the risk of QT prolongation after citalopram overdose. Annals of emergency medicine. 2007;50(5):593-600, .e1-46.
810. Zisook S, Trivedi MH, Warden D, Lebowitz B, Thase ME, Stewart JW, et al. Clinical correlates of the worsening or emergence of suicidal ideation during SSRI treatment of depression: an examination of citalopram in the STAR D study. Journal of Affective Disorders. 2009;117(1-2):63-73.
811. Wood DM, Rajalingam Y, Greene SL, Morgan PE, Gerrie D, Jones AL, et al. Status epilepticus following intentional overdose of fluvoxamine: a case report with serum fluvoxamine concentration. Clin Toxicol (Phila). 2007;45(7):791.
812. Neckelmann D, Maehlum E, Waage IM. Sertindole and fluoxetine overdose with benign outcome. Nord J Psychiatry. 2010;64(4):288.
813. Wittebole X, Hantson P, Wallemacq P. Prolonged hypotension due to deliberate trazodone overdose in the presence of fluoxetine. Ann Clin Psychiatry. 2007;19(3):201-2.
814. Wu ML, Deng JF. Fatal serotonin toxicity caused by moclobemide and fluoxetine overdose. Chang Gung Med J. 2011;34(6):644-9.
815. Cooper JM, Duffull SB, Saiao AS, Isbister GK. The pharmacokinetics of sertraline in overdose and the effect of activated charcoal. Br J Clin Pharmacol. 2015;79(2):307-15.
816. Byard RW, Riches KJ, Kostakis C, Felgate HE. Diabetic ketoacidosis--a possible complicating factor in deaths associated with drug overdose: two case reports. Med Sci Law. 2006;46(1):81-4.
817. Vanderburg DG, Batzar E, Fogel I, Kremer CME. A pooled analysis of suicidality in double-blind, placebo-controlled studies of sertraline in adults. J Clin Psychiatry. 2009;70(5):674-83.
818. Mohammed R, Norton J, Geraci SA, Newman DB, Koch CA. Prolonged QTc interval due to escitalopram overdose. J Miss State Med Assoc. 2010;51(12):350-3.
819. van Gorp F, Duffull S, Hackett LP, Isbister GK. Population pharmacokinetics and pharmacodynamics of escitalopram in overdose and the effect of activated charcoal. Br J Clin Pharmacol. 2012;73(3):402-10.
820. LoVecchio F, Watts D, Winchell J, Knight J, McDowell T. Outcomes after supratherapeutic escitalopram ingestions. J Emerg Med. 2006;30(1):17-9.
821. van Gorp F, Whyte IM, Isbister GK. Clinical and ECG effects of escitalopram overdose. Annals of emergency medicine. 2009;54(3):404-8.
822. Francesconi G, Orsolini L, Papanti D, Corkery JM, Schifano F. Venlafaxine as the 'baby ecstasy'? Literature overview and analysis of web-based misusers' experiences. Hum. 2015;30(4):255-61.
823. Essizoglu A, Yasan A, Bulbul I, Karabulut E, Gurgen F. Venlafaxine addiction without a history of alcohol and substance abuse: A case report. Dusunen Adam. 2012;25(4):376-8.
824. Namdari B. Venlafaxine abuse in a patient with schizophrenia and prior history of substance dependence: a case report. Journal of Addictive Diseases. 2013;32(4):393-5.

825. Song JH, Yu BH, Lee D, Yoon SC, Jeon HJ. Uncontrolled self-medication with venlafaxine in a patient with major depressive disorder. Psychiatry Investigation. 2011;8(1):74-6.
826. Quaglio G, Schifano F, Lugoboni F. Venlafaxine dependence in a patient with a history of alcohol and amineptine misuse. Addiction (Abingdon, England). 2008;103(9):1572-4.
827. Wilson AD, Howell C, Waring WS. Venlafaxine ingestion is associated with rhabdomyolysis in adults: a case series. J Toxicol Sci. 2007;32(1):97-101.
828. Ware TL, McCloskey K, Ryan MM, Cranswick N. Venlafaxine ingestion in a 4-year-old girl. J Paediatr Child Health. 2012;48(11):1047-8.
829. Godkar D, Stensby J, Sinnapunayagam S, Niranjan S. Venlafaxine induced acute myocardial infarction with normal coronary arteries. American Journal of Therapeutics. 2009;16(4):365-6.
830. Taylor D. Venlafaxine and cardiovascular toxicity. Bmj. 2010;340:c411.
831. Deshauer D. Venlafaxine (Effexor): concerns about increased risk of fatal outcomes in overdose. Cmaj. 2007;176(1):39-40.
832. Caroselli C, Ricci G. The venlafaxine "heart revenge:" a short report. Clin Cardiol. 2010;33(4):E46-7.
833. Kontio T, Salo A, Kantola T, Toivonen L, Skrifvars MB. Successful use of therapeutic hypothermia after cardiac arrest due to amitriptyline and venlafaxine intoxication. Ther. 2015;5(2):104-9.
834. Vinetti M, Haufroid V, Capron A, Classen JF, Marchandise S, Hantson P. Severe acute cardiomyopathy associated with venlafaxine overdose and possible role of CYP2D6 and CYP2C19 polymorphisms. Clin Toxicol (Phila). 2011;49(9):865-9.
835. Paulzen M, Henkel K, Tauber S, Reich A, Eap CB, Grunder G. Plasma levels and cerebrospinal fluid penetration of venlafaxine in a patient with a nonfatal overdose during a suicide attempt. J Clin Psychopharmacol. 2014;34(3):398-9.
836. Megarbane B, Bloch V, Deye N, Baud FJ. Pharmacokinetic/pharmacodynamic modelling of cardiac toxicity in venlafaxine overdose. Intensive Care Medicine. 2007;33(1):195-6; author reply 7.
837. Varatharaj A, Moran J. Pendular nystagmus associated with venlafaxine overdose: a forme fruste of the serotonin syndrome? BMJ Case Rep. 2014;06:06.
838. Neil CJ, Chong CR, Nguyen TH, Horowitz JD. Occurrence of Tako-Tsubo cardiomyopathy in association with ingestion of serotonin/noradrenaline reuptake inhibitors. Heart Lung Circ. 2012;21(4):203-5.
839. Kaufman KR, Levitt MJ, Schiltz JF, Sunderram J. Neuroleptic malignant syndrome and serotonin syndrome in the critical care setting: case analysis. Ann Clin Psychiatry. 2006;18(3):201-4.
840. Brvar M, Kozelj G, Masic LP. Hypoglycemia in venlafaxine overdose: a hypothesis of increased glucose uptake. Eur J Clin Pharmacol. 2015;71(2):261-2.
841. Francino MC, Bretaudeau Deguigne M, Badin J, Turcant A, Perrotin D. Hypoglycaemia: a little known effect of Venlafaxine overdose. Clin Toxicol (Phila). 2012;50(3):215-7.
842. Djogovic D, Hudson D, Jacka M. Gastric bezoar following venlafaxine overdose. Clin Toxicol (Phila). 2007;45(6):735.
843. Bosse GM, Spiller HA, Collins AM. A fatal case of venlafaxine overdose. J Med Toxicol. 2008;4(1):18-20.
844. Hojer J, Hulting J, Salmonson H. Fatal cardiotoxicity induced by venlafaxine overdosage. Clin Toxicol (Phila). 2008;46(4):336-7.
845. Klys M, Kowalski P, Rojek S, Gross A. Death of a female cocaine user due to the serotonin syndrome following moclobemide-venlafaxine overdose. Forensic Sci Int. 2009;184(1-3):e16-20.
846. Garcia-Cabeza I, de Blas MM, Epifanio MM, de Chavez MG. Cognitive deterioration after venlafaxine overdose. J Emerg Med. 2011;40(5):e103-6.
847. Dennison EA, Raidoo BM, Cruz R, Raidoo D. A case of high-dose venlafaxine-related psychosis. J Clin Psychopharmacol. 2013;33(1):134-6.
848. Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. Br J Clin Pharmacol. 2007;64(2):192-7.
849. Christoph M, Ebner B, Stolte D, Ibrahim K, Kolschmann S, Strasser RH, et al. Broken heart syndrome: Tako Tsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor Venlafaxine. European Neuropsychopharmacology. 2010;20(8):594-7.
850. Lin YH, Huang E, Chien YL. Bilateral pallidal necrosis and cardiac toxicity in a patient with venlafaxine and bupropion overdose. Am J Psychiatry. 2012;169(9):993-4.
851. Miller T, McGoodwin L, Hagemann T. Anticholinergic-type effects following a pediatric venlafaxine overdose. Clin Toxicol (Phila). 2008;46(4):338-9.
852. Hudson D, Djogovic D. Alternate venlafaxine kinetics in overdose patients. J Clin Pharm Ther. 2007;32(1):109.
853. Paparrigopoulos T, Tzavellas E, Karaiskos D, Ilias I, Liappas I. Acute eosinophilic pneumonia after venlafaxine overdose. J Clin Psychopharmacol. 2011;31(2):258-9.
854. Verheijden NAF, Koch BC, Brkic Z, Alsma J, Klein Nagelvoort-Schuit SCE. A 45-year-old woman with an anticholinergic toxidrome. Neth J Med. 2016;74(3):133-5.
855. Forrester MB, Lizette Villarreal C. Comparison of desvenlafaxine and venlafaxine ingestions reported to Texas Poison Centers. Journal of Pharmacy Technology. 2011;27(1):35-40.
856. Darracq MA, Clark A, Qian L, Cantrell FL. A retrospective review of isolated duloxetine-exposure cases. Clin Toxicol (Phila). 2013;51(2):106-10.
857. Paulzen M, Hiemke C, Grunder G. Plasma levels and cerebrospinal fluid penetration by duloxetine in a patient with a non-fatal overdose during a suicide attempt. International Journal of Neuropsychopharmacology. 2009;12(10):1431-2.
858. Scanlon KA, Stoppacher R, Blum LM, Starkey SJ. Comprehensive Duloxetine Analysis in a Fatal Overdose. J Anal Toxicol. 2016;40(2):167-70.
859. Kruithof MK, Bruins NA, van Roon EN. Coma after overdose with duloxetine. Ann Pharmacother. 2011;45(1):e5.
860. Vey EL, Kovelman I. Adverse events, toxicity and post-mortem data on duloxetine: Case reports and literature survey. Journal of Forensic and Legal Medicine. 2010;17(4):175-85.

861. Tatli O, Karaca Y, Gunaydin M, Yurtsever S, Tuten G. Cerebellitis developing after tricyclic antidepressant poisoning. Am J Emerg Med. 2013;31(9):1419.e3-5.
862. Veris-van Dieren J, Valk L, van Geijlswijk I, Tjan D, van Zanten A. Coma with ECG abnormalities: consider tricyclic antidepressant intoxication. Neth J Med. 2007;65(4):142-6.
863. Helm C. Country cardiograms case 27. Overdose from tricyclics. Can J Rural Med. 2005;10(3):171, 91-2.
864. Nutt DJ. Death by tricyclic: the real antidepressant scandal? Journal of Psychopharmacology. 2005;19(2):123-4.
865. Tan C, Pillai S, Manning PG. Electrocardiographical case. A man found unconscious. Singapore Med J. 2006;47(8):730-4; quiz 5.
866. Blaber MS, Khan JN, Brebner JA, McColm R. "Lipid rescue" for tricyclic antidepressant cardiotoxicity. J Emerg Med. 2012;43(3):465-7.
867. Nair A, Paul FK, Protopapas M. Management of near fatal mixed tricyclic antidepressant and selective serotonin reuptake inhibitor overdose with Intralipid20% emulsion. Anaesth Intensive Care. 2013;41(2):264-5.
868. Eyer F, Stenzel J, Schuster T, Felgenhauer N, Pfab R, von Bary C, et al. Risk assessment of severe tricyclic antidepressant overdose. Hum Exp Toxicol. 2009;28(8):511-9.
869. Miura N, Saito T, Taira T, Umebachi R, Inokuchi S. Risk factors for QT prolongation associated with acute psychotropic drug overdose. Am J Emerg Med. 2015;33(2):142-9.
870. Citak A, Soysal DD, Ucsel R, Karabocuoglu M, Uzel N. Seizures associated with poisoning in children: tricyclic antidepressant intoxication. Pediatrics International. 2006;48(6):582-5.
871. Doak MW, Nixon AC, Lupton DJ, Waring WS. Self-poisoning in older adults: patterns of drug ingestion and clinical outcomes. Age Ageing. 2009;38(4):407-11.
872. Sinyor M, Howlett A, Cheung AH, Schaffer A. Substances used in completed suicide by overdose in Toronto: an observational study of coroner's data. Can J Psychiatry. 2012;57(3):184-91.
873. Gallagher LM, Kappatos D, Tisch C, Ellis PM. Suicide by poisoning in New Zealand--a toxicological analysis. New Zealand Medical Journal. 2012;125(1362):15-25.
874. Perza MN, Schneider LA, Rosini JM. Suspected tricyclic antidepressant overdose successfully treated with lipids. J Emerg Nurs. 2013;39(3):296-8.
875. Agrawal P, Nadel ES, Brown DF. Tricyclic antidepressant overdose. J Emerg Med. 2008;34(3):321-5.
876. Koegelenberg CF, Joubert ZJ, Irusen EM. Tricyclic antidepressant overdose necessitating ICU admission. Samj, S. 2012;102(5):293-4.
877. Thanacoody HK, Thomas SH. Tricyclic antidepressant poisoning : cardiovascular toxicity. Toxicol Rev. 2005;24(3):205-14.
878. Pierog JE, Kane KE, Kane BG, Donovan JW, Helmick T. Tricyclic antidepressant toxicity treated with massive sodium bicarbonate. Am J Emerg Med. 2009;27(9):1168.e3-7.
879. Dianat S, Zarei MR, Hassanian-Moghaddam H, Rashidi-Ranjbar N, Rahimian R, Rasouli MR. Tricyclic antidepressants intoxication in Tehran, Iran: epidemiology and associated factors. Hum Exp Toxicol. 2011;30(4):283-8.
880. Barry JD, Durkovich DW, Williams SR. Vasopressin treatment for cyclic antidepressant overdose. J Emerg Med. 2006;31(1):65-8.
881. Zuidema X, Dunser MW, Wenzel V, Rozendaal FW, de Jager CP. Terlipressin as an adjunct vasopressor in refractory hypotension after tricyclic antidepressant intoxication. Resuscitation. 2007;72(2):319-23.
882. Hutton J, Dent A, Buykx P, Burgess S, Flander L, Dietze P. The characteristics of acute non-fatal medication-related events attended by ambulance services in the Melbourne Metropolitan Area 1998-2002. Drug Alcohol Rev. 2010;29(1):53-8.
883. Caksen H, Akbayram S, Odabas D, Ozbek H, Erol M, Akgun C, et al. Acute amitriptyline intoxication: an analysis of 44 children. Hum Exp Toxicol. 2006;25(3):107-10.
884. Kiyan S, Aksay E, Yanturali S, Atilla R, Ersel M. Acute myocardial infarction associated with amitriptyline overdose. Basic Clin Pharmacol Toxicol. 2006;98(5):462-6.
885. Paksu S, Duran L, Altuntas M, Zengin H, Salis O, Ozsevik SN, et al. Amitriptyline overdose in emergency department of university hospital: evaluation of 250 patients. Hum Exp Toxicol. 2014;33(9):980-90.
886. Howell B, Chauhan A. Amitriptyline overdose treatment by pegylated anionic liposomes. J Colloid Interface Sci. 2008;324(1-2):61-70.
887. Deegan C, O'Brien K. Amitriptyline poisoning in a 2-year old. Paediatr Anaesth. 2006;16(2):174-7.
888. Allibe N, Eysseric-Guerin H, Kintz P, Bartoli M, Bost-Bru C, Grenier F, et al. Amitriptyline poisoning of a baby: how informative can hair analysis be? Forensic Sci Int. 2015;249:53-8.
889. Bebarta VS, Waksman JC. Amitriptyline-induced Brugada pattern fails to respond to sodium bicarbonate. Clin Toxicol (Phila). 2007;45(2):186-8.
890. Guloglu C, Orak M, Ustundag M, Altunci YA. Analysis of amitriptyline overdose in emergency medicine. Emerg Med J. 2011;28(4):296-9.
891. Perichon D, Turfus S, Gerostamoulos D, Graudins A. An assessment of the in vivo effects of intravenous lipid emulsion on blood drug concentration and haemodynamics following oro-gastric amitriptyline overdose. Clin Toxicol (Phila). 2013;51(4):208-15.
892. Palaniswamy C, Selvaraj DR, Chugh T, Singh T, Khalique O, Tsai F, et al. Brugada electrocardiographic pattern induced by amitriptyline overdose. American Journal of Therapeutics. 2010;17(5):529-32.
893. Bek K, Ozkaya O, Mutlu B, Dagdemir A, Sungur M, Acikgoz Y, et al. Charcoal haemoperfusion in amitriptyline poisoning: experience in 20 children. Nephrology. 2008;13(3):193-7.
894. Clement A, Raney JJ, Wasserman GS, Lowry JA. Chronic amitriptyline overdose in a child. Clin Toxicol (Phila). 2012;50(5):431-4.
895. Olgun H, Yildirim ZK, Karacan M, Ceviz N. Clinical, electrocardiographic, and laboratory findings in children with amitriptyline intoxication. Pediatr Emerg Care. 2009;25(3):170-3.
896. Levine M, Brooks DE, Franken A, Graham R. Delayed-onset seizure and cardiac arrest after amitriptyline overdose, treated with intravenous lipid emulsion therapy. Pediatrics. 2012;130(2):e432-8.
897. Mbuvah F, Petrosyan F, Thiruchelvam N, Kistangari G. Electrocardiographic changes in amitriptyline overdose. Cleve Clin J Med. 2015;82(7):396-8.

898. Engels PT, Davidow JS. Intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose. Resuscitation. 2010;81(8):1037-9.
899. Kiberd MB, Minor SF. Lipid therapy for the treatment of a refractory amitriptyline overdose. CJEM, Can. 2012;14(3):193-7.
900. Celik U, Celik T, Avci A, Annagur A, Yilmaz HL, Kucukosmanoglu O, et al. Metabolic acidosis in a patient with type 1 diabetes mellitus complicated by methanol and amitriptyline intoxication. Eur J Emerg Med. 2009;16(1):45-8.
901. Bynum ND, Poklis JL, Gaffney-Kraft M, Garside D, Ropero-Miller JD. Postmortem distribution of tramadol, amitriptyline, and their metabolites in a suicidal overdose. J Anal Toxicol. 2005;29(5):401-6.
902. Smith JC, Curry SC. Prolonged toxicity after amitriptyline overdose in a patient deficient in CYP2D6 activity. J Med Toxicol. 2011;7(3):220-3.
903. Chan HY, Chan YC, Lau FL. Reversal of Brugada electrocardiographic pattern with sodium bicarbonate solution after amitriptyline overdose. Clin Toxicol (Phila). 2008;46(9):892-6.
904. Ramasubbu B, James D, Scurr A, Sandilands EA. Serum alkalinisation is the cornerstone of treatment for amitriptyline poisoning. BMJ Case Rep. 2016;2016:10.1136/bcr-2016-214685.
905. Aslan S, Emet M, Cakir Z, Akoz A, Akgol Gur ST. Suicide attempts with amitriptyline in adults: A prospective, demographic, clinical study. Turkish Journal of Medical Sciences. 2011;41(2):243-9.
906. Kolsal E, Tekin IO, Piskin E, Aydemir C, Akyuz M, Cabuk H, et al. Treatment of severe amitriptyline intoxication with plasmapheresis. J Clin Apheresis. 2009;24(1):21-4.
907. Prahlow JA, Landrum JE. Amitriptyline abuse and misuse. American Journal of Forensic Medicine and Pathology. 2005;26(1):86-8.
908. Seale JP, Dittmer T, Sigman EJ, Clemons H, Johnson JA. Combined abuse of clonidine and amitriptyline in a patient on buprenorphine maintenance treatment. J Addict Med. 2014;8(6):476-8.
909. Sein Anand J, Chodorowski Z, Habrat B. Recreational amitriptyline abuse. Przegl Lek. 2005;62(6):397-8.
910. Birns J, Henderson K, Bhalla A. Recreational amitriptyline toxicity mimicking basilar artery stroke. Eur J Emerg Med. 2013;20(2):139-40.
911. Avella J, Katz M, Lehrer M. Assessing free and total morphine following heroin overdose when complicated by the presence of toxic amitriptyline levels. J Anal Toxicol. 2007;31(8):540-2.
912. Chakrabarti S, Fraser J, Tsai-Goodman B. Accidental ingestion of dosulepin presenting as atrial flutter in a child. European Journal of Pediatrics. 2010;169(1):113-5.
913. Howell BA, Chauhan A. Binding of imipramine, dosulepin, and opipramol to liposomes for overdose treatment. J Pharm Sci. 2009;98(10):3718-29.
914. Boegevig S, Rothe A, Tfelt-Hansen J, Hoegberg LC. Successful reversal of life threatening cardiac effect following dosulepin overdose using intravenous lipid emulsion. Clin Toxicol (Phila). 2011;49(4):337-9.
915. Roelofsen EE, Wilhelm AJ, Sinjewel A, Franssen EJ. Toxicokinetics of dothiepin: 2 case reports. Ther Drug Monit. 2008;30(5):638-41.
916. Kiran HS, Ravikumar YS, Jayasheelan MR, Prashanth. Brugada like pattern in ECG with drug overdose. J Assoc Physicians India. 2010;58:120-2.
917. Meert A, Vermeersch N, Beckers R, Hoste W, Brugada P, Hubloue I. Brugada-like ECG pattern induced by tricyclic antidepressants. Eur J Emerg Med. 2010;17(6):325-7.
918. Hendron D, Menagh G, Sandilands EA, Scullion D. Tricyclic antidepressant overdose in a toddler treated with intravenous lipid emulsion. Pediatrics. 2011;128(6):e1628-32.
919. Lepping P, Menkes DB. Abuse of dosulepin to induce mania. Addiction (Abingdon, England). 2007;102(7):1166-7.
920. Kinoshita H, Taniguchi T, Kubota A, Nishiguchi M, Ouchi H, Minami T, et al. An autopsy case of imipramine poisoning. Am J Forensic Med Pathol. 2005;26(3):271-4.
921. Hon KL, Fung CK, Lee VW, Cheung KL, Wong W, Leung AK. Neurologic and Cardiovascular Complications in Pediatric Life Threatening Imipramine Poisoning. Curr Drug Saf. 2015;10(3):261-5.
922. Rosenbaum TG, Kou M. Are one or two dangerous? Tricyclic antidepressant exposure in toddlers. J Emerg Med. 2005;28(2):169-74.
923. Agarwala R, Ahmed SZ, Wiegand TJ. Prolonged use of intravenous lipid emulsion in a severe tricyclic antidepressant overdose. J Med Toxicol. 2014;10(2):210-4.
924. Zuidema X, de Jager CP. Terlipressin and tricyclic antidepressant intoxication. Neth J Med. 2007;65(8):313-4.
925. Gronewold A, Dettling A, Haffner HT, Skopp G. Doxepin and nordoxepin concentrations in body fluids and tissues in doxepin associated deaths. Forensic Sci Int. 2009;190(1-3):74-9.
926. Rademacher S, Dietz R, Haverkamp W. QT prolongation and syncope with methadone, doxepin, and a beta-blocker. Ann Pharmacother. 2005;39(10):1762-3.
927. Magdalan J, Zawadzki M, Sloka T, Sozanski T. Suicidal overdose with relapsing clomipramine concentrations due to a large gastric pharmacobezoar. Forensic Sci Int. 2013;229(1-3):e19-22.
928. De Roock S, Beauloye C, De Bauwer I, Vancraynest D, Gurne O, Gerber B, et al. Tako-tsubo syndrome following nortriptyline overdose. Clin Toxicol (Phila). 2008;46(5):475-8.
929. England R. A legal way to obtain pleasure. BMJ (Online). 2013;346 (7904) (no pagination)(f2337).
930. De Sousa A. Ramelteon dose escalation in a patient with substance misuse. J Clin Psychopharmacol. 2012;32(5):738-9.
931. Waring WS, Good AM, Bateman DN. Lack of significant toxicity after mirtazapine overdose: a five-year review of cases admitted to a regional toxicology unit. Clin Toxicol (Phila). 2007;45(1):45-50.
932. Berling I, Isbister GK. Mirtazapine overdose is unlikely to cause major toxicity. Clin Toxicol (Phila). 2014;52(1):20-4.
933. Kuliwaba A. Non-lethal mirtazapine overdose with rhabdomyolysis. Aust N Z J Psychiatry. 2005;39(4):312-3.
934. LoVecchio F, Riley B, Pizon A, Brown M. Outcomes after isolated mirtazapine (Remeron) supratherapeutic ingestions. J Emerg Med. 2008;34(1):77-8.

935. Sinyor M, Howlett A, Cheung AH, Schaffer A. Substances used in completed suicide by overdose in Toronto: An observational study of coroner's data. Canadian Journal of Psychiatry. 2012;57(3):184-91.
936. Liveri K, Constantinou MA, Afxentiou M, Kanari P. A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus. Forensic Sci Int. 2016;265:160-5.
937. Bandinelli PL, Polselli GM. Asymptomatic reboxetine overdose. International Journal of Neuropsychopharmacology. 2006;9(2):257.
938. Brvar M, Stajer D, Kozelj G, Osredkar J, Mozina M, Bunc M. Urinary serotonin level is associated with serotonin syndrome after moclobemide, sertraline, and citalopram overdose. Clin Toxicol (Phila). 2007;45(5):458-60.
939. O'Malley PA. Looking "fit and thin" to win: diuretic drug abuse in and outside the arena. Clinical nurse specialist CNS. 2015;29(4):203-6; quiz E9.
940. Keller K, Beule J, Dippold W. Gitelman syndrome DD thiazide diuretics abuse. Central European Journal of Medicine. 2014;9(3):495-9.
941. Sekulic D, Peric M, Rodek J. Substance use and misuse among professional ballet dancers. Substance Use & Misuse. 2010;45(9):1420-30.
942. Senthilkumaran S, Menezes RG, Jena NN, Thirumalaikolundusubramanian P. Clinical, laboratory, and educational challenges of diuretic doping. Am J Emerg Med. 2013;31(2):420-1.
943. Cain AS, Epler AJ, Steinley D, Sher KJ. Concerns related to eating, weight, and shape: Typologies and transitions in men during the college years. International Journal of Eating Disorders. 2012;45(6):768-75.
944. Mascolo M, Chu ES, Mehler PS. Abuse and clinical value of diuretics in eating disorders therapeutic applications. International Journal of Eating Disorders. 2011;44(3):200-2.
945. Heise CW, Beutler D, Bosak A, Orme G, Loli A, Graeme K. Massive Atenolol, Lisinopril, and Chlorthalidone Overdose Treated with Endoscopic Decontamination, Hemodialysis, Impella Percutaneous Left Ventricular Assist Device, and ECMO. J Med Toxicol. 2015;11(1):110-4.
946. Forney KJ, Buchman-Schmitt JM, Keel PK, Frank GK. The medical complications associated with purging. International Journal of Eating Disorders. 2016;49(3):249-59.
947. Yu TC, Hsu YH. Furosemide overuse-related acute and chronic tubulointerstitial nephritis: A case report. Journal of Internal Medicine of Taiwan. 2015;26(4):217-26.
948. Hendricks EJ, Srisurapanont M, Schmidt SL, Haggard M, Souter S, Mitchell CL, et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. International Journal of Obesity. 2014;38(2):292-8.
949. Lee S, Kim J, In S, Choi H, Chung H, Chung KH. Detection of phentermine in hair samples from drug suspects. Forensic Sci Int. 2011;207(1-3):e5-e7.
950. Alexander J, Cheng YH, Choudhary J, Dinesh A. Phentermine (Duromine) precipitated psychosis. Australian and New Zealand Journal of Psychiatry. 2011;45(8):684-5.
951. Gjerden P, Bramness JG, Slordal L. The use and potential abuse of anticholinergic antiparkinson drugs in Norway: A pharmacoepidemiological study. Br J Clin Pharmacol. 2009;67(2):228-33.
952. Guettard E, Goguillot S, Creusat M, Dumont P. One Ditropan© is fine, but six. Beware of the havoc!, Un Ditropan© ca va, six Ditropan©. Bonjour les degats!. [French, English]. Annals of Physical and Rehabilitation Medicine. 2012;55:e383+e5.
953. Rao MG, Varambally S, Raveendranathan D, Venkatasubramanian G, Gangadhar B. Trihexyphenidyl use and dependence: A case report. Mental Health and Substance Use. 2014;7(4):258-62.
954. Nappo SA, de Oliveira LG, van der Meer Sanchez Z, de Araujo Carlini E. Trihexyphenidyl (Artane): A Brazilian Study of Its Abuse. Substance Use & Misuse. 2005;40(4):473-82.
955. Pauly V, Lapeyre-Mestre M, Braunstein D, Thirion X, Micallef J. Signals of drug abuse and dependence: An application of disproportionality measures to the french addictovigilance system. Drug Safety. 2013;36 (9):918-9.
956. Debruyne D, Frauger E, Collin C, Le Boisselier R, Coquerel A. A recent evaluation of trihexyphenidyl hydrochloride (Artane) abuse and misuse. Fundamental and Clinical Pharmacology. 2012;26:73.
957. Younis AA, Moselhy HF. Benzhexol-dependence resulting from self-medication for intermittent explosive disorder. International Journal of Psychiatry in Clinical Practice. 2009;13(1):11-5.
958. Frauger E, Nordmann S, Orleans V, Pradel V, Pauly V, Thirion X, et al. Which psychoactive prescription drugs are illegally obtained and through which ways of acquisition? About OPPIDUM survey. Fundamental and Clinical Pharmacology. 2012;26(4):549-56.
959. Evans AH, Lawrence AD, Cresswell SA, Katzenschlager R, Lees AJ. Compulsive use of dopaminergic drug therapy in Parkinson's disease: Reward and anti-reward. Movement Disorders. 2010;25(7):867-76.
960. Kaye S. Compulsive use of dopamine replacement therapy among Parkinson's disease patients: if it looks like a duck, swims like a duck and quacks like a duck. Addiction (Abingdon, England). 2012;107(2):251-3.
961. Brown RM, Lawrence AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: insights into the neurobiology of addiction. Addiction (Abingdon, England). 2012;107(2):250-1.
962. Ambermoon P, Carter A, Hall W, Dissanayaka N, O'Sullivan J. Compulsive use of dopamine replacement therapy: a model for stimulant drug addiction? Addiction (Abingdon, England). 2012;107(2):241-7.
963. Zaharna M, Pandya M. Levodopa addiction and factitious disorder in a patient with idiopathic Parkinson's disease. Journal of Neuropsychiatry and Clinical Neurosciences. 2010;22(3):E11-E2.
964. Borek LL, Friedman JH. Levodopa addiction in idiopathic Parkinson disease. Neurology. 2005;65(9):1508.
965. Mursaleen LR, Stamford JA. Drugs of abuse and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:209-17.
966. Delmas G, Rothmann C, Flesch F. Acute overdose with controlled-release levodopa-carbidopa. Clin Toxicol (Phila). 2008;46(3):274-7.
967. Affaticati A, Gerra ML, Amerio A, Inglese M, Antonioni MC, Marchesi C. The controversial case of biperiden: From prescription drug to drug of abuse. J Clin Psychopharmacol. 2015;35(6):749-50.
968. Guloksuz S, Eren K, Gurol DT. A case of oxybutynin dependency. Gen Hosp Psychiatry. 2010;32(4):e5-e6.
969. Mutlu EA. Oxybutynin dependence: a case presentation. Turk Psikiyatri Derg. 2011;22(2):131-2.

970. Gahr M, Freudenmann RW, Eller J, Schonfeldt-Lecuona C. Abuse liability of centrally acting non-opioid analgesics and muscle relaxants-A brief update based on a comparison of pharmacovigilance data and evidence from the literature. International Journal of Neuropsychopharmacology. 2014;17(6):957-9.
971. Happe S, Sommer M, Meller J, Trenkwalder C, Paulus W. Dyskinesias due to intravenous apomorphine abuse in a patient without basal ganglia disorder. Movement Disorders. 2005;20(1):105-8.
972. Tellez C, Bustamante M, Toro P, Venegas P. Addiction to apomorphine: A clinical case-centred discussion. Addiction (Abingdon, England). 2006;101(11):1662-5.
973. Kobayashi T, Saito N, Suda S, Shioda K, Kato S. Pharmacoresistant convulsions and visual hallucinations around two weeks after selegiline overdose: a case report. Pharmacopsychiatry. 2011;44(7):346-7.
974. Fujita Y, Takahashi K, Takei M, Niitsu H, Aoki Y, Onodera M, et al. Detection of levorotatory methamphetamine and levorotatory amphetamine in urine after ingestion of an overdose of selegiline. Yakugaku Zasshi. 2008;128(10):1507-12.
975. Nakai K, Takeda K, Kimura H, Miura S, Maeda A. Obstructive acute renal failure related to amantadine intoxication. Am J Emerg Med. 2009;27(3):371.e5-.e7.
976. Claudet I, Marechal C. Status epilepticus in a pediatric patient with amantadine overdose. Pediatr Neurol. 2009;40(2):120-2.
977. Schwartz M, Patel M, Kazzi Z, Morgan B. Cardiotoxicity after massive amantadine overdose. J Med Toxicol. 2008;4(3):173-9.
978. Jensen LS, Pagsberg AK, Dalhoff KP. Differences in abuse potential of ADHD drugs measured by contrasting poison centre and therapeutic use data. Clin Toxicol (Phila). 2015;53(4):210-4.
979. Clemow DB, Walker DJ. The potential for misuse and abuse of medications in ADHD: A review. Postgraduate Medicine. 2014;126(5):64-81.
980. Jensen LS, Pagsberg AK, Dalhoff KP. Non-medical use of attention deficit hyperactivity disorder drugs by adults: A comparative study of atomoxetine versus methylphenidate. Clinical Toxicology. 2014;52:333.
981. Kollins SH. A qualitative review of issues arising in the use of psychostimulant medications in patients with ADHD and co-morbid substance use disorders. Current Medical Research and Opinion. 2008;24(5):1345-57.
982. Jasinski DR, Faries DE, Moore RJ, Schuh LM, Allen AJ. Abuse liability assessment of atomoxetine in a drug-abusing population. Drug and Alcohol Dependence. 2008;95(1-2):140-6.
983. Schubiner H. Substance abuse in patients with attention-deficit hyperactivity disorder : therapeutic implications. CNS Drugs. 2005;19(8):643-55.
984. Upadhyaya HP, Desaiah D, Schuh KJ, Bymaster FP, Kallman MJ, Clarke DO, et al. A review of the abuse potential assessment of atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder. Psychopharmacology (Berl). 2013;226(2):189-200.
985. Spiller HA, Hays HL, Aleguas A, Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. CNS Drugs. 2013;27(7):531-43.
986. Kashani J, Ruha AM. Isolated atomoxetine overdose resulting in seizure. J Emerg Med. 2007;32(2):175-8.
987. Lovecchio F, Kashani J. Isolated atomoxetine (Strattera) ingestions commonly result in toxicity. J Emerg Med. 2006;31(3):267-8.
988. Garside D, Ropero-Miller JD, Riemer EC. Postmortem tissue distribution of atomoxetine following fatal and nonfatal doses--three case reports. Journal of Forensic Sciences. 2006;51(1):179-82.
989. Cantrell FL, Nestor M. Benign clinical course following atomoxetine overdose. Clin Toxicol (Phila). 2005;43(1):57.
990. Cairns R, Daniels B, Wood DA, Brett J. ADHD medication overdose and misuse: The NSW poisons information centre experience, 2004-2014. Med J Aust. 2016;204(4):154.e1-.e7.
991. Monte AA, Ceschi A, Bodmer M. Safety of non-therapeutic atomoxetine exposures - A national poison data system study. Hum. 2013;28(5):471-6.
992. Leung NY, Whyte IM, Isbister GK. Baclofen overdose: defining the spectrum of toxicity. Emerg Med Australas. 2006;18(1):77-82.
993. Reeves RR, Ladner ME, Perry CL, Burke RS, Laizer JT. Abuse of medications that theoretically are without abuse potential. South Med J. 2015;108(3):151-7.
994. Gahr M, Freudenmann RW, Eller J, Schonfeldt-Lecuona C. Abuse liability of centrally acting non-opioid analgesics and muscle relaxants--a brief update based on a comparison of pharmacovigilance data and evidence from the literature. International Journal of Neuropsychopharmacology. 2014;17(6):957-9.
995. Wood DM, Green JL, Le Lait MC, Dargan PI. Is there evidence of misuse of Baclofen, Gabapentin and Pregabalin in the United Kingdom (UK)? Clinical Toxicology. 2013;51 (7):663.
996. Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the gamma-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol. 2014;78(1):190-1.
997. Nasti JJ, Brakoulias V. Chronic baclofen abuse and withdrawal delirium. Australian and New Zealand Journal of Psychiatry. 2011;45(1):86-7.
998. Masi G, Mucci M, Liboni F, Ferrari A, Sicca F. Self-induced multiple comas with recreational baclofen overdoses in an adolescent girl. J Clin Psychopharmacol. 2013;33(6):830-2.
999. Kamal RM, Qurishi R, De Jong CAJ. Baclofen and gamma-hydroxybutyrate (GHB), a dangerous combination. J Addict Med. 2015;9(1):75-7.
1000. Weishaar GF, Hoemberg M, Bender K, Bangen U, Herkenrath P, Eifinger F, et al. Baclofen intoxication: a "fun drug" causing deep coma and nonconvulsive status epilepticus--a case report and review of the literature. European Journal of Pediatrics. 2012;171(10):1541-7.
1001. Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. Clin Toxicol (Phila). 2012;50(2):141-4.
1002. Giobellina C, Vallotton L, Yersin B, Carron P-N. Baclofen poisoning: Specific aspects and medical management. Alcoologie et Addictologie. 2015;37(2):145-8.
1003. Yelnik AP, Sportouch P, Questel F. Flaccid paralysis due to chronic baclofen overdosage. Alcohol Alcohol. 2013;48(3):375.
1004. Holla B, Gowda GS, Prabhu L, Baby S, Viswanath B, Chand P, et al. High doses of Baclofen as suicide attempt in patients with alcohol use disorders-A serious concern. Asian J Psychiatr. 2015;17:99-100.
1005. Wall GC, Wasiak A, Hicklin GA. An initially unsuspected case of baclofen overdose. Am J Crit Care. 2006;15(6):611-3.

1006. Kiel LB, Hoegberg LCG, Jansen T, Petersen JA, Dalhoff KP. A nationwide register-based survey of baclofen toxicity. Basic and Clinical Pharmacology and Toxicology. 2015;116(5):452-6.
1007. Caron E, Morgan R, Wheless JW. An unusual cause of flaccid paralysis and coma: baclofen overdose. J Child Neurol. 2014;29(4):555-9.
1008. Franchitto N, Pelissier F, Lauque D, Simon N, Lancon C. Self-intoxication with baclofen in alcohol-dependent patients with co-existing psychiatric illness: an emergency department case series. Alcohol Alcohol. 2014;49(1):79-83.
1009. Pommier P, Debaty G, Bartoli M, Viglino D, Carpentier F, Danel V, et al. Severity of deliberate acute baclofen poisoning: a nonconcurrent cohort study. Basic Clin Pharmacol Toxicol. 2014;114(4):360-4.
1010. Pal S. Nonmedical psychotherapeutic drug use among mentally ill patients. US Pharmacist. 2014;39(11).
1011. McLean MM, Sherwin H, Madabhushi V, Tilney PV. A 17-Year-Old Female Patient With a Lithium Overdose. Air Med J. 2015;34(4):162-5.
1012. Goel S, Nasa P, Gupta A, Gupta R, Taneja S. Lithium overdose: early hemodialysis is the key! Saudi J Kidney Dis Transpl. 2015;26(1):122-4.
1013. Bretaudeau Deguigne M, Hamel JF, Boels D, Harry P. Early digestive tract decontamination in acute-on-chronic lithium poisoning does not call conventional therapy into question. Clin Toxicol (Phila). 2013;51(8):809.
1014. Vodovar D, Megarbane B. Maintaining lithium elimination is at least as important as early gastrointestinal decontamination in acute-on-chronic poisonings. Clin Toxicol (Phila). 2013;51(8):808.
1015. Bretaudeau Deguigne M, Hamel JF, Boels D, Harry P. Lithium poisoning: the value of early digestive tract decontamination. Clin Toxicol (Phila). 2013;51(4):243-8.
1016. Lopez JC, Perez X, Labad J, Esteve F, Manez R, Javierre C. Higher requirements of dialysis in severe lithium intoxication. Hemodialysis International. 2012;16(3):407-13.
1017. Kayrak M, Ari H, Duman C, Gul EE, Ak A, Atalay H. Lithium intoxication causing ST segment elevation and wandering atrial rhythms in an elderly patient. Cardiol J. 2010;17(4):404-7.
1018. Offerman SR, Alsop JA, Lee J, Holmes JF. Hospitalized lithium overdose cases reported to the California Poison Control System. Clin Toxicol (Phila). 2010;48(5):443-8.
1019. Puhr J, Hack J, Early J, Price W, Meggs W. Lithium overdose with electrocardiogram changes suggesting ischemia. J Med Toxicol. 2008;4(3):170-2.
1020. Kung SW, Chan YC, Lau FL. Lithium overdose causing non-convulsive status epilepticus: the importance of lithium levels and the electroencephalography in diagnosis. Hong Kong Med. 2008;14(1):81-2.
1021. Yip KK, Yeung WT. Lithium overdose causing non-convulsive status epilepticus--the importance of lithium levels and the electroencephalography in diagnosis. Hong Kong Med. 2007;13(6):471-4.
1022. Borras-Blasco J, Sirvent AE, Navarro-Ruiz A, Murcia-Lopez A, Romero-Crespo I, Enriquez R. Unrecognized delayed toxic lithium peak concentration in an acute poisoning with sustained release lithium product. South Med J. 2007;100(3):321-3.
1023. Sood MM, Richardson R. Negative anion gap and elevated osmolar gap due to lithium overdose. Cmaj. 2007;176(7):921-3.
1024. Eyer F, Pfab R, Felgenhauer N, Lutz J, Heemann U, Steimer W, et al. Lithium poisoning: pharmacokinetics and clearance during different therapeutic measures. J Clin Psychopharmacol. 2006;26(3):325-30.
1025. Seale J, Dittmer T, Sigman EJ, Clemons H, Johnson J. Combined abuse of clonidine and amitriptyline in a patient on buprenorphine maintenance treatment. J Addict Med. 2014;8(6):476-8.
1026. Khosla N, Juon HS, Kirk GD, Astemborski J, Mehta SH. Correlates of non-medical prescription drug use among a cohort of injection drug users in Baltimore City. Addictive Behaviors. 2011;36(12):1282-7.
1027. Shruti, Dhiman V, Kataria D. Does clonidine has an abuse potential? A case report. Indian Journal of Psychiatry. 2014;56:S94.
1028. Ahmad SA, Scolnik D, Snehal V, Glatstein M. Use of naloxone for clonidine intoxication in the pediatric age group: case report and review of the literature. American Journal of Therapeutics. 2015;22(1):e14-6.
1029. Roussin A, Bouyssi A, Pouche L, Pourcel L, Lapeyre-Mestre M. Misuse and dependence on non-prescription codeine analgesics or sedative H1 antihistamines by adults: a cross-sectional investigation in France. PLoS ONE. 2013;8(10):e76499.
1030. Sen A, Akin A, Craft KJ, Canfield DV, Chaturvedi AK. First-generation H1 antihistamines found in pilot fatalities of civil aviation accidents, 1990-2005. Aviation, Space, and Environmental Medicine. 2007;78(5, Sect 1):514-22.
1031. Carrascosa MF, Caviedes JR, Lucena MI, Cuadrado-Lavin A. Syndrome of inappropriate antidiuresis in doxylamine overdose. BMJ Case Rep. 2012;19:19.
1032. Jo YI, Song JO, Park JH, Koh SY, Lee SM, Seo TH, et al. Risk factors for rhabdomyolysis following doxylamine overdose. Hum Exp Toxicol. 2007;26(8):617-21.
1033. Kim HJ, Oh SH, Youn CS, Wee JH, Kim JH, Jeong WJ, et al. The associative factors of delayed-onset rhabdomyolysis in patients with doxylamine overdose. Am J Emerg Med. 2011;29(8):903-7.
1034. Schafer CN, Guldager H, Jorgensen HL. Multi-organ dysfunction in bodybuilding possibly caused by prolonged hypercalcemia due to multi-substance abuse: case report and review of literature. International Journal of Sports Medicine. 2011;32(1):60-5.
1035. Creado S, Reardon C. The sports psychiatrist and performance-enhancing drugs. International Review of Psychiatry. 2016;28(6):564-71.
1036. Cooper C. Drug cheating at the Olympics: Who, what, and why? The Lancet. 2012;380(9836):21-2.
1037. Eichner E. Blood doping: Infusions, erythropoietin and artificial blood. Sports Medicine. 2007;37(4-5):389-91.
1038. Citartan M, Gopinath SC, Chen Y, Lakshmipriya T, Tang TH. Monitoring recombinant human erythropoietin abuse among athletes. Biosensors & bioelectronics. 2015;63:86-98.
1039. Almeida CB, Rodrigues DN, Barros EC. EPO use by Brazilian athletes since 2000. Substance use & misuse. 2014;49(9):1126-31.
1040. Oliveira CD, Bairros AV, Yonamine M. Blood doping: risks to athletes' health and strategies for detection. Substance use & misuse. 2014;49(9):1168-81.
1041. Heuberger JAAC, Cohen Tervaert JM, Schepers FML, Vliegenthart ADB, Rotmans JI, Daniels JMA, et al. Erythropoietin doping in cycling: Lack of evidence for efficacy and a negative risk-benefit. Br J Clin Pharmacol. 2013;75(6):1406-21.

1042. Debeljak N, Sytkowski AJ. Erythropoietin and erythropoiesis stimulating agents. Drug Testing and Analysis. 2012;4(11):805-12.
1043. Balestra C, Germonpre P. EPO and doping. European journal of applied physiology. 2010;109(5):1001-2.
1044. Thevis M, Schanzer W. Emerging drugs - Potential for misuse in sport and doping control detection strategies. Mini-Reviews in Medicinal Chemistry. 2007;7(5):533-9.
1045. Barroso O, Mazzoni I, Rabin O. Hormone abuse in sports: The antidoping perspective. Asian Journal of Andrology. 2008;10(3):391-402.
1046. Wanjek B, Rosendahl J, Strauss B, Gabriel HH. Doping, drugs and drug abuse among adolescents in the state of Thuringia (Germany): Prevalence, knowledge and attitudes. International Journal of Sports Medicine. 2007;28(4):346-53.
1047. Eichner ER. Blood doping: Infusions, erythropoietin and artificial blood. Sports Medicine. 2007;37(4-5):389-91.
1048. Scott J, Phillips GC. Erythropoietin in sports: a new look at an old problem. Current sports medicine reports. 2005;4(4):224-6.
1049. Dharmarajan TS, Widjaja D. Erythropoiesis-Stimulating Agents in Anemia: Use and Misuse. Journal of the American Medical Directors Association. 2009;10(9):607-16.
1050. Buemi M, Lacquaniti A, Bolignano D, Cernaro V, Campo S, Grasso G, et al. Down with the erythropoietin. Long live the erythropoietin! Current Drug Targets. 2009;10(10):1028-32.
1051. Salamin O, Kuuranne T, Saugy M, Leuenberger N. Erythropoietin as a performance-enhancing drug: Its mechanistic basis, detection, and potential adverse effects. Molecular and Cellular Endocrinology. 2017;10.
1052. Lage JMM, Panizo C, Masdeu J, Rocha E. Cyclist's doping associated with cerebral sinus thrombosis. Neurology. 2002;58(4):665.
1053. Tentori L, Graziani G. Doping with growth hormone/IGF-1, anabolic steroids or erythropoietin: is there a cancer risk? Pharmacological Research. 2007;55(5):359-69.
1054. Sagoe D, Huang K, Molde H, Andreassen CS, Pallesen S. Perceived anabolic-androgenic steroid use is associated with perceived neuroticism. Journal of Substance Use. 2016;21(3):263-7.
1055. Sagoe D, McVeigh J, Bjornebekk A, Essilfie M-S, Andreassen CS, Pallesen S. Polypharmacy among anabolic-androgenic steroid users: A descriptive metasynthesis. Substance Abuse Treatment, Prevention, and Policy Vol 10 2015, ArtID 12. 2015;10.
1056. Vari CE, Osz BE, Miklos A, Berbecaru-Iovan A, Tero-Vescan A. Aromatase inhibitors in men - off-label use, misuse, abuse and doping. Farmacia. 2016;64(6):813-8.
1057. Baker JS, Graham MR, Davies B. Steroid and prescription medicine abuse in the health and fitness community: A regional study. European Journal of Internal Medicine. 2006;17(7):479-84.
1058. Caplan JP, Epstein LA, Quinn DK, Stevens JR, Stern TA. Neuropsychiatric effects of prescription drug abuse. Neuropsychology Review. 2007;17(3):363-80.
1059. Papamitsou T, Barlagiannis D, Papaliagkas V, Kotanidou E, Dermentzopoulou-Theodoridou M. Testosterone-induced hypertrophy, fibrosis and apoptosis of cardiac cells - an ultrastructural and immunohistochemical study. Med Sci Monit. 2011;17(9):BR266-BR73.
1060. Timour Chah Q, Belhani D, Vaillant F, Dehina L, Jacquet A, Descotes J. Cardiac lesions induced by testosterone: Protective effects of dexrazoxane and trimetazidine. European Journal of Heart Failure, Supplement. 2010;9:S155.
1061. Vougiouklakis T, Mitselou A, Batistatou A, Boumba V, Charalabopoulos K. First case of fatal pulmonary peliosis without any other organ involvement in a young testosterone abusing male. Forensic Sci Int. 2009;186(1-3):e13-6.
1062. Brennan BP, Kanayama G, Pope Jr HG. Performance-enhancing drugs on the web: A growing public-health issue. Am J Addict. 2013;22(2):158-61.
1063. Clement CL, Marlowe DB, Patapis NS, Festinger DS, Forman RF. Nonprescription steroids on the Internet. Substance Use & Misuse. 2012;47(3):329-41.
1064. Krug O, Thomas A, Walpurgis K, Piper T, Sigmund G, Schanzer W, et al. Identification of black market products and potential doping agents in Germany 2010-2013. Eur J Clin Pharmacol. 2014;70(11):1303-11.
1065. Burke J. Drug diversion and abuse: Anabolic steroids: The china connection. Pharmacy Times. 2013;79(5).
1066. Handelsman DJ. Testosterone: use, misuse and abuse. Med J Aust. 2006;185(8):436-9.
1067. Handelsman DJ, Heather A. Androgen abuse in sports. Asian Journal of Andrology. 2008;10(3):403-15.
1068. Sottas PE, Saudan C, Schweizer C, Baume N, Mangin P, Saugy M. From population- to subject-based limits of T/E ratio to detect testosterone abuse in elite sports. Forensic Sci Int. 2008;174(2-3):166-72.
1069. Westerman ME, Charchenko CM, Ziegelmann MJ, Bailey GC, Nippoldt TB, Trost L. Heavy Testosterone Use Among Bodybuilders: An Uncommon Cohort of Illicit Substance Users. Mayo Clinic Proceedings. 2016;91(2):175-82.
1070. Higgins JP, Heshmat A, Higgins CL. Androgen abuse and increased cardiac risk. South Med J. 2012;105(12):670-4.
1071. Geraci MJ, Cole M, Davis P. New onset diabetes associated with bovine growth hormone and testosterone abuse in a young body builder. Hum Exp Toxicol. 2011;30(12):2007-12.
1072. Goebel C, Howe CJ, Ho KK, Nelson A, Kazlauskas R, Trout GJ. Screening for testosterone abuse in male athletes using the measurement of urinary LH, a revision of the paradigm. Drug Testing and Analysis. 2009;1(11-12):511-7.
1073. Heshmat H, Dashti R, Aljarallah M. Combined anabolic steroids and testosterone abuse; a possible cause of myocardial infarction in young age: Case report. Experimental and Clinical Cardiology. 2014;20(8):2685-7.
1074. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: Expanding the spectrum of prescription drug misuse. Med J Aust. 2013;199(8):548-51.
1075. Mascarenhas A, Khan S, Sayal R, Knowles S, Gomes T, Moore JE. Factors that may be influencing the rise in prescription testosterone replacement therapy in adult men: a qualitative study. Aging Male. 2016;19(2):90-5.
1076. Randall-Thompson J, Lerner A, Hunt J, Klein M. Assessing potential abuse and misuse of testosterone and other anabolic steroids among middle-aged and older men prescribed steroids. Drug and Alcohol Dependence. 2015;156:e185-e6.

Chapter 6 references

1. Smith N, Quansah K, Chelak K, Fitzsimmons H. Narcotics, benzodiazepines, stimulants, and gabapentin: policies, initiatives, and practices across Canada, 2014. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014. (Environmental Scan; issue 45)
2. Furu, K.. Establishment of the nationwide Norwegian Prescription Database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. Norsk Epidemiologi 2008; 18 (2): 129-136

Chapter 7 references

1. Clark T, Eadie J, Knue P, Kreiner P, Strickler G. Prescription Drug Monitoring Programs: An Assessment of the Evidence for Best Practices. The Prescription Drug Monitoring Program Center of Excellence2012.
2. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. Pain physician. 2007;10.
3. OARRS (Ohio Automated Rx Reporting System) 2016 Annual Report. State of Ohio Board of Pharmacy; 2016.
4. Li G, Brady JE, Lang BH, Giglio J, Wunsch H, DiMaggio C. Prescription drug monitoring and drug overdose mortality. Inj Epidemiol. 2014;1(1):9.
5. Blumenschein K, Fink JL, Freeman PR, James K, Kirsch KL, Steinke DT, et al. Kentucky All Schedule Prescription Electronic Reporting Program (KASPER) Evaluation Team. Review of Prescription Drug Monitoring Programs in the United States. Lexington, KY: Institute for Pharmaceutical Outcomes and Policy, Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky; 2010.
6. Brady JE, Wunsch H, DiMaggio C, Lang BH, Giglio J, Li G. Prescription drug monitoring and dispensing of prescription opioids. Public Health Rep. 2014;129(2):139-47.
7. Pardo B. Do More Robust Prescription Drug Monitoring Programs Reduce Prescription Opioid Overdose? Addiction (Abingdon, England). 2016;23:23.
8. Data-Driven Multidisciplinary Approaches to Reduce Prescription Drug Abuse in Kentucky: Second Action Team Meetng Data Update. Kentucky Injury Prevention and Research Center; 2015 12/06/2015.
9. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. Jama. 2011;305.
10. Cooper H, Moore L, Gruskin S, Krieger N. The impact of a police drug crackdown on drug injectors' ability to practice harm reduction: a qualitative study. Soc Sci Med. 2005;61.
11. Zullich SG, Grasela TH, Jr., Fiedler-Kelly JB, Gengo FM. Impact of triplicate prescription program on psychotropic prescribing patterns in long-term care facilities. Ann Pharmacother. 1992;26(4):539-46.
12. Weintraub M, Singh S, Byrne L, Maharaj K, Guttmacher L. Consequences of the 1989 New York State triplicate benzodiazepine prescription regulations. Jama. 1991;266(17):2392-7.
13. Simoni-Wastila L, Ross-Degnan D, Mah C, Gao X, Brown J, Cosler LE, et al. A retrospective data analysis of the impact of the New York triplicate prescription program on benzodiazepine use in medicaid patients with chronic psychiatric and neurologic disorders. Clin Ther. 2004;26(2):322-36.
14. Wagner AK, Ross-Degnan D, Gurwitz JH, Zhang F, Gilden DB, Cosler L, et al. Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. Ann Intern Med. 2007;146(2):96-103.
15. Ross-Degnan D, Simoni-Wastila L, Brown JS, Gao X, Mah C, Cosler LE, et al. A controlled study of the effects of state surveillance on indicators of problematic and non-problematic benzodiazepine use in a Medicaid population. Int J Psychiatry Med. 2004;34(2):103-23.
16. Schwartz HI, Blank K. Regulation of benzodiazepine prescribing practices: clinical implications. Gen Hosp Psychiatry. 1991;13(4):219-24.
17. Fisher J, Sanyal C, Frail D, Sketris I. The intended and unintended consequences of benzodiazepine monitoring programmes: A review of the literature. Journal of Clinical Pharmacy and Therapeutics. 2012;37(1):7-21.
18. Lee D, Delcher C, Maldonado-Molina MM, Bazydlo LA, Thogmartin JR, Goldberger BA. Trends in licit and illicit drug-related deaths in Florida from 2001 to 2012. Forensic Sci Int. 2014;245:178-86.
19. Prescription Behavior Surveillance System (PBSS) Surveillance Report: Kentucky, 2013. Waltham, MA: PDMP Center of Excellence, Heller School for Social Policy and Management, Brandeis University; 2015.
20. Johnson H, Paulozzi L, Porucznik C, Mack K, Herter B, Hal Johnson C, et al. Decline in drug overdose deaths after state policy changes - Florida, 2010-2012. MMWR Morb Mortal Wkly Rep. 2014;63(26):569-74.
21. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445-52.
22. Bachhuber MA, Maughan BC, Mitra N, Feingold J, Starrels JL. Prescription monitoring programs and emergency department visits involving benzodiazepine misuse: Early evidence from 11 United States metropolitan areas. International Journal of Drug Policy. 2016;28:120-3.
23. Maughan BC, Bachhuber MA, Mitra N, Starrels JL. Prescription monitoring programs and emergency department visits involving opioids, 2004-2011. Drug Alcohol Depend. 2015;156:282-8.
24. E-FORCSE 2015-2016 Prescription Drug Monitoring Program Annual Report. Florida Health; 2016.

25. Dormuth CR, Miller TA, Huang A, Mamdani MM, Juurlink DN. Effect of a centralized prescription network on inappropriate prescriptions for opioid analgesics and benzodiazepines. Cmaj. 2012;184(16):E852-6.
26. Gomes T, Juurlink D, Yao Z, Camacho X, Paterson JM, Singh S, et al. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. CMAJ Open. 2014;2(4):E256-61.
27. Delcher C, Wang Y, Wagenaar AC, Goldberger BA, Cook RL, Maldonado-Molina MM. Prescription and Illicit Opioid Deaths and the Prescription Drug Monitoring Program in Florida. Am J Public Health. 2016;106(6):e10-1.
28. Reisman RM, Shenoy PJ, Atherly AJ, Flowers CR. Prescription opioid usage and abuse relationships: an evaluation of state prescription drug monitoring program efficacy. Subst Abus. 2009;3:41-51.
29. New York State Opioid Poisoning, Overdose and Prevention 2015 Report to the Governor and NYS Legislature. New York State Department of Health; 2015.
30. Reifler LM, Droz D, Bailey JE, Schnoll SH, Fant R, Dart RC, et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? Pain medicine (Malden, Mass). 2012;13.
31. Bao Y, Pan Y, Taylor A, Radakrishnan S, Luo F, Pincus HA, et al. Prescription Drug Monitoring Programs Are Associated With Sustained Reductions In Opioid Prescribing By Physicians. Health Aff (Millwood). 2016;35(6):1045-51.
32. Ali MM, Dowd WN, Classen T, Mutter R, Novak SP. Prescription drug monitoring programs, nonmedical use of prescription drugs, and heroin use: Evidence from the National Survey of Drug Use and Health. Addictive Behaviors. 2017;69:65-77.
33. Paone D, Tuazon E, Kattan J, Nolan ML, Bradley O'Brien D, Dowell D, et al. Decrease in rate of opioid analgesic overdose deaths- Staten Island, New York City, 2011-2013. CDC- Morbidity & Mortality Weekly Report. 2015;64(18):491-4.
34. Meara E, Horwitz JR, Powell W, McClelland L, Zhou W, O'Malley AJ, et al. State Legal Restrictions and Prescription-Opioid Use among Disabled Adults. N Engl J Med. 2016;375(1):44-53.
35. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory Provider Review And Pain Clinic Laws Reduce The Amounts Of Opioids Prescribed And Overdose Death Rates. Health Aff (Millwood). 2016;35(10):1876-83.
36. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. Pain Medicine. 2011;12(5):747-54.
37. Paulozzi LJ, Stier DD. Prescription drug laws, drug overdoses, and drug sales in New York and Pennsylvania. J Public Health Policy. 2010;31(4):422-32.
38. Gilson AM, Fishman SM, Wilsey BL, Casamalhuapa C, Baxi H. Time series analysis of California's prescription monitoring program: Impact on prescribing and multiple provider episodes. The Journal of Pain. 2012;13(2):103-11.
39. Hansen H, Mendoza S, Nunes EV, Rotrosen J. Impact of prescription monitoring on care of opioid-dependent patients. Drug and Alcohol Dependence. 2015;156:e89.
40. Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation Of Prescription Drug Monitoring Programs Associated With Reductions In Opioid-Related Death Rates. Health Aff (Millwood). 2016;35(7):1324-32.
41. Piper BJ, Desrosiers CE, Lipovsky JW, Rodney MA, Baker RP, McCall KL, et al. Use and misuse of opioids in Maine: Results from pharmacists, the prescription monitoring, and the diversion alert programs. Journal of Studies on Alcohol and Drugs. 2016;77(4):556-65.
42. Simoni-Wastila L, Qian J. Influence of prescription monitoring programs on analgesic utilization by an insured retiree population. Pharmacoepidemiol Drug Saf. 2012;21(12):1261-8.
43. Ringwalt C, Garrettson M, Alexandridis A. The effects of North Carolina's prescription drug monitoring program on the prescribing behaviors of the state's providers. J Prim Prev. 2015;36(2):131-7.
44. Baehren DF, Marco CA, Droz DE, Sinha S, Callan EM, Akpunonu P. A Statewide Prescription Monitoring Program Affects Emergency Department Prescribing Behaviors. Annals of emergency medicine. 2010;56(1):19-23.e3.
45. McAllister MW, Aaronson P, Spillane J, Schreiber M, Baroso G, Kraemer D, et al. Impact of prescription drug-monitoring program on controlled substance prescribing in the ED. Am J Emerg Med. 2015;33(6):781-5.
46. Rutkow L, Turner L, Lucas E, Hwang C, Alexander GC. Most primary care physicians are aware of prescription drug monitoring programs, but many find the data difficult to access. Health Aff (Millwood). 2015;34(3):484-92.
47. Pomerleau AC, Nelson LS, Hoppe JA, Salzman M, Weiss PS, Perrone J. The Impact of Prescription Drug Monitoring Programs and Prescribing Guidelines on Emergency Department Opioid Prescribing: A Multi-Center Survey. Pain Medicine. 2016;19:19.
48. Curtis LH, Stoddard J, Radeva JI, Hutchison S, Dans PE, Wright A, et al. Geographic variation in the prescription of schedule II opioid analgesics among outpatients in the United States. Health Serv Res. 2006;41(3 Pt 1):837-55.
49. Delcher C, Wagenaar A, Goldberger B, Maldonado-Molina M. Florida's prescription drug monitoring program and oxycodone-caused mortality: A monthly time series analysis, 2003-2012. Drug and Alcohol Dependence. 2015;146:e260.
50. Rutkow L, Chang HY, Daubresse M, Webster DW, Stuart EA, Alexander GC. Effect of Florida's Prescription Drug Monitoring Program and Pill Mill Laws on Opioid Prescribing and Use. JAMA Intern Med. 2015;175(10):1642-9.
51. Surratt HL, O'Grady C, Kurtz SP, Stivers Y, Cicero TJ, Dart RC, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. Pharmacoepidemiol Drug Saf. 2014;23(3):314-20.
52. Lee D, Delcher C, Maldonado-Molina MM, Bazydlo LAL, Thogmartin JR, Goldberger BA. Trends in licit and illicit drug-related deaths in Florida from 2001 to 2012. Forensic Sci Int. 2014;245:178-86.
53. Chang HY, Lyapustina T, Rutkow L, Daubresse M, Richey M, Faul M, et al. Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis. Drug Alcohol Depend. 2016;165:1-8.
54. Delcher C, Wagenaar AC, Goldberger BA, Cook RL, Maldonado-Molina MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. Drug Alcohol Depend. 2015;150:63-8.

55. Murphy Y, Goldner EM, Fischer B. Prescription opioid use, harms and interventions in canada: A review update of new developments and findings since 2010. Pain physician. 2015;18(4):E605-E14.

Chapter 8 references

nil

Appendix

A.1. Defined daily dose/1000 people/day data extracted from the Australian Statistics on Medicines reports, 2008-2015

	2008	2009	2010	2011	2012	2013	2014	2015
codeine - combin - PBS	5.414	5.245	5.289	5.365	5.37625	5.27548	5.18097	5.08961
codeine - combin - UND					1.59585	1.77171	1.78055	1.64604
codeine - combin - PRI	2.062	2.164	1.872	1.92				
Total codeine - combin	*7.47600*	*7.40900*	*7.16100*	*7.28500*	*6.97210*	*7.04719*	*6.96152*	*6.73565*
codeine - plain - PBS	0.127	0.126	0.126	0.126	0.12721	0.12692	0.12783	0.12734
codeine - plain - UND					0.01371	0.00953	0.01007	0.00995
codeine - plain - PRI	0.04	0.035	0.034	0.039				
Total codeine - plain	*0.16700*	*0.16100*	*0.16000*	*0.16500*	*0.14092*	*0.13645*	*0.13790*	*0.13729*
Total codeine	7.64300	7.57000	7.32100	7.45000	7.11302	7.18364	7.09942	6.87294
TRAMADOL - PBS	2.674	2.709	2.799	2.886	2.70779	2.50844	2.53918	2.53813
TRAMADOL - UND					0.62637	0.69033	0.74629	0.75234
TRAMADOL - PRI	0.554	0.59	0.614	0.651				
Total tramadol	3.22800	3.29900	3.41300	3.53700	3.33416	3.19877	3.28547	3.29047
FENTANYL - PBS	0.675	0.882	1.067	1.183	1.23848	1.24977	1.22491	1.17189
FENTANYL - UND					0.00022	0.00432	0.01362	0.01672
FENTANYL - PRI	0.007	0.007	0.009	0.008				
Total fentanyl	0.68200	0.88900	1.07600	1.19100	1.23870	1.25409	1.23853	1.18861
QUETIAPINE - PBS	1.368	1.646	1.952	2.246	2.44397	2.61331	2.66479	2.69766
QUETIAPINE - UND					0.00045	0.00066	0.02356	0.02587
QUETIAPINE - PRI	0.118	0.113	0.098	0.103				
Total quetiapine	1.48600	1.75900	2.05000	2.34900	2.44442	2.61397	2.68835	2.72353
OLANZAPINE - PBS	3.046	3.019	3.012	3.085	3.10859	3.14213	3.09196	3.01055
OLANZAPINE - UND					0.00009	0.00162	0.04008	0.15076
OLANZAPINE - PRI	0.069	0.065	0.043	0.034				
Total olanzapine	3.11500	3.08400	3.05500	3.11900	3.10868	3.14375	3.13204	3.16131
RISPERIDONE - PBS	1.682	1.481	1.492	1.506	1.426	1.33578	1.26433	1.20384
RISPERIDONE - UND					0.00938	0.01953	0.03522	0.05765
RISPERIDONE - PRI	0.021	0.018	0.021	0.022				
Total risperidone	1.70300	1.49900	1.51300	1.52800	1.43538	1.35531	1.29955	1.26149
DIAZEPAM - PBS	4.933	4.816	4.682	4.641	4.58897	4.54032	4.5815	4.46345
DIAZEPAM - UND					1.26	1.37743	1.44698	1.47264
DIAZEPAM - PRI	1.593	1.516	1.548	1.611				
Total diazepam	6.52600	6.33200	6.23000	6.25200	5.84897	5.91775	6.02848	5.93609
ALPRAZOLAM - PBS	3.861	3.89	3.833	3.735	3.57312	3.16768	2.05304	1.77579
ALPRAZOLAM - UND					0.69311	0.67459	0.45398	0.39790
ALPRAZOLAM - PRI	2.225	2.307	2.298	2.444				
Total alprazolam	6.08600	6.19700	6.13100	6.17900	4.26623	3.84227	2.50702	2.17369
TEMAZEPAM – PBS	3.474	3.264	3.075	2.963	2.77928	2.63274	2.46047	2.32668

TEMAZEPAM - UND					0.70342	0.79195	0.77569	0.75878
TEMAZEPAM - PRI	1.085	1.042	0.974	1.001				
Total temazepam	4.55900	4.30600	4.04900	3.96400	3.48270	3.42469	3.23616	3.08546
OXAZEPAM - PBS	2.02	1.878	1.752	1.659	1.55457	1.46192	1.40218	1.32713
OXAZEPAM - UND					0.1806	0.19783	0.19989	0.19789
OXAZEPAM - PRI	0.433	0.409	0.387	0.381				
Total oxazepam	2.45300	2.28700	2.13900	2.04000	1.73517	1.65975	1.60207	1.52502
CLONAZEPAM - PBS	0.15	0.132	0.128	0.127	0.12042	0.11361	0.11016	0.10724
CLONAZEPAM - UND					0.01596	0.0167	0.01601	0.01529
CLONAZEPAM - PRI	0.214	0.221	0.226	0.218				
Total clonazepam	0.36400	0.35300	0.35400	0.34500	0.13638	0.13031	0.12617	0.12253
NITRAZEPAM - PBS	1.705	1.549	1.419	1.304	1.18408	1.08342	0.98587	0.89069
NITRAZEPAM - UND					0.11605	0.12327	0.11318	0.10371
NITRAZEPAM - PRI	0.303	0.286	0.283	0.271				
Total bromazepam	2.00800	1.83500	1.70200	1.57500	1.30013	1.20669	1.09905	0.99440
BROMAZEPAM - PBS	0.006	0.00500	0.004	0.004	0.00352	0.00321	0.00273	0.00242
BROMAZEPAM - UND								
BROMAZEPAM - PRI	0.15	0.13400	0.12	0.128				
Total bromazepam	0.15600	0.13900	0.12400	0.13200	0.00352	0.00321	0.00273	0.00242
MIRTAZAPINE - PBS	4.862	4.698	5.057	5.46	5.47303	5.44745	5.6517	5.89659
MIRTAZAPINE - UND					1.02389	1.48632	1.6625	1.81341
MIRTAZAPINE - PRI	0.405	0.813	0.756	0.74				
Total mirtazapine	5.26700	5.51100	5.81300	6.20000	6.49692	6.93377	7.31420	7.71000
AMITRIPTYLINE - PBS	2.803	2.849	2.949	3.088	3.17031	3.22423	3.28213	3.30230
AMITRIPTYLINE - UND					1.02856	1.18836	1.23951	1.27587
AMITRIPTYLINE - PRI	0.893	0.882	0.863	0.908				
Total amitriptyline	3.69600	3.73100	3.81200	3.99600	4.19887	4.41259	4.52164	4.57817
CITALOPRAM - PBS	5.963	5.823	5.717	5.381	4.50395	4.17478	4.05617	3.99285
CITALOPRAM - UND					2.50559	2.87768	2.89705	2.89666
CITALOPRAM - PRI	2.229	1.991	1.746	2.08				
Total citalopram	8.19200	7.81400	7.46300	7.46100	7.00954	7.05246	6.95322	6.88951
ZOPICLONE - PBS	0.105	0.1	0.097	0.095	0.09208	0.08935	0.08716	0.08662
ZOPICLONE - UND					0.00001	0.00001	0.00001	0.00001
ZOPICLONE - PRI	0.34	0.379	0.407	0.513				
Total zopiclone	0.44500	0.47900	0.50400	0.60800	0.09209	0.08936	0.08717	0.08663
PREGABALIN - PBS	0.034	0.06	0.075	0.087	0.09923	2.51557	5.1303	6.75486
PREGABALIN - UND					0.00000	0.0175	0.04377	0.06418
PREGABALIN - PRI	0.307	0.403	0.489	0.58				
Total pregabalin	0.34100	0.46300	0.56400	0.66700	0.09923	2.53307	5.17407	6.81904
GABAPENTIN - PBS	0.294	0.288	0.286	0.289	0.294	0.29132	0.26268	0.25113
GABAPENTIN - UND					0.0013	0.00187	0.01223	0.02098
GABAPENTIN - PRI	0.163	0.178	0.183	0.205				
Total gabapentin	0.45700	0.46600	0.46900	0.49400	0.29530	0.29319	0.27491	0.27211

A.2. Peer-reviewed literature: search strategy

Standard peer reviewed literature databases were searched: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), PsycInfo and Embase. The search was restricted to articles that were published between 2005-2017. All types of articles were included and articles written in a language other than English were not excluded until full text review commenced. This search was not conducted strictly as a 'systematic review,' as limitations on time allowed to complete the review and the broad research question lead to large numbers of articles returned during a full systematic search. Search terms were prioritised in order to return manageable numbers of articles for the timeframe given.

Individual Schedule 4 medicines and where relevant, medicine classes were used as search terms. Terms used were a mixture of textword search (.tw) and subject headings (where these existed within the database). Adjacency operators were used in some cases to capture informal drug class terms for example "z drugs" for zolpidem and zopiclone ("Z adj3 drugs")When a drug class inclusion delivered results with inappropriate "noise" these class terms were excluded to improve specificity where appropriate. See table _ in appendix _ for specific drug terms used during this search.

The Cochrane library was searched with the terms "prescription drug misuse", "prescription drug abuse" and "overdose" without returning any relevant results.

Trove was excluded from this search as this database is made up of newspaper articles, a form of article which is excluded in the research protocol.

The form of MEDLINE used included all of the contents of PubMed and therefore this database was not searched separately.

Trip database appears to contain no new literature beyond what was returned from the primary databases.

During the second stage of screening of articles in the full text form, all articles were scanned for relevant references to include in this review where required to answer the research question and if appropriate.

Objective One: Which schedule 4 medicines are involved in drug overdose deaths in Victoria and nationally?

Objective one returned 3896 articles for screening by title and abstract within this search and 297 were included within the second stage of screening. Of this collection of articles 65 were retained and deemed relevant to the research question.
Six other articles/reports were included in the final review from additional sources, (e.g. Google Scholar) using the terms "prescription drug overdose Australia" and through expert follow up. The groups of drugs which are notoriously harmful in overdose, such as tricyclic antidepressants, antipsychotics and codeine, were searched first within separate categories rather than together, which helped to validate the search methodology. During the search for these drugs, other drugs of harm emerged and these were added to the list of Schedule 4 drugs to be searched within all objectives resulting in an iterative search process.
A range of search terms to capture the Australian setting was used across different databases, including use of "exp Australia/" or "exp Australian/" as a subject heading, as well as searching for "Australia.af" for author affiliations and "Australia.cp" for country of publication. The exact term used was adjusted per database to ensure that the right articles were captured.
The drug overdose terminology used included terms such as "exp drug intoxication/", "exp drug overdose/", "accidental death/" or "suicide/".

Objective Two: Which Schedule 4 medicines are involved in patient referrals to drug addiction treatment services in Victoria and nationally?

Objective Two returned 612 articles for screening by title and abstract within this search and 26 were included within the second stage of screening of full text. The same search terms to capture Australian articles were utilised for this search as in Objective One. The terms searched for capturing patient referrals to addiction drug services were "drug adj3 rehabilitat*", "addiction adj3 service*", "addiction adj3 treatment", "drug adj3 counselling", "withdrawal service*", "pharmacotherapy service*.tw" and "drug adj3 driving service*" (no results.) Individual drug classes were not targeted specifically within this search as the articles returned a low yield and were captured using the Australian setting and the Rehabilitation terms. No relevant articles were returned from Google Scholar for the keywords "prescription drug Australia rehabilitation."

Objective Three: Which Schedule 4 medicines are subject to misuse and abuse in Australia and overseas?
This search is extremely broad and encompasses all areas of the world, not just Australia and all forms of misuse of Schedule 4 drugs. The PsycINFO subject headings for misuse used were "drug seeking/", "exp drug abuse/" and "exp drug dependency/". In MEDLINE these search terms translated to "behaviour, Addictive/", "substance-related disorders/", and "prescription drug misuse". In Embase the subject headings used were "exp drug abuse/" and "exp drug dependence/". These search terms returned large numbers of articles, which were then broken down per drug of interest and screened for title and abstract in chunks. The total number of articles screened for Objective 3 across all databases was 15,087. This resulted in a total of 2384 to be screened again for relevance in full text, resulting in 1225 articles included in this objective final analysis. Given the amount of "noise" which occurred throughout this search, in many drug classes the textword for a drug of interest was included rather than the subject heading. Again, this review was limited by the time available. It was deemed sufficient to answer the question whether or not a particular drug was misused through a search such as this. It was also not deemed necessary to supplement this extensive search with a Google Scholar search.

Objectives Four and Five: Which of the identified Schedule 4 medicines have been monitored in prescription drug monitoring programs overseas? What are the outcomes of evaluations, where available, of including Schedule 4 medicines for monitoring in prescription drug monitoring programs overseas?
Objectives Four and Five were searched concurrently as the same articles were available to describe the prescription drug monitoring programs (PDMP) available overseas, as well as the evaluations and impact studies, which were derived from the use of them. Search terms were difficult to apply as PDMP have different names in different countries. A Google search to identify names of PDMPs was the first step in determining the appropriate search terms. Some keyword searching was utilised under the terms "controlled prescription program".mp or "triplicate prescription program".mp or "prescription review program".mp or "narcotics monitoring program".mp or "prescription drug monitoring program".mp or "PDMP".mp or "prescription monitoring program".mp. The indexing of relevant articles returned from this search was reviewed to identify other useful search terms. In Embase the subject headings "prescription drug" and "drug surveillance program" were combined. In MEDLINE the additional combined subject headings "substance related disorders/pc [prevention and control]" and "prescription drug/" were added to the search to generate a wider range of results as. In PsychInfo, the keyword search was again utilised but also "drug abuse prevention/" and "monitoring/". In Google Scholar the terms "narcotic monitoring system", "triplicate prescription program", "prescription drug monitoring program" and "prescription monitoring program" returned a further 6 articles, some of which were outside the target date range but deemed important to retain for the final discussion as they were highly relevant. These searches returned a total of 1039 articles to be screened for title and abstract. Of these articles, 177 total were retained for the next step of screening in full text after removal of duplicates. This resulted in 49 articles included in the final report.

Drug class/group	Drugs included	Example search terms used (not all included)
Antipsychotics	Amisulpride Aripiprazole	exp atypical antipsychotic agent/ exp neuroleptic agent

	Asenapine Chlorpromazine Clozapine Droperidol Flupenthixol Fluphenazine Haloperidol Lurasidone Olanzapine Paliperidone Pericyazine Quetiapine Risepridone Trifluoperazine Ziprasidone Zuclopenthixol	amisulpride.tw aripiprazole.tw asenapine.tw chlorpromazine.tw clozapine.tw droperidol.tw flupenthixol.tw fluphenazine.tw haloperidol.tw lurasidone.tw olanzapine.tw paliperidone.tw pericyazine.tw quetiapine.tw risperidone.tw trifluoperazine.tw ziprasidone.tw zuclopenthixol.tw
Benzodiazepines (s4), barbiturates and other muscle relaxants	Bromazepam Clobazam Clonazepam Diazepam Lorazepam Midazolam Nitrazepam Oxazepam Temazepam Baclofen Phenobarbitone Primidone	exp benzodiazepine derivative bromazepam.tw clobazam.tw clonazepam.tw diazepam.tw lorazepam.tw midazolam.tw nitrazepam.tw oxazepam.tw temazepam.tw baclofen/ baclofen.tw barbiturate*.tw phenobarb*.tw primidone.tw phenobarbital/ primidone/
Opioids (s4)	Tramadol Dextropropoxyphene Codeine (s4 combination)	tramadol/ tramadol.tw codeine/ cocodamol/ codeine.tw panadeine.tw mersyndol.tw paracetamol adj3 codeine dextropropoxyphene plus paracetamol/ dextropropoxyphene adj2 paracetamol dextropropoxyphene, dextropropoxyphene.tw,

		Di-gesic.tw
Antidepressants (TCA, SSRI, SNRI, other)	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Amitriptyline Clomipramine Dothiepin Dosulepin Doxepin Imipramine Nortriptyline Desvenlafaxine Venlafaxine Duloxetine Mirtazapine Mianserin Agomelatine Reboxetine Vorioxetine moclobemide	mirtazapine/ mirtazapine.tw citalopram.tw escitalopram.tw fluoxetine.tw fluvoxamine.tw paroxetine.tw sertraline.tw serotonin reuptake.tw SSRI.tw exp serotonin uptake inhibitor/ amitriptyline.tw clomipramine.tw dothiepin.tw dosulepin.tw doxepin.tw imipramine.tw nortriptyline.tw tricyclic antidepressant.tw TCA.tw exp tricyclic antidepressant agent/ desvenlafaxine.tw venlafaxine.tw duloxetine.tw serotonin noradrenalin reuptake.tw, SNRI.tw exp serotonin noradrenalin reuptake inhibitor/ agomelatine.tw mianserin.tw moclobemide.tw reboxetine.tw vorioxetine.tw mianserin/ moclobemide/
Z drugs	Zolpidem zopiclone	zolpidem.tw zopiclone.tw Z-drug.tw Z adj2 drug Z adj2 hypnotic zolpidem tartrate/ zopiclone/
Anticonvulsants	Acetazolamide Carbamazepine Ethosuximide Gabapentin	Antiepileptic.tw acetazolamide.tw carbamazepine.tw ethosuximide.tw

	Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Perampanel Phenytoin Pregabalin Sulthiame Tiagabine Topiramate Valproate Valproid acid Vigabatrin Zonisamide	gabapentin.tw lacosamide.tw lamotrigine.tw levetiracetam.tw oxcarbazepine.tw perampanel.tw phenytoin.tw pregabalin.tw sulthiame.tw tiagabine.tw topiramate.tw valproate.tw valproic acid.tw vigabatrin.tw zonisamide.tw harkoseride/ levetiracetam/ acetazolamide/ carbamazepine/ ethosuximide/ gabapentin/ lamotrigine/ oxcarbazepine/ perampanel/ phenytoin/ pregabalin/ sultiame/ tiagabine/ topiramate/ valproic acid/ vigabatrin/ zonisamide/
Stimulants (s4)	Modafinil atomoxetine	modafinil/ modafinil.tw atomoxetine.tw atomoxetine/
Anabolic agents	Testosterone Mesterolone Nandrolone	exp anabolic agent/, testosterone.tw
Anorectics	Phentermine diuretics	phentermine resin/ phentermine/ diuretic agent/ phentermine.tw,
Antiparkinson and anticholinergic	Apomorphine Bromocriptine Benzhexol benztropine	apomorphine.tw pramipexole.tw ropinirole.tw bromocriptine.tw

	Cabergoline Pramipexole Ropinirole Darifenacin Orphenadrine Oxybutynin Solifenacin Tolterodine Propantheline Rasageline Selegiline Amantadine Entacapone Levodopa	cabergoline.tw benzhexol.tw trihexyphenidyl.tw benztropine.tw darifenacin.tw orphenadrine.tw oxybutynin.tw solifenacin.tw tolterodine.tw propantheline.tw rasageline.tw selegiline.tw amantadine.tw entacapone.tw levodopa.tw antiparkinson.tw exp antitremor drugs/ apomorphine/ bromocriptine/ cabergoline/ solifenacin succinate/ tolteridone tartrate/ propantheline/ exp antiparkinson agents/
Other	Clonidine Doxylamine Epoetin Darbepoetin Lithium Tamoxifen Toremifene Letrozole Exemestane	clonidine/ clonidine.tw. doxylamine/ doxylamine.tw mersyndol.tw exp antianemic agent/ lithium carbonate/ lithium.tw tamoxifen.tw toremifene.tw anastrazole.tw exemestane.tw letrozole.tw exp aromatase inhibitor/ selective estrogen receptor modulator/ tamoxifen/ toremifene/

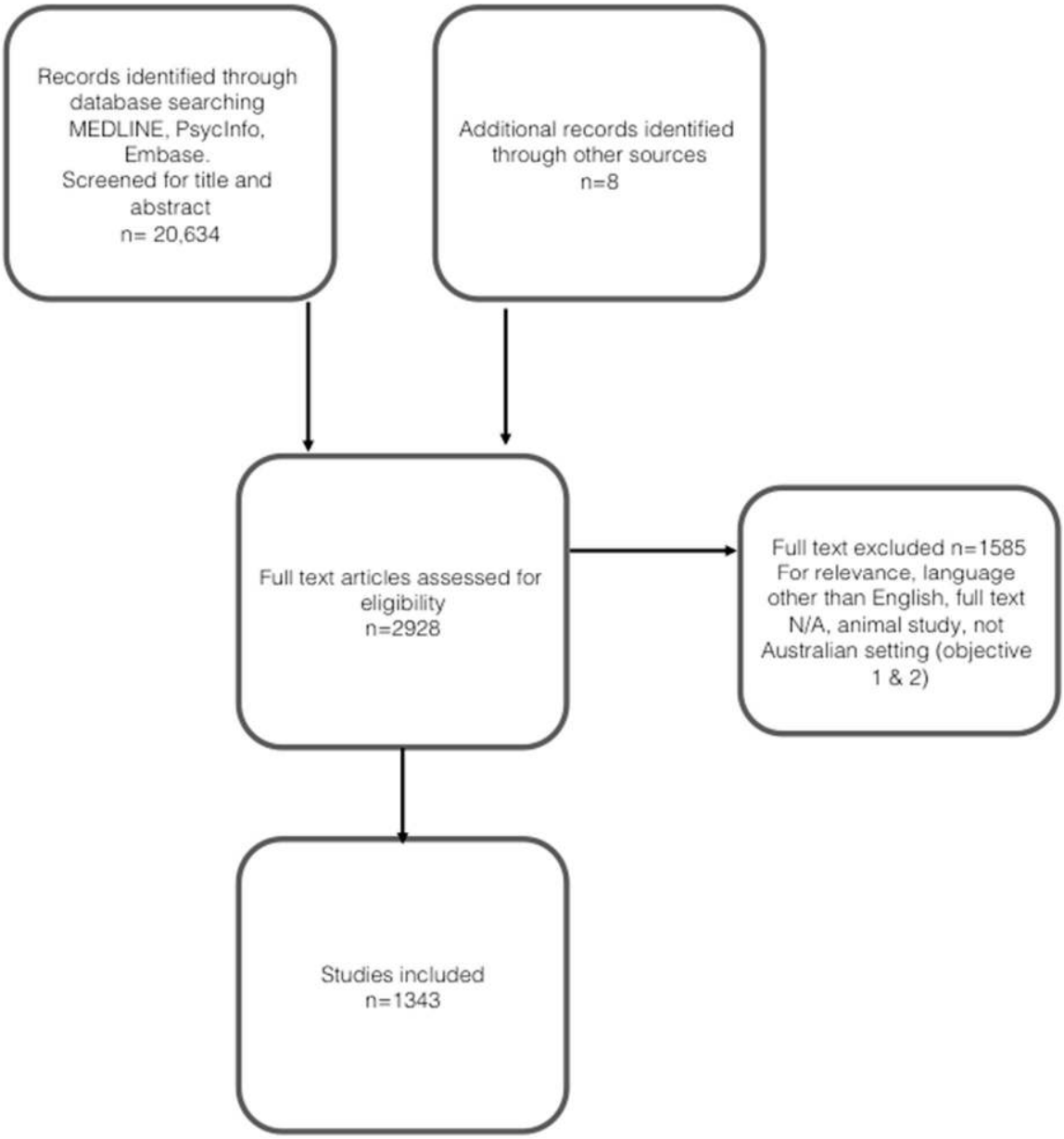

Figure A.2.1. Search strategy

A.3. Victoria Police Forensic Services Department data

Victoria Police Forensic Services Department data for the number of pharmaceutical preparations seized by Victoria Police between 2012 and 2016.

Drug	No received
alprazolam	25931
pseudoephedrine	20808
diazepam	11558
paracetamol	6584
sildenafil	3298
buprenorphine	2900
tamoxifen	2866
quetiapine	2859
clonazepam	2381
oxycodone	2273
diphenhydramine	2184
ephedrine	1479
temazepam	1444
oxazepam	1376
clenbuterol	1363
frusemide	1307
olanzapine	1078
tramadol	1042
acamprosate calcium	977
metformin	943
clomiphene	879
anastrozole	862
methylphenidate	826
tadalafil	771
nitrazepam	676
salbutamol	656
morphine	608
codeine	594
mirtazapine	589
ibuprofen	585
metoclopramide	442
sodium valproate	423
amitriptyline	402
doxycycline	395
pheniramine	367

pregabalin	365
ondansetron	341
finasteride	338
methadone	337
potassium chloride	327
lignocaine	308
dextromethorphan	301
diclofenac	293
thyroxine	273
haloperidol	262
zopiclone	262
clozapine	250
carbamazepine	249
amphetamine	238
cyproterone	231
Modafinil	228
cetirizine	214
naltrexone	212
aspirin	210
cyproheptadine	209
clonidine	205
prednisolone	189
phenytoin	180
tenofovir	178
baclofen	171
pantoprazole	171
indomethacin	170
escitalopram	164
naproxen	161
chlorpheniramine	160
verapamil	158
phentermine	151
diltiazem	150
Nolvadex	150
nicotinamide	144
phenylephrine	144
Gemfibrezil	143
methorphan	139
doxylamine	137
doxepin	134
ranitidine	133
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ketamine	2
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clarithromycin	1
cyclizine	1
fluticasone	1
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imipramine	1
methoxyphenamine	1
mometasone	1
nicotine	1
orlistat	1
perindopril erbumine	1
phenothiazine	1
piracetam	1
procaine penicillin	1
sodium tetradecylsulfate	1
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