Evidence informing the inclusion of gabapentinoids and tramadol on Victoria's SafeScript: a 2021 update

Medicines Optimisation Service
A joint initiative of the Pharmacy Department and the Department of Clinical Pharmacology and Therapeutics at Austin Health

December 2021

Medicines Optimisation Service, Austin Health
Level 5, Lance Townsend Building
Austin Hospital
145 Studley Road
Heidelberg, Victoria 3084
Australia

mos@austin.org.au

Commissioned by Medicines and Poisons Regulation,
Department of Health, Victorian Government.

Evidence informing the inclusion of gabapentinoids and tramadol on Victoria's SafeScript: a 2021 update

David Liew
Vincent Chan
Alice Kochman
Elizabeth Su
Christopher McMaster
Kent Garrett
Albert Frauman

The report was authored by the Medicines Optimisation Service at Austin Health, a joint initiative of the Pharmacy Department and the Department of Clinical Pharmacology and Therapeutics at Austin Health.

December 2021

Contents

Acknowledgments

We would like to thank the following people for their generous contribution to the content of this report:

- Dr Jeremy Dwyer (Coroners Court of Victoria; CCoV)
- A/Prof Rohan Elliott and Alice Norvill (Victorian Poisons Information Centre; VPIC)
- Dr Roderick McRae (AMA Victoria), Dr Zeff Koutsogiannis (TAPNA), Dr Martyn Lloyd-Jones (VAILA), John Jackson (PSA Victoria), Angelo Pricolo (Pharmacy Guild of Australia Victoria Branch), Nicole O'Shea (VPIC)

and our multiple overseas colleagues who were generous with their information and advice regarding prescription drug monitoring programs.

It should be noted that their contribution does not indicate the endorsement of this report or its findings by these individuals or the organisations that they represent. The findings of this report have been derived independently of them.

The Medicines Optimisation Service is a project supported by Austin Health, for the improvement of use of medicines in the fields of equity of access, safety, and innovation. We would like to thank the Austin Health administration for supporting our service, both in development and in ongoing function.

List of tables and figures

Executive Summary

In contrast to previous editions of this report, which were required to answer questions about included medications being culpable for definite harm such as prescription medication-related death, the maturity of SafeScript's use now allows for a broader mandate for inclusion of medications. This is possible because of the hard-won acceptance of Australia's first truly real-time prescription monitoring service, which despite being implemented as mandatory during the most challenging of pandemic times, has been largely embraced as necessary and useful by end users in Victoria because of careful planning, execution, and respect of the evidence. Caution must be taken to ensure that the best decisions are made, as hasty inclusion may bring clear risks to both patients and SafeScript itself.

This broader mandate brings different considerations to this edition of the report. Harms apart from death may suffice, although may still not necessarily carry equal weight. Medications to be included also need not be directly culpable themselves, but may be considered for inclusion if they are surrogate markers which flag high-risk use of other medications, such as opioids. The 'innocent bystander' frequently at the scene should trigger further enquiries regardless of culpability, and some of the greatest utility from real-time prescription monitoring comes from revealing unexpected utilisation of other medications. As such, this report brings a different view even to evidence previously reported.

Gabapentinoids were already of some concern in the 2019 report, although overall metrics of death at that time were not remarkable. This has not changed, and in fact has stabilised. Having said this, other harm associated with gabapentinoids is even clearer from the international peer-reviewed literature, including high-risk misuse, abuse, and intentional poisonings, consistent across multiple different varied contexts, suggesting likely relevance to the Victorian context. More damningly, clear from the Australian data is a highly concerning relationship with the highest risk opioid-related harm. In national data, persistently high pregabalin use is associated with escalations in prescription opioid use, and in Victorian data analysed for this edition of the report, pregabalin is increasingly represented in prescription opioid-related death. Gabapentinoids' presence is disproportionately represented in the most serious opioid-related harm compared to less serious harm and in prescription opioid utilisation; causality may be hard to determine, but presence is far clearer. The role of gabapentinoids as a surrogate to flag high-risk opioid use, added to the spectrum of harms associated with it, provide a compelling rationale to prioritise inclusion of gabapentinoids on SafeScript.

It is worth reiterating that including one gabapentinoid but not another would be merely to invite the substitution effect. This has been seen elsewhere and is likely to hold in Victoria.

The case for tramadol remains less certain. Harms do exist, although less clearly than some pharmacoepidemiological studies would suggest. Victorian data suggests that tramadol has similar rates of harm as other opioids with respect to ambulance attendances for extramedical prescription opioid use, including conscious state and progression to hospital, and emergency department presentations for prescription opioid-related poisonings, including progression to inpatient admission. It is however plausible that tramadol's imperfect pharmacological properties may, in practice, buffer its most serious risk. Rates of tramadol-related death remain stable and low in normalised terms, and internationally tramadol less frequently leads to death from overdose than other opioids.

Other considerations therefore must inform decisions about tramadol. Harmonisation with other jurisdictions at some stage would be ideal, although the magnitude of harm from disconcordance across borders on tramadol is less definite. Unintended consequences are of concern; possibilities include reverse substitution to more harmful prescription opioids, displacement to ilicit opioids, the 'chilling' effect, and stigmatisation of pain patients. To minimise such consequences and to improve end-user acceptance, inclusion would need to be accompanied by investment in evaluation, mitigation, and support, to keep individual patients safe, but also to avoid implemented changes acting as a lightning rod for broader end-user disenchantment. Unlike gabapentinoids, where a strong clinical imperative exists, decisions regarding tramadol's selection for SafeScript, and the timing of implementation, may eventually represent an exercise in priority setting and appetite for risk.

Please note that the discussion in Chapter 8 addresses all these issues more comprehensively.

Chapter 1. Introduction and rationale of research question

1.1 Relationship to the Initial Report

This report is designed to complement the original report, written in April 2017, entitled 'Evidence to inform the inclusion of Schedule 4 prescription medications on a real-time prescription monitoring system'(1) and the subsequent report, written in May 2019, entitled 'Evidence to inform the inclusion of additional Schedule 4 prescription medications on the Victorian real-time prescription monitoring system: an updated report'(2).

It is intended as an update to the previous two editions of the report and has been written by authors from the same organisation as that report, with many of the same authors. We acknowledge and applaud the adaptation of our recommendations following both reports, and we maintain our belief in the durability of the evidence-based approach that we adopted at that time. In the 2017 report we however identified the need to review the research question on an ongoing basis, to identify new data and detect emerging trends. This report has been commissioned and is written in this spirit, and such commitments have been taken by other jurisdictions who have drawn on this precedent.

Some content is necessarily adapted from the previous editions of the report in order that this document can be read independently of them. Any adapted content has been modified for the current circumstance.

1.2 What is the purpose of a RTPM?

The rationale of a real time prescription monitoring system (RTPM) was articulated in previous editions of this report, but for reference 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 is intended to reduce inappropriate multiple prescribing events, particularly by multiple providers, reduce fraudulent prescribing, provide alerts about opioid doses above a risky threshold or in risky combinations, and improve quality of care by facilitating a patient-centred approach in addressing prescription medication misuse(3). 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.

The Victorian RTPM (SafeScript) is primarily designed to help prescribers and pharmacists to identify patients at risk of harm. This has therefore been the primary consideration in designing the approach to this report. It should be noted that this report was commissioned in the context of an existing, functioning RTPM which started as a trial in western Victoria in 2018 and was made accessible across Victoria in April 2019. Its use was made mandatory, with some exceptions, in 2020 and is in widespread use at the time of writing. This report therefore does not seek to examine the structure or function of this RTPM, but examines the research question in the context of SafeScript and its associated legislation.

The authors strongly support the implementation of SafeScript and the pragmatic approach taken by the Victorian Government in implementing a successful and well-accepted program. End user satisfaction is a necessity in ensuring the durability of SafeScript and its capacity to derive important clinical outcomes, and we applaud the Victorian Government Department of Health and Human Services (DHHS) RTPM Taskforce for their work to this point in delivering such a program, and their dedication to evidence-based policy.

1.3 How does TGA scheduling relate to inclusion of a medication on the Victorian RTPM?

SafeScript includes all medications on Schedule 8 of the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons), and some medications included in Schedule 4.

The Therapeutic Goods Administration (TGA) manages the scheduling of pharmaceutical medications under the 'cascading' guidelines detailed in the Australian Health Ministers' Advisory Council's Scheduling Policy Framework(4). Regulation under the Poisons Standard is heavily structured, with the intent of ensuring that the associated regulation is justifiable.

The inclusion of Schedule 4 medications is warranted because such medications may still lead to significant harm as a consequence of misuse, abuse or illicit use and yet not meet the factors necessary for inclusion on Schedule 8:

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.

In the same way that the Poisons Standard does, it is important that any RTPM should be balanced in terms of its approach to inclusion of medications. It should be sufficiently inclusive as to adequately perform its purpose in mitigating harm without 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 must take this into account.

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

This report was commissioned by the Victorian Government Department of Health to derive, in a limited timeframe, analysis of existing evidence and already collected data to assist the decision as to whether gabapentinoids or tramadol should be included on SafeScript.

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

This report is only for internal distribution within the Victorian Government Department of Health, and may not be more broadly distributed (in part or in entirety) without expressed permission from the Department of Health and the authors.

Data from local databases has been supplied from the owners and administrators of these databases with the intention that it may not be distributed more widely without expressed permission from them.

It should be noted that their contribution does not indicate the endorsement of this report or its findings by these individuals or the organisations that they represent. The findings of this report have been derived independently of them and have not been sighted or approved by them.

Chapter 2. Scope of this report

This report is designed to inform a decision as to whether additional Schedule 4 prescription medications should be included on the Victorian RTPM (SafeScript). This decision will be made by an advisory committee, and was commissioned by the Department of Health. This scope was agreed to prior to this report being written.

The scope for this edition of the report, as request by the Department of Health, differs somewhat from previous editions. This is particularly notable in two main ways:

- This report will examine all harms as being relevant to inclusion of medications on SafeScript, not just 'definite harm' in the form of death;
- medications need not be directly culpable in order to be included if they can otherwise prove useful to monitor.

This scope has therefore shaped this report.

To achieve this, this report includes literature review of peer-reviewed and 'grey literature' sources, analysis of available relevant local data, and commentary relevant to the purpose and stated aims. Where possible, the authors explored the potential for readily identifiable subgroups at particular risk. International precedent has also been considered.

This report is designed to be read in the context of previous reports, and only to assess gabapentinoids and tramadol. No other medications, currently included or otherwise, are being considered for a change in status. Other medications will only be assessed in order to contextualise the magnitude of harm assessed to be attributable to other candidate medications, as justified throughout the report.

The commentary attempts to address the potential implications of inclusion of examined medications on SafeScript, both in terms of the harm attributable to the medications themselves and harm otherwise attributable that may be consequent to inclusion. As articulated after the last report, and noted on page 56, criteria were established to help guide decision making about inclusion of medications:

1. Evidence of harms
2. Trends in prescribing, misuse and abuse
3. 'Substitution effect'
4. 'Chilling effect'
5. Regulatory burden and cost-benefit
6. Inter-jurisdictional approaches

This report is written with this in mind, with the knowledge that a full regulatory impact statement will be required to assess the consequences of implementation.

This report will address relevant evidence to the scope, and seek to interpret significance to a Victorian RTPM, but the authors acknowledge no evidence or precedent will be able to guarantee the appropriateness or otherwise of including a medication. As discussed in the 2017 Report (Chapter 2, p5)(1):

"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… effective programs have rarely achieved their goals without a coordinated multi-faceted response. Precedents may speak to the effectiveness of a similar intervention in Australia but only if viewed through the correct lens."

The role of the advisory committee in translating this report into a recommendation is therefore paramount.

Chapter 3. Approach to the research question

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

Many different sources of harm may be relevant to inclusion of a medication on SafeScript. While previous reports have sought primacy in data related to overdose-related deaths, given the current maturity of use of SafeScript, it is reasonable to consider data regarding misuse, abuse, ambulance attendances, emergency department presentations, admissions, and poisoning calls as well. Given that context is critical to interpretation of the data, data from contexts similar to Victoria, and ideally Victoria, will best inform Victoria's needs.

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 medication by other jurisdictions does not mean it is appropriate, nor does apparent failure mean that the intervention is unsuccessful. The escalation over the last 15 years 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 SafeScript, but no evidence will be able to guarantee the appropriateness or otherwise of including a medication.

Combinations of individual medications contributing to harm in an individual

One factor affecting the attribution of causality to individual medications 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 additive combination of medications leading to pharmacodynamic drug interactions such as between related medications (such as gabapentin and pregabalin) and medications with similar toxicities (such as medications 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. While these risks are now well understood, new risks may start to be better understood as a consequence of real-life experience, although given the often complex clinical situations in which these medications are concomitantly given, their impact cannot be realistically appreciated without pharmacoepidemiological assessment.

The presence of such a drug combination helps to suggest that harm has been directly derived from the administration of medications constituting the combination, and it would seem plausible that a RTPM 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 medication-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 medication-related harm in Victoria, however, has repetitively been shown to come about from unintentional harm associated with therapeutic misadventure. Many data sets have come to document perceived intent as this may be important in targeting preventative interventions. Given that a RTPM 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 of substantive value in specific circumstances to allow for interpretation of future risk following mandatory utilisation of a RTPM.

Demographic data associated with medication-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, 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 (e.g. crime associated with the theft of prescription medications) is unlikely to be affected by a RTPM. A RTPM will be likely to affect indirect harm from diversion (e.g. 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 (e.g. overdose-related deaths). For these reasons, diversion has not been specifically examined in this assessment and this report was asked to not consider the role of diversion in determining which medications might be included on SafeScript.

Nevertheless, the concept of diversion is worth consideration in contextualising this report. It should be noted that diversion might complicate estimations of use. Data in this report will capture diversion from individual prescriptions filled in Victoria but may not capture data from non-prescription diversion or access from other jurisdictions. It may also impair the impact of SafeScript, and interstate exchange between RTPMs in other states might help to further bolster this program.

In the same way, 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 Pharmaceutical Benefits Scheme (PBS) or the Repatriation Pharmaceutical Benefits Scheme (RPBS) and the absence of regulation. Future assessments following the implementation of a RTPM should consider the role of importation if possible as increased monitoring may lead to a preference for access through this method.

How can we interpret data related to harm from prescription medications in the context of changing use and supply?

For a prescription medication to warrant increased monitoring on a RTPM it is more important to consider the proportionate harm that might arise in the context of its usage, such as that nominally arising from an individual prescription, rather than the overall burden of harm to the community. Medications which are frequently used would be expected to inflict greater total harm to the community compared with less frequently used medications and therefore total harm may not accurately reflect the risk posed by an individual prescription medication; paracetamol is an example of a relatively safe medication which has a large overall burden of morbidity associated with it, and it is inconceivable that it would be regulated on a RTPM without dramatic changes in medication regulation in Australia.

Furthermore, increased usage of a medication 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.

Estimating harm per prescription

The estimation of harm proportional to usage is complicated by the difficulty in estimating usage in any given jurisdiction. Given that this report focuses on a RTPM for Victoria and utilises Victorian data, metrics of use are focused on Victoria. The method by which these have been estimated is detailed in Appendix 2. A limitation is that private prescriptions are not included in this estimation. It is possible that individuals may seek private prescriptions for medications with cost per prescription above the PBS co-payment (currently $6.60/prescription for Health Care Card holders, $41.30 for non-Health Care Card holders(5)) that might otherwise be available on the PBS in order to remain undetected by the PBS Prescription Shopper Information Service(6). The lack of ready accessibility to this service, including a high threshold for capture, has limited its utilisation, and there are unlikely to be many private prescriptions for these medications not already captured in under co-payment data(7), as broadly accepted in other Australian pharmacoepidemiological studies.

It should be noted that the presence of private prescriptions would reduce estimated metrics of harm (by increasing the denominator). This is discussed further in Chapter 4.2. The limitations of estimating codeine-related metrics of harm are articulated in the Initial report but the underlying principles are broadly applicable across other medications. Due to its importance in contextualising the difficulties of estimating risk, it is replicated below.

Finally, this report concentrates on utilisation on a per prescription basis, as it might be considered that this is a better consideration for the risk of overdose that might be improved by a RTPM. It nevertheless 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. If these data are to be extrapolated outside of the RTPM context, it may be utile to consider harm by other contextually appropriate measures including per individual, or per defined daily dose.

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(8) 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 coordinated 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 likely to include contribution from 2016 Schedule 2 and Schedule 3 codeine, who have not yet realised benefit from rescheduling

Table 3.2.1. Potential confounders for estimating codeine's toxicity, as an example for interpretation of metrics for other medications. Replicated directly from the 2017 report (Table 4.2.1, p23).

3.2 Consideration of the role of harm attributable to specific combinations of medications

One of the key criticisms of medication regulation is that it often inconveniences many safe users. Risk across a population is rarely homogenous and individual risk varies significantly. For some medications, there may be subgroups of patients which are at such grossly disproportionate risk that regulation across the whole population of patients taking that medication might be justified to largely benefit those patients within that subgroup, particularly when that subgroup cannot be specifically targeted.

Ordinarily, this subgroup is not able to be differentiated from the remainder of patients taking that medication by the intervention itself, and therefore remains in the overall compartment. This justifies consideration of the risk attributable to the overall compartment, and an overall metric of harm is an appropriate indicative measure.

It should be noted that, nevertheless, arguments can be made on the basis of specific risk to high-risk subgroups if medications can identify these groups. If risk prediction for harm can be derived on the basis of a prescribing profile, then depending on the size and importance of that subgroup, such surrogate flagging may be important to consider for the overall system.

Practical therapeutic contextualisation of each of these steps by appropriately skilled and experienced individuals is key, but some metrics may assist in assessing these questions (although should not be considered in isolation).

3.3 Alternative considerations to inclusion of medications as monitored supply poisons

The purpose of this report is only to consider the evidence to support inclusion of a medication in entirety, but the adoption of more detailed, sophisticated steps might abrogate the need to consider some of these questions. Other steps that might be considered include:

- inclusion only of higher dosage tablets for monitoring, with exemption for lower dosage tablets (e.g. for pregabalin 150mg and 300mg tablet prescriptions to be included, with exemption for pregabalin 25mg and 75mg tablet prescriptions, if it was shown that lower dosage tablets were less associated with high-risk use),
- the use of 'monitored poisons' in addition to 'monitored supply poisons', to allow for monitoring of medications without mandatory checks, with potential benefits for both prescribers of that medication, as well as prescribers of medications with potential combination toxicity (e.g. inclusion of pregabalin as a 'monitored poison' so that interested clinicians can determine whether patients are receiving pregabalin from other prescribers, but also so that prescribers of opioids to the same patient can determine that the patient has also been co-prescribed pregabalin with the potential for combination toxicity).

While these might be possible to accommodate under current legislation, it has been discussed that practically this still remains difficult for implementation from an end user perspective and therefore cannot be considered in lieu of blanket inclusion of a medication on SafeScript.

3.4 Recommendations of the Victorian Coroner

We would like to acknowledge that there are a number of recommendations from Victorian coronial reports regarding gabapentinoids which are relevant to this report. We have sought to address the rationale behind these recommendations, in order to provide decision makers with adequate information to make informed choices.

We review three relevant reports here. Specific recommendations made by the coroner regarding pregabalin was extracted here from the coronial reports for the purpose and context of this report. In Pursuant of the Act, these finding are published on the Coroners Court of Victoria website in accordance with the rules.

In the inquest into the death of Samantha Louise Leech (*Coroners Court of Victoria* COR 2019 7144), the cause of death was reported as 'Complications of a seizure in the setting of prescription medication abuse (pregabalin)'. In Pursuant to section 72(2) of the Act, the coroner made the following two recommendations in relation to pregabalin:

- *"1. With the aim of promoting public health and safety and preventing similar deaths, I recommend that the Victorian Department of Health review the circumstances of Ms Leech's death including but not necessarily limited to the apparent ease with which she presented to multiple clinics, registered as a patient under her maiden surname and altered date of birth and was prescribed significant quantities of pregabalin, implicated in her death."* (p. 12).
- *"2. With the aim of promoting public health and safety and preventing similar deaths, I recommend that the Victorian Department of Health's review should be expedited and aimed at including pregabalin to the list of medicines monitored through the SafeScript system and any other measures that could enhance patient safety in this regard."* (p. 12).

In the inquest into the death of Daniel Joseph Herbert (*Coroners Court of Victoria* COR 2018 005440), the cause of death was reported as 'Combined drug toxicity (methadone, fentanyl, diazepam and pregabalin)'. In Pursuant to section 67(3) of the Act, the coroner made the following additional comments in relation to pregabalin:

- *"Victorian Coroners have previously highlighted the harms associated with pregabalin. This case is a further example that pregabalin is not a harmless drug."* (p. 10).
- *"This finding will be provided to the Royal Australian College of General Practitioners and consideration should be had in relation to warning their members that when prescribing pregabalin with repeats, they should treat it with the same caution as any other drug of dependence"* (p. 10).

In the inquest into the death of NJ (*Coroners Court of Victoria* COR 2015 0022127), the cause of death was reported as 'Combined Drug Toxicity'. In Pursuant to section 67(3) of the Act, the coroner made the following additional comments in relation to pregabalin:

- *"At present, the DHHS's Real-Time Prescription Monitoring Taskforce is considering what drugs outside Schedule 8 should be included in the scope of monitored drugs. This question is directly relevant to the circumstances of NJ's death. At least four of the contributing drugs (pregabalin, diazepam, oxazepam and mirtazapine) are not Schedule 8 drugs, and yet appropriate prescribing decisions could not be made unless NJ's doctors knew of her use of these drugs. Over the past four years, I with several of my colleagues, have made comments and recommendations in findings regarding the need for Victorian's real-time prescription monitoring system to monitor dispensing of all prescribed drugs. The circumstances of NJ's death provide further support for this position."* (p. 19).

- *"I distribute this finding for information to the DHHS's Real-Time Prescription Monitoring Taskforce, to assist and inform their implementation efforts and particularly their consideration of what drugs outside Schedule 8 should be included in the scope of the drugs monitored."* (p. 20).
- *"I distribute this finding to the Royal Australian College of General Practitioners for training and education purposes generally, but particularly in relation to the drug pregabalin. I have grave concerns that not all College members fully appreciate the risk of pregabalin misuse and its potential to interact with other prescribed drugs."* (p. 20).

Furthermore, in Pursuant to section 72(2) of the Act, the coroner made the following recommendation in relation to pregabalin:

- *I recommend that the Royal Australian college of General Practitioners provide education to its members as to the need for caution in prescribing pregabalin due to its risk of misuse and its potential for harm."* (p. 20).

We thank Victorian coroners for highlighting this as an ongoing issue, and seek to provide evidence and analysis to address the questions raised which remain outstanding.

Chapter 4. Evidence of harm in Australia from Schedule 4 medications not already included on the Victorian RTPM (SafeScript)

The first factor considered in understanding the suitability of medications for inclusion for monitoring on a RTPM 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

A number of important reports have been published in peer-reviewed form since the last edition of this report, and similarly this section has been presented in narrative form, specifically with view to providing context relevant to the potential monitoring of gabapentinoids and tramadol on the Victorian real-time prescription monitoring service. Relevant peer-reviewed literature has been identified using the methodology contained in Appendix 1.

It is of importance that the descriptions in this section are not considered in isolation as they are not a comprehensive assessment of local evidence for harm. While they often are based on data from local databases, further detail regarding harm is available in most cases from *de novo* analysis of data from local databases. The following descriptions are nevertheless largely notable, but also additionally have guided the approach to assessment of data regarding definite harm from local databases.

4.2 Gabapentinoids

Background

As important context to the subsequent discussion, we have replicated the same background here as detailed in previous editions of the report. For greater detail regarding trends prior to 2019, we strongly recommend referring to the 2019 and 2017 reports.

The gabapentinoid medications primarily utilised in Australia, pregabalin and gabapentin, were originally intended as anti-epileptic agents but have subsequently gained both TGA indications and PBS reimbursement for neuropathic pain. Changes in PBS funding arrangements to allow pregabalin to be accessed on the general schedule under streamlined authority led to substantial escalations to pregabalin use in Australia (detailed in depth in Chapter 3.2 of the Initial Report(1)), although the escalation in their prescription use has subsequently plateaued with maturity of market utilisation.

While there are some notable pharmacological differences between pregabalin and gabapentin which might alter harm potential, including absorption kinetics and target binding receptor, due to their functional similarity, this report will consider pregabalin and gabapentin in synchrony. This is primarily due to their susceptibility to interconnected substitution, demonstrated by trends in the United States, where pregabalin regulation has led to preferential misuse and abuse of gabapentin, which is not regulated. In addition, given the relatively limited utilisation of gabapentin in Australia, metrics of harm attributable solely to gabapentin are hard to estimate. It is therefore conceivable that inclusion of one, but not the other, would simply lead to a transfer of attributable harm to the medication not included.

Regulation of gabapentinoids in the United Kingdom changed as of 1 April 2019, with pregabalin and gabapentin reclassified to Schedule 3 of the relevant UK schedule(9). This change will mandate that these medications require a prescription validity of 28 days after being written, and are subject to special prescription writing requirements including physical signature, and not allowing repeatable dispensing. They were however specifically given exemption from standard provisions, and thus do not require recording in the Controlled Drugs register, do not require a witness for destruction, and are excluded from safe custody requirements. There is no exactly analogous regulatory category in Australia. This change is largely changing because of concerns about misuse, illegal diversion, and addiction as raised by the Advisory Council on the Misuse of Drugs in 2016(10), mirroring justifications for regulatory inclusion in the US. This is therefore not directly relevant to this report, but the original advice did cite a limited number of deaths at that time, and the subsequent press release stated that "(the) move comes after experts highlighted rising numbers of fatalities linked to the drugs"(11).

Key background from previous reports regarding gabapentinoids

Noting that the scope of previous reports is different to this one, there is much relevant from previous reports regarding trends in gabapentinoid use, even though there had been an absence of robust local data to provide evidence of definitive harm attributable to gabapentinoids. Below we summarise key reports that were highlighted in detail in the previous edition of this report (2019 report, p16-22).

Prominent in these reports were population-based nested case-control studies from Canada(12, 13), which suggested that pregabalin and gabapentin were associated with increased risk of opioid-related death after adjustment for confounders. Our analysis from the previous edition focused on to what extent such a relationship might have demonstrated causality, partially in exploring a dose-response relationship, and partially examining for the possibility of residual confounding from channeling bias. The questions that remained

regarding causality in that relationship was aptly captured in the corresponding editorial, which we specifically quoted, and which stated that "understanding how patients come to be prescribed both an opioid and a gabapentinoid would be of great value"(14), a sentiment echoed by a report from the Pharmaceutical Benefits Advisory Committee Drug Utilisation Subcommittee (PBAC DUSC) highlighting the need for a systematic approach in understanding contextual mechanisms of harm in Australia(15).

It should be noted that this commentary was particularly relevant when the purpose of that edition of the report was to determine to what extent there definitely was an increased risk of harm, namely death, as a consequence of pregabalin. In this edition, considering that inclusion on SafeScript might be adequately supported by pregabalin acting as a surrogate, flagging high-risk opioid utilisation rather than having to be responsible for causing death, then it is less necessary to explore causality in such a concerning relationship.

We also reviewed Australian data, the most useful of which was published by Cairns et al. regarding intentional poisonings related to pregabalin from the NSW Poisons Information Centre, and pregabalin-associated deaths captured by the National Coronial Information System (see below) in NSW(16). Notably, while intentional poisonings appears to rise in synchrony with the rise in pregabalin utilisation in Australia during the corresponding period of time, one-seventh of these patients demonstrated prescribing characteristics concerning for misuse, which would likely have been detected by a real-time prescription monitoring service inclusive of pregabalin. If prevention of such intentional poisoning is, at this stage of the system's maturity, a valid aim of SafeScript, then such data would suggest that monitoring pregabalin on SafeScript would be likely to be effective in identifying at least some patients destined for pregabalin-related intentional overdose.

Furthermore, these data also suggested that pregabalin-opioid co-ingestion was disproportionately represented in pregabalin-related deaths compared to pregabalin-related poisonings or overall utilisation (see table 4.2.1). This demonstrated that pregabalin and opioids are often concomitantly found in at-risk individuals and in patients who experience harm, and while once again causality could not be identified in order to satisfy the burden of proof from the previous edition of this report, the data from Cairns et al. would suggest that, at minimum, pregabalin could be used as a surrogate for high-risk opioid utilisation.

	PBS 10% sample: co-prescribed with pregabalin in the whole population (2013-2017)	NSW PIC: pregabalin (2004-2016)	NSW PIC: carbamazepine (comparator) (2004-2016)	Hospital toxicology: pregabalin (2012-2015)	Hospital toxicology: carbamazepine (comparator) (2012-2015)	NSW NCIS deaths: pregabalin-associated (2005-2016)
Total	58,921	1158	1589	73	40	88
Co-ingested opioids	**49.6%**	**31%**	5%	**33%**	3%	**80%**
Co-ingested benzodiazepines/z-drugs	24.7%	25%	12%	30%	20%	67%

Table 4.2.1. Data on co-ingestion of opioids and benzodiazepines/z-drugs, in pregabalin poisonings and pregabalin-associated deaths compared with carbamazepine poisonings (shaded) and overall PBS 10% sample co-prescription, derived from Cairns et al.(16) (originally 2019 report, Table 4.1.3)

The data from Crossin et al. were also described, which examined ambulance attendances related to pregabalin misuse in Australia(17). Ambulance attendances may be multifactorial, and the context of their occurrence can be hard to delineate, including the final outcomes, as acknowledged by the authors. In those data, while there was a marked increase in ambulance attendances, this correlated with a similar increase in prescriptions issued. This data, combined with that of Cairns et al., would suggest that any pregabalin-related harm may not necessarily be associated with more general measures of harm, such as ambulance attendances or even poisonings, but may be important in specific prescribing contexts with the highest risk leading to death, where pregabalin's contribution to causality is at least possible, but noting its presence may be particularly useful.

Evidence from Australian literature on harm related to gabapentinoids, new in the updated report

Given the importance of local utilisation trends in determining the suitability of monitoring gabapentinoids, particularly with the context of use in mind, local data is considered to be particularly important in this assessment. Selected reports regarding utilisation, new to this edition of the report, are therefore covered in depth in this edition of the report.

'Characteristics of fatal gabapentinoid-related poisoning in Australia, 2000-2020' by Shane Darke et al. (*Clinical Toxicology* 2021)

In addition to the data analysed by Cairns et al., as mentioned above, the first edition of this report addressed data from the National Coronial Information System (NCIS), a trans-national database aggregating information from all jurisdictions across Australia and New Zealand, although only Australia data were interrogated at that time. While there are some limitations in the interpretation of the data, primarily regarding differences in reporting and attributing causality between different jurisdictions, overall trends are useful from this data source when investigating causes regarding prescription medicine-related deaths.

To this end, the data reported by Darke et al. from the NCIS are highly useful(18). They performed a retrospective study of all deaths collected in the NCIS where gabapentinoids were considered to be a contributory mechanism between 2000 and 2020. This covers the entire accessible period of contemporaneous gabapentinoid use in Australia. As illustrated in previous editions of this report, gabapentinoid utilisation prior to this in Australia was low.

This study primarily reviewed the clinical, toxicological, and autopsy characteristics of the 887 deaths included in this report, noting that 721 cases (81.3%) were deemed accidental rather than intentional toxicity. Notably, while in all of these cases pregabalin was coded as being contributory, this determination has been variably interpreted at different points (2019 report, p20), and in those whose peripheral blood concentrations were assessed, 481 of 803 (59.4%) had relatively modest levels quantified at ≤10mg/L.

Of the 887 deaths, 871 had other drugs detected as present, and of these, over 90% had opioids detected as well, substantially more than other psychoactive drugs (Table 4.2.2.). While this may relate to prescribing indication, it emphasizes the extent to which the importance of gabapentinoids as medications which might be monitored relates closely to opioid utilisation.

	Accidental	Intentional	All cases
Deaths included in report	721	166	887
Deaths where other drugs were detected	710	161	871
Deaths where other psychoactive drugs were detected	708	161	869
Opioids	661 (93.1%)	124 (77.0%)	785 (90.1%)
Antidepressants	412 (58.0%)	122 (75.8%)	527 (60.5%)
Antipsychotics	267 (37.6%)	58 (36.0%)	325 (37.3%)
Psychostimulants	148 (20.4%)	38 (23.6%)	158 (18.1%)

Table 4.2.2. Co-detected drugs detected in deaths where gabapentinoids were considered to be a contributory mechanism, captured on the NCIS 2000-2020 (selected data replicated from Darke et al.(18), percentages are of 'Deaths where other drugs were detected'). It is notable that opioids were present in the vast majority of cases, far more than other prescription and non-prescription drugs.

These data in and of themselves can only give a limited indication as to the role of the synergistic combination of opioids and gabapentinoids. Not only do these data not reflect a denominator of overall use, they do not delineate the context in which harm occurred, and whether this might represent confounding by indication, given both opioids and gabapentinoids might be used for the treatment of pain. Nevertheless, they do suggest a relationship of concern between gabapentinoids and opioids which, even if not causal, might warrant further interrogation as to whether it might be associated with a population of interest. In this respect, they provide important context as to the nature of deaths potentially caused by gabapentinoids, and the co-administrations that might be relevant to it.

It should be noted that, in the 2019 report, we highlighted the work of Lyndon et al(19) (2019 repot, p17-18) which examined similar data from the UK Office of National Statistics, where 79% of pregabalin-related deaths were associated with opioids. This, as well as Victorian data which we update in Chapter 5.2, helps to confirm the disproportionate involvement of opioids in pregabalin-related deaths.

Complementing the work of Darke et al., two other reports of Australian data examine the context of gabapentinoid and opioid co-utilisation.

'Patterns and correlates of prescribed and non-prescribed pregabalin use among a sample of people who inject drugs in Australia' by Rachel Sutherland et al. (*Drug and Alcohol Review* 2020)

Of particular concern amongst gabapentinoid users are those who inject drugs, and in this respect important data regarding context comes from the 2018 Illicit Drug Reporting System, a cross-sectional sample of 905 people who inject drugs in Australian state capital cities(20). Participants were reimbursed $40 for their time, and the study is co-ordinated by the National Drug and Alcohol Research Centre, but involves collaborators from multiple states including Victoria.

Notably, amongst the 905 participants in this survey, 225 (25%) identified having used pregabalin within the last six months. Of these 225, 41% had used prescribed pregabalin, 62% non-prescribed and 3% a combination of prescribed and non-prescribed. Based on prescribed and non-prescribed use of pregabalin, a bivariate analysis was performed for associations with factors relating to demographic, drug use, drug-related harm, and health, and a multivariate analysis was subsequently performed (Table 4.2.3).

	Bivariate, no pregabalin use (n = 678) vs.		Multivariate, no pregabalin use (n = 678) vs.	
	Prescribed use only (n = 86) RRR (95%CI;P-value)	Non-prescribed use only (n = 133) RRR (95%CI;P-value)	Prescribed use Only (n = 86) ARRR (95%CI;P-value)	Non-prescribed use only (n = 133) ARRR (95%CI;P-value)
Heroin use	**1.65 (1.04, 2.63; 0.034)**	1.32 (0.91, 1.93; 0.148)	1.30 (0.74, 2.30; 0.363)	0.77 (0.47, 1.27; 0.307)
Prescribed pharmaceutical opioid use	**2.30 (1.27, 4.14; 0.006)**	0.82 (0.42, 1.59; 0.549)	1.26 (0.61. 2.64; 0.534)	0.74 (0.33, 1.67; 0.467)
Non-prescribed pharmaceutical opioid use	**2.44 (1.54, 3.88; <0.001)**	**2.69 (1.84, 3.94; <0.001)**	**2.39 (1.37, 4.14; 0.002)**	**2.75 (1.70, 4.47; <0.001)**
Prescribed benzodiazepine use	**3.52 (2.23, 5.57; <0.001)**	**1.58 (1.06, 2.36; 0.025)**	**3.02 (1.76, 5.19; <0.001)**	**2.03 (1.23, 3.35; 0.006)**
Non-prescribed benzodiazepine use	1.42 (0.87, 2.32; 0.157)	**3.85 (2.62, 5.66; <0.001)**	1.15 (0.63, 2.10; 0.642)	**3.82 (2.34, 6.26; <0.001)**
Stimulant use	1.28 (0.73, 2.25; 0.381)	**3.51 (1.85, 6.67; <0.001)**	1.70 (0.80, 3.62; 0.166)	**3.25 (1.39, 7.60; 0.007)**
Overdose (past year)	**2.09 (1.24, 3.50; 0.005)**	**2.54 (1.65, 3.91; <0.001)**	1.47 (0.81, 2.67; 0.202)	**2.31 (1.38, 3.87; 0.002)**
Pain or discomfort (day of interview)	**4.15 (2.35, 7.32; <0.001)**	1.12 (0.77, 1.63; 0.555)	**3.34 (1.76, 6.34; <0.001)**	1.13 (0.70, 1.85; 0.615)

Table 4.2.3. Associations of pregabalin use in people who inject drugs in respondents to the Illicit Drug Reporting System survey (selected data replicated from Sutherland et al.(20)). Results statistically significant to a value of p<0.05 are highlighted in bold.

Notably, in these data, pregabalin demonstrated robust associations with non-prescribed pharmaceutical opioid use, which may not otherwise be captured in SafeScript. Conversely, non-prescribed benzodiazepine use was also associated with pregabalin use that was not prescribed, but not with that which was prescribed. Similarly, overdose was associated with non-prescribed pregabalin but not prescribed pregabalin; it is hard to determine how well such use may be monitored by a prescription monitoring service such as SafeScript.

In this population, prescribed pharmaceutical opioid use did not appear to correlate with prescribed pregabalin use after multivariable logistic regression, which might suggest that concordant prescribing indication is less relevant in this at-risk population, although there was a robust association between prescribed pregabalin and pain on the day of interview.

These data would suggest that, amongst the at-risk population of people who inject drugs, prescribed pregabalin might help to flag patients using non-prescribed opioids, but it is non-prescribed pregabalin, which SafeScript may be less relevant to, that is not clearly correlated with measures of harm such as overdose. It therefore bears considering that its utility of flagging at-risk patients, when considered as a dichotomous variable (recent use or no recent use), may not be definite. While it is not certain how these trends might extrapolate to the broader population, they certainly are of relevance in a sub-population of people who are at greater risk of prescription medicine-related harm.

'Trajectories of pregabalin use and their association with longitudinal changes in opioid and benzodiazepine use' by Andrea Schaffer et al. (*Pain* 2021)

In order to understand more generalizable trends of co-administration between pregabalin and other prescription drugs such as opioids, with the nuance of prescribing dosage, it is necessary to look at Pharmaceutical Benefits Scheme (PBS) data, although such granular data is increasingly harder to access. Data between July 1, 2012 and December 31, 2019 captured in the PBS 10% random sample not only capture the period of time of interest of pregabalin use, but given the subsequent scarcity of such data, may represent data practically most likely to understand the most contemporary trends of use.

Schaffer et al. analysed these data in all people aged >18 years old, and stratified them by trajectories of pregabalin use, based on clinical relevant and technical statistical criteria and using analysis of 30 day intervals of pregabalin prescribing(21). It should be noted that pregabalin in Australia is commercially available in 25mg, 75mg, 150mg, and 300mg tablets, allowing for quite dramatic differences in daily dosage and pharmacological risk with similar numbers of prescriptions, and that prescriptions for higher tablet dosages may carry higher risk, as noted in the last edition of our report (2019 report, p13).

These trajectories are shown in Figure 4.2.1. It is notable that a majority of use is either very short-term use (49.4%) or short-term use (14.0%), which might be out of keeping with patterns of widespread dependence which might warrant up-front regulation of individual prescriptions for pregabalin, but that a small proportion of patients have very high, persistent use, increasing over months and sustaining over the course of a 12 month period, which might be best monitored through a real-time prescription monitoring system such as SafeScript.

This image has been excluded from the public version.
Reproduction rights were only sought for internal circulation, and have not been sought for public release.

Original image displayed was:
Figure 1, Schaffer et al. Pain 2021
Trajectories of pregabalin daily dose in the year after initiation (n5142,776). The gray shaded area represents the range of recommended daily doses for long-term use for neuropathic pain or seizures in adults with normal renal function.
https://journals.lww.com/pain/pages/imagegallery.aspx?year=2022&issue=05000&article=00008

Figure 4.2.1.. Trajectories of pregabalin use, as estimated from the PBS 10% sample between 2012 and 2019 inclusive (replicated from Schaffer et al.).

This analysis subsequently went on to examine which medicines were most frequently co-dispensed in the 90 day period before or after pregabalin initiation. Notably, in this general prescribing population, opioids were the most commonly prescribed, ranging from 52.2% of the very short-term trajectory patients up to 78.5% of the highest dose persistent use patients. The overall percentage, 56.7%, was substantially higher than that for the next most common classes of co-administered medicines: antidepressants (35.7%) and prescription NSAIDs (35.6%), both of which were less than even 'strong opioids' by themselves (37.3%).

This complements the data Darke et al. from NCIS pregabalin-contributory deaths by providing a potential denominator. The rates of co-prescription in Schaffer et al., despite being high, are substantially lower those seen in deaths in the Darke et al. data, suggesting that risk

might be somewhat enriched in those patients co-administered opioids as well as pregabalin. It is plausible that this risk might be concentrated in the persistent use of highest dose trajectory, or that not all patients taking pregabalin who died of opioid-related deaths were captured in the NCIS data, but nevertheless these data would appear to support the proposition that patients co-prescribed opioids and pregabalin are of concern.

Possibly with this synergism in mind, as reported in other reports (and detailed in international reports and previous editions of this report), the authors analysed whether pregabalin initiation was associated with increases in predicted geometric mean daily doses of prescription opioids and benzodiazepines, standardised to oral morphine equivalents and daily diazepam equivalents respectively (Figure 4.2.2.).

These data show an increase in both opioid and benzodiazepine prescribing, measured dichotomously, at the time of pregabalin initiation. This is not unexpected, given that this is likely to represent a point of clinical intervention. It is notable, however, that the effect on benzodiazepines is modest and short-lived, whereas the effect in opioid prescribing was more pronounced and sustained at higher-dose trajectories of pregabalin.

Crucially, analysis using standardised daily doses shows that oral morphine equivalent dosing of prescription opioids increases after pregabalin initiations, and increased over time. This was statistically significant across all pregabalin trajectories, but led to particularly high absolute dosage increases in persistent users not on the lowest dose. A correlate phenomenon is not seen with diazepam equivalent doses of benzodiazepines.

This image has been excluded from the public version.
Reproduction rights were only sought for internal circulation, and have not been sought for public release.

Original image displayed was:
Figure 3, Schaffer et al. Pain 2021
Probability of any use of an opioid or benzodiazepine, and predicted geometric mean daily dose among people exposed to an opioid or benzodiazepine,
estimated by GLM model by month and pregabalin use trajectory. The estimated monthly dose is adjusted for the proportion of new opioid or benzodiazepine
users in each month. GLM, generalised linear model; OME mg, oral morphine equivalents in mg.
https://journals.lww.com/pain/pages/imagegallery.aspx?year=2022&issue=05000&article=00008

Figure 4.2.2.. Opioid (A and B) and benzodiazepine (C and D) use at the time of pregabalin initiation, by binary prescribing status (A and C) and standardised mean daily dose (B and D), stratified by trajectories of pregabalin use (replicated from Schaffer et al.(21)). Notably, while benzodiazepine prescribing does not undergo any substantive changes with pregabalin initiation apart from a brief increase in prescription concordant with initiation – and, importantly, no increase in standardised daily dose – opioid mean daily dose increases after pregabalin initiation in patients who are on persistent non-lowest doses of pregabalin.

These data would seem to indicate that pregabalin use, particularly in a persistent higher-dose trajectory, herald increasing utilisation of prescription opioids, a risk which would certainly add weight to pregabalin being included for monitoring on SafeScript.

Evidence from the non-Australian literature on harm related to gabapentinoids, new in the updated report

There has been substantial further progression, since the last edition of this report, in the understanding regarding the extent of misuse of gabapentinoids internationally. This relates to a greater appreciation about links with death (irrespective of whether causality can be demonstrated), potentially dangerous co-administration with opioids, and harms directly attributable to the toxidrome. In addition, misuse, abuse, and addiction continue to be described, while the opioid-sparing effect of gabapentinoids, while proposed, has not been demonstrated by robust evidence.

While causation remains uncertain, associations between gabapentinoid misuse and death have been increasingly observed, including in the United States, where analysis of Food and Drug Administration Adverse Events Reporting System (FAERS) pharmacovigilance data from the US from October 2012 to December 2016 for both gabapentin and pregabalin(22). This showed substantial and increasing numbers of abuse and misuse of these gabapentinoids, overdose as the second most common type of ADE report for both gabapentin and pregabalin, and 106 fatalities were reported among gabapentin abuse-related events, while 24 fatalities amongst pregabalin abuse-related events, although the authors were clear in indicating that the role of gabapentinoids in causality remains uncertain. Similarly, amongst those using illicit drugs, evidence of widespread misuse amongst heroin users on post-mortem assessment has been noted in the UK(23, 24). While causality cannot be certain in either of these data sets, these observations add further weight to the suggestion that gabapentinoids might act as a surrogate of high-risk opioid use in populations similar to Australia's.

Similar observations have been made elsewhere, extending from practices of co-prescribing as an emerging phenomenon. A recent review of new prescriptions of gabapentinoids being co-prescribed with opioids in the UK from 1993-2017 report this practice increasing in recent years, particularly in Ireland(25), and this concurrent use and prescribing of opioids with gabapentinoids has been associated with opioids-related deaths(26). Furthermore, a US retrospective case-control study by Minhaj et al.(27) also support the fact that use of gabapentinoids is a significant risk factor and predictor associated with inpatients developing serious opioid-related adverse drug events requiring the use of naloxone.

Dangerous co-prescribing with gabapentinoids and death has also been reported in a recent Scottish study where significant increase in both pregabalin and gabapentin prescriptions resulted in an increase in age-standardised death rate; of these, 60% were co-prescribed an opioid, benzodiazepine, or both(28). In another UK study in those being treated for opioid dependency using opioid agonist treatment, it was found that co-prescription with gabapentinoids was associated with an increased mortality risk, however the increased mortality risk was not specific to the drug-related poisonings as the study did not show a significant association between co-prescription of gabapentinoids to patients receiving opioid agonist treatment and increased risk of drug-related poisonings(29).

Similar conclusions regarding the risk of opioids and gabapentinoids were made in other recent Finnish studies. In a three-year study period from 2016 to 2018, it was reported that in most of the fatal gabapentinoid poisoning cases, opioids or other central nervous system depressants were additionally detected in relevant concentrations, thus reinforcing the previous findings that gabapentinoids are mostly implicated in fatal poisoning together with opioids(30). In another study, of all the cases of buprenorphine poisoning deaths from 2016-2019, concomitant gabapentinoids was found in 50% of the cases (pregabalin 41%)(31).

The known toxidrome profile of gabapentinoids by themselves, while often considered to be relatively benign compared to opioids, may lead to harm in itself such as road traffic incidents and violent crimes in a population-based cohort study from Sweden(32). However,

intentional misuse, abuse, and addiction remain of more clear concern, and also have been more clearly articulated since the last edition of the report, even if the causal contribution to any subsequent mortality remains somewhat unclear.

This concern regarding misuse and abuse extends across jurisdictions and settings, suggesting that it might be at least partially independent of societal context. Using the National Self-Harm Registry data examining intentional pregabalin and gabapentin drug overdose data from Ireland from 2007-2015, Daly et al.(33) reported gabapentinoids contributing to 2.9% of the intentional drug overdose cases reported. French data would also suggest that deaths have emerged from gabapentinoid abuse, in keeping with more widespread utilisation(34). Similarly, in a cross-sectional population study from Singapore, gabapentin (0.6% of respondents) was the 5th highest drug for past-year misuse, as well as 0.9% reporting a history of lifetime misuse(35).

Finally, some of the proposed benefits of gabapentinoids in this situation have yet to have their benefits clearly demonstrated – particularly regarding the concept that gabapentinoids might be used as an opioid-sparing agent. In a recent review of opioids and gabapentinoids utilisation and mortality-related trends across the four UK countries, an overall significant increasing trend in gabapentinoid utilization (205-207%) was reported, and despite the utilisation trends levelling off after 2016, this was not translated into comparable reduction in opioids and gabapentinoids-related mortality(36). Similarly, women receiving treatment with gabapentin for chronic pelvic pain in a multicentre randomised double-blind placebo-controlled trial did not result in significantly lower pain scores in these women with chronic pelvic pain(37).

Summary of peer-reviewed evidence surrounding gabapentinoids

The local evidence regarding gabapentinoids has more clearly articulated the relationship between gabapentinoids and high-risk opioid utilisation. To some extent, this had already been evident in the literature reviewed in the 2019 report: that there was a clear association, although culpability from such pharmacoepidemiological studies was dependent on context, and that opioids were more likely to be co-implicated in the most serious harm, death.

New data reviewed in this edition of the report show a strong presence of opioid utilisation amongst gabapentinoid-related deaths in a comprehensive capture of data, far more seen in other forms of harm, and have showed pregabalin predicting non-prescribed pharmaceutical opioid use amongst high-risk individuals such as people who inject drugs. Indeed, such patterns of high-risk are much of what SafeScript seeks to identify, irrespective of which medication is responsible for risk.

In a well-considered analysis of PBS data, high and persistent use of pregabalin is associated with escalations in prescription opioid use. Escalation in prescription opioid consumption is a high-risk clinical situation which often benefits from early intervention and clinicians would like to identify earlier; currently, this is hard to do, but pregabalin use may be extremely helpful in this.

Finally, gabapentinoid harm globally has been better recognised, particularly regarding misuse across a variety of different jurisdictions and settings, which would suggest that reports of misuse in Australia are more likely to be robust. Claims regarding the opioid-sparing nature of gabapentinoids have not been demonstrated in pharmacoepidemiological studies or randomized clinical trials, and the harm from gabapentinoids combined with opioids is clearer too.

All of this cumulatively adds further weight to a picture of harm contextually associated with gabapentinoids, even if it arises more clearly from other medications.

4.3 Tramadol

Background

Tramadol is a frequently utilised weak opioid analgesic with serotonergic effects. Its utilisation escalated rapidly globally in the early 2010s. It remains one of a limited number of Schedule 4 opioids, with codeine the other readily accessible Schedule 4 opioid.

In both the 2017 and 2019 editions of this report, it has been unclear whether tramadol was genuinely associated with low rates of harm, or whether during that period relatively easy access to medications with higher abuse potential, such as codeine, might mean that if it was not included on the RTPM that it might be vulnerable to the substitution effect, where high-risk opioid prescribing traditionally associated with other opioids might flow to it. It also remains possible that the qualities which are clinically inconvenient for tramadol as an analgesic, including its serotonergic effect, may make it less prone to harm stemming from misuse and abuse, and that excluding it from SafeScript has channeled high-risk opioid prescribing to it, with less harmful impacts. While this report only can draw on limited data from the period after SafeScript was instituted in Victoria, it can examine the context around either of these possible effects.

Key background from previous reports regarding tramadol

At the time of the first 2017 edition of the report, there were few data regarding risks associated with tramadol. In the subsequent edition in 2019, two reports showed relatively low fatal toxicity indices (deaths normalised for either prescriptions or oral morphine equivalent), although neither captured contemporaneous prescribing and use, having only covered data up until 2012. It has been noted that, while the period until 2013 encompassed escalating utilisation of tramadol, this stabilised in the period of time after 2013. At that time, it was therefore of lesser concern as to whether tramadol would lead to deaths following misuse or abuse.

In the US Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system Poison Center Program database, data from between 2010-2016 showed that deaths attributable to tramadol occurred over five times less frequently per prescription compared to those from oxycodone and morphine, and major medical effects, hospitalisations, and serious adverse events attributed to tramadol were substantially less as well(38). It should be noted that this system may not comprehensively capture such outcomes, and this remains merely indicative.

A large UK general practice data network was used to perform, in patients with osteoarthritis over the age of 50 years old, a sequential, propensity score-matched cohort study comparing mortality risk after tramadol to that of one of four non-steroidal anti-inflammatory drugs (NSAIDs) or codeine(39). In this, tramadol was associated with a statistically significant increase in death within the first year of prescribing compared to the NSAIDs but not to codeine, a result which held when stratified on the basis of exposure to previous opioids.

A serious concern from this study, relevant to the discussion in this updated edition of the report which includes many such pharmacoepidemiological studies, is that there might be residual confounding by indication, given the place in the therapeutic algorithm that tramadol occupies, and a reluctance to prescribe NSAIDs to frailer patients. This was supported by the demonstration of relationships in this study which have little plausible explanation, such as tramadol having a statistically significantly increased risk of cancer within the first year versus NSAIDs, from a hazard radio of 1.86 versus naproxen up to 2.93 versus celecoxib. Such residual confounding may influence statistically significant findings about tramadol in such studies, even despite rigorous propensity score matching.

Evidence from Australian literature on harm related to tramadol, new in the updated report

Compared to previous editions of the report, there has been an increasing focus on opioid-related harm attributable to specific pharmaceutical opioids in the overall class. This focus likely relates to a number of practically important reasons, including the largely commercial promotion of tapentadol as an opioid with differing mechanisms possibly relevant for toxicity, reflection on the impact of the addition of naloxone to oxycodone in relation to opioid-related adverse events, and a justified reflection on codeine's place in compound with simple analgesics such as paracetamol. It is notable that all other prescription opioids included in such assessments, including morphine, codeine, fentanyl, oxycodone, oxycodone-naloxone, and tapentadol, are all already on SafeScript.

Two papers are particularly relevant to the Victorian context, both from the same research group (Monash Addiction Research Centre/Turning Point), and are addressed in detail here. It should also be noted that during the period since the last edition of this report, a study has been published looking at opioid-related clinical incidents in Western Australian public hospitals. Tapentadol was the most frequently involved prescription opioid with 131 episodes, and tramadol was the least involved prescription opioid prescribed primarily for pain, with 54 episodes, but the nature of these episodes was varied and utilisation in that jurisdiction varies substantially from that in Victoria; as a consequence, it will not be further examined in this report.

'Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Victoria, Australia from 2013 to 2018' by Suzanne Nielsen et al. (*Addiction* 2020)

While ambulance attendance data primarily relates to service provision, and a noted limitation is always that outcomes following such attendances are variable in nature and severity, such data may capture important segments of opioid-related harm. In this respect, Nielsen et al. add an important dimension in assessing tramadol's relative risk, in looking the number and nature of ambulance attendances for the extramedical use of different opioids in Victoria for a nearly six-year period ending in September 2018(40).

This analysis was based on data from the National Ambulance Surveillance System, where dispatch details and other clinical data aggregated from routine care are coded for subsequent analysis. Such a system enables 'extramedical' (i.e. over-appropriate or inappropriate) use to be captured for individual opioid types, including multiple types of opioids. This assessment is made by the attending ambulance based on the history taken at that time, and physical evidence. It should be noted that this study was funded by an untied educational grant from Sequirus, the Australian manufacturer of tapentadol.

The first part of this study entailed normalising attendances, categorised by whether they were for an opioid by itself or for multiple opioids, by oral morphine equivalent (OME) dosing. While this analysis is designed to examine toxicity based on a given level of opioid effect, in reality weaker opioids are rarely dosed to the same level as more potent ones. Given this, such a correction is likely to suggest a greater burden of comorbidity-related impact on harm for weaker opioids, given the greater number of individuals required to achieve the same oral morphine equivalent, and therefore such an analysis might bias against weaker opioids.

Furthermore, to assess suitability for a prescription monitoring system, analyses should ideally make a correction per prescribing episode (2017 report, page 9-10). While this may be harder to determine from wholesaling data, given that no prescribing data is captured form this and that dosing is variable, a WHO defined daily dose (DDD) may be a better representation, although this remains imperfect for contemporary practice too. This was highlighted separately by the same authors, who performed a survey of 1101 Australians with

chronic non-cancer pain in community-based treatment settings during 2012-2013 in the POINT study(41). In this study, they assessed how many DDD constituted the median dose in an Australian sample, and this may be a more appropriate metric given much prescribing monitored by SafeScript will occur in similar patients.

In the published analysis, correction for OME led to codeine having by far the highest rate of corrected ambulance attendances, by a factor of over five times. Tramadol had a similar rate to both morphine and oxycodone. If the analysis was change to correct for DDD or median dose instead of OME instead (not included in the paper but calculated post-hoc here), which is potentially more relevant for SafeScript, tramadol demonstrated metrics which more clearly lay lower than oxycodone and within the lower end of the captured spectrum, but still remained similar to other opioids such as codeine and fentanyl (Table 4.3.1).

	Single opioid (/100,000mg OME)	Multiple opioid (/100,000mg OME)	Single opioid (/DDD)	Multiple opioid (/DDD)	Single opioid (median dose)	Multiple opioid (median dose)
codeine	0.273	0.040	2.73	0.40	2.73	0.40
fentanyl	0.019	0.004	2.14	0.45	2.14	0.45
morphine	0.050	0.011	5.00	1.10	3.00	0.66
oxycodone	0.113	0.003	12.71	0.34	31.78	0.84
oxycodone-naloxone	0.031	0.016	3.49	1.80	8.72	4.50
tapentadol	0.006	0.003	0.45	0.23	-	-
tramadol	0.045	0.015	2.70	0.90	4.05	1.35

Table 4.3.1. Ambulance attendances, normalised for wholesale data by oral morphine equivalent (OME), for different prescription opioids as described in Nielsen et al. Addiction 2020(40). For this report, this has also been expressed as normalised for defined daily dose (DDD). Using data from Nielsen et al. Pharmacopepi Drug Saf. 2017 (POINT study(41)), median doses from a national survey of chronic pain patients were used to normalise this to median doses from the same authors. Note that tapentadol was not captured in the POINT study, and therefore results normalised for median dose for tapentadol are not displayed.

In addition, any such analysis is an amalgam of the pharmacological properties themselves and the context in which the opioid is used, This difference was evidenced in oxycodone's mean supply-adjusted rate being over triple that of oxycodone-naloxone (0.113 vs 0.031 incidents/100,000mg OME), which may represent channeling of prescribing to overall more responsible practice, independent of the actual merit of a naloxone-containing compound. While these analyses may not precisely detail the risk from purely pharmacologically, such an amalgam nevertheless is a highly relevant consideration in determining whether a medicine should be monitored.

To better understand this context of prescribing, the authors performed logistic regression across a variety of different demographic and addiction-related clinical characteristics. Notably, for tramadol compared to morphine, non-opioid extramedical pharmaceutical use, comorbid suicidal thoughts, and past history of psychiatric issues all had statistically significant higher odds ratios, although oxycodone-naloxone and tapentadol demonstrated similar or more pronounced characteristics. It does suggest, however, that patients with similar clinical backgrounds are receiving ambulance attendances for extramedical use.

By the nature of the way the data are acquired, there is limited quantification of further harm from this study, with no follow-up data regarding outcomes. Nevertheless, some potentially indicative surrogates of this are noted, include the Glasgow Coma Scale (to measure conscious state on attendance) and transport to hospital. For all of these metrics, tramadol performed similarly to other opioids (Table 4.3.2). It should be noted that all of these outcomes are likely to be multifactorial but suggest that tramadol does not substantially

differentiate itself from other opioids as far as ambulance attendance rates or surrogate outcomes are concerned.

	GCS severe impairment (ref. non-responsive)	GCS moderate impairment (ref. non-responsive)	GCS minor-no impairment (ref. non-responsive)	Transport to hospital
morphine	ref	ref	ref	ref
codeine	2.66	2.81	4.53	2.63
fentanyl	0.83	0.56	0.19	0.50
oxycodone	1.41	1.84	2.06	1.20
oxycodone-naloxone	4.48	4.48	9.55	1.37
tapentadol	-	2.99	5.96	2.82
tramadol	2.46	3.67	3.96	1.42

Table 4.3.2. Odds ratios on multinomial logistic regression for Glasgow Coma Scale (GCS) score outcomes on ambulance attendance, and transport to hospital, in comparison to morphine. Given that a non-responsive state is the comparator, large odds ratios in the GCS columns (particularly in the minor-no impairment category) favour better outcomes in terms of conscious state, and smaller numbers in the transport to hospital column favour better outcomes in terms of subsequent need for hospital review.

In short, these data suggest that ambulance attendances for tramadol are not markedly distinguished from those for other prescription opioids, either based on number, background characteristics, or limited measures of harm such as conscious state or transportation to hospital. While these metrics largely capture service provision, and it is uncertain how these correlate to downstream measures of harm, they nevertheless represent resource consumption and an indication that tramadol may not differ in this respect.

'Pharmaceutical opioid poisonings in Victoria, Australia: rates and characteristics of a decade of Emergency Department presentations across nine pharmaceutical opioids' by Tina Lam et al. (*Addiction* 2021)

The same group of investigators therefore performed a further study addressing the next consequent point of harm: emergency department (ED) presentations(42). For this, they captured data from the Victorian Emergency Minimum Dataset, which captures data from all 38 public hospitals whose EDs are continuously open. Data from 2009-2019 was assessed, using coding to capture 'poisoning by narcotics and psychodysleptics' and then largely free text search to identify opioid type, an approach which may be imperfect but gives a reasonable representation of attributable harm. The protocol was published in advance of analysis. It should be noted that, similar to the previously described study, this study was funded by an untied educational grant from Seqirus, the Australian manufacturer of tapentadol.

While emergency department attendances also represent service utilisation, they are more closely related to morbidity and mortality, are subject to more detailed (and arguably more rigorous) documentation, and also consume substantial resources at a state government level.

In this paper, a corresponding analysis approach was taken to that of the ambulance attendance study, in that harm was adjusted for supply based on oral morphine equivalents, and then characteristics of presentations were captured using multinomial logistic regression. In this report, we have also applied the same analyses regarding DDD and median dose, with the same justification; this is shown in Table 4.3.3. Tramadol has similar numbers of ED presentations compared to many other prescription opioids, even after normalizing to median dose. Oxycodone and oxycodone-naloxone are associated with higher rates of ED presentations compared to other prescription opioids.

	ED presentations (/100,000mg OME)	ED presentations (/DDD)	ED presentations (/median dose)
codeine	0.076	0.760	0.760
fentanyl	0.003	0.338	0.338
morphine	0.010	1.000	0.600
oxycodone	0.029	3.263	8.156
oxycodone-naloxone	0.008	0.900	2.250
tapentadol	0.004	0.300	-
tramadol	0.015	0.900	1.350

Table 4.3.3. ED presentations by prescription opioid, normalised for wholesale data by oral morphine equivalent (OME), for different prescription opioids as described in Lam et al. Addiction 2021(42). For this report, this has also been expressed as normalised for defined daily dose (DDD) and median dose (based on the POINT study(41), described in Table 4.3.1).

Subsequently, the analysis examined characteristics of these ED presentations, including one subsequent outcome in terms of admission outcome (i.e. whether the episode led to an inpatient admission, or was an ED presentation only) (Table 4.3.4). This is of substantive importance as inpatient admissions not only imply substantially increased morbidity and mortality, but also cost of resource utilisation.

	ED presentation only without admission
morphine	ref
codeine	1.27
fentanyl	2.01
oxycodone	1.53
oxycodone-naloxone	1.74
tapentadol	1.22
tramadol	1.07

Table 4.3.4. Odds ratios on multinomial logistic regression for ED admissions, in comparison to morphine. Given that admission is the comparator, large odds ratios favour better outcomes in terms of ED presentations resulting in admission. It should be noted that this is relative to the number of ED presentations; for example, oxycodone-naloxone has a high odds ratio that ED presentations will not result in admission, but also a relatively high number of ED presentations.

It is notable that there were "fewer than five deaths" relating to opioid poisoning captured in this dataset. It is unclear whether this is an artefact of data collection (e.g. death was only documented during subsequent inpatient admissions) or represents low rates of mortality associated with these emergency department episodes. Finally, it should be noted that these data overwhelmingly precede the widespread use of SafeScript and are unlikely to reflect any impact from this; additionally, much of the data was from prior to the rescheduling of codeine.

These data therefore suggest that tramadol does not distinguish itself from other opioids, already monitored on SafeScript, when it comes to ambulance attendances for extramedical use, ED presentations pharmaceutical opioid poisoning, or subsequent hospital inpatient admission following such a presentation. This likely does reflect the context of ingestion and prescribing, although all of these are relevant to decisions regarding suitability for prescription monitoring. The subsequent impact on 'harder' metrics such as death should not be extrapolated from these data, especially as they are unlikely to be consistent between prescription opioids, but while such data would have only been indicative in previous editions of this report, this impact is worth consideration in terms of the harm that they directly bring.

Evidence from the non-Australian literature on harm related to tramadol, new in the updated report

The impact of tramadol, particularly in prescription opioid overdose and consequent harm, has been an increasing focus across multiple jurisdictions. The relevance of all of these studies is hard to determine for the Australian context, given large differences in regulation and prescribing contexts of opioids in these varied jurisdictions; these are often not analogous to the Australian context. In the interests of completeness, this edition of the report nevertheless summarises below all the reports captured in the search terms.

In a recent study using data from 2015-2020 from American Association of Poison Control Centers' National Poison Data System (NPDS), Choi et al.(43) reported high rates of opioid overdose and suicide among the 50+ age group. Multivariable analyses from the study also reported that amongst prescription opioid only cases, tramadol (Incidence Rate Ratio = 1.12, 95% CI = 1.06-1.47) was associated with higher risk of suspected suicides than intentional misuse/abuse without suicidal intent (i.e. unintentional poisoning), while morphine, buprenorphine, prescription fentanyl, hydromorphone, and codeine were associated with lower risk of suspected suicide compared to unintentional poisonings. Similarly, data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database also identified tramadol as the opioid with the 5th highest number (9% of total) of associated deaths (after oxycodone, hydrocodone, morphine and fentanyl), however it has a lower death-to-drug-count proportion compared to most other opioids(44).

In another recent study by Champagne-Langabeer et al.(45) looking at opioid overdose fatalities in Texas, USA, using 2013 to 2017 data, it was reported that tramadol was the second most prescribed opioid (after hydrocodone), however the prescribing rate of tramadol appears to be increasing. Furthermore, the authors also reported total overdose fatalities increased 42% during this time, however, specific data regarding tramadol and overdose fatalities was not presented. It should be noted that this study examined opioid prescribing behavior and overdose fatalities in one large state prior to state-mandated usage of a prescription drug monitoring program.

In a multicentre study from England examining intentional self-poisoning and fatality data from 2005 to 2012, it was reported that case fatality index for tramadol (OR 4.05, 95% CI 3.38-4.85) was significantly higher than for paracetamol(46). The study also reported the total death rate of tramadol as 0.095 per 100,000 population, and a self-poisoning rate of 14.4 per 100,000 population. While this study found that tramadol was more harmful in self-poisoning compared to many other prescription medications, the only opioid analgesic examined in this study that is marketed in Australia was codeine.

Using 2007-2014 data from Ireland's National Self-Harm Registry, and the National Drug-Related Deaths Index, for tramadol, Daly et al.(47) reported an overall incidence rate of 4.93 per 100,000 for intentional drug overdose; with 0.09 per 100,000 for fatal intentional drug overdose; and an associated case-fatality risk of 1.8%. This, however, represented a substantially lesser case-fatality risk than attributed to either oxycodone or morphine, both of which had rates over five times that of tramadol.

A number of descriptive studies across international jurisdictions have looked at tramadol-related poisonings in the context of other related opioids. In a US study comparing tramadol with hydrocodone, codeine and oxycodone in adolescents, it was found that the incidence of opioid-related adverse events per 10 000 person-years of opioid exposure was highest for tramadol, with hazard ratios for tramadol in comparison with hydrocodone for all and serious events being 2.98 and 2.94 respectively(48). In a study of severe opioid-related poisonings and fatalities in France, Caré et al.(49) reported that tramadol contributed to 43% of opioid-related poisonings that required medical management, and 24% of the overall fatalities. Poly drug use

deaths involving tramadol as well as acute poisonings by tramadol have also been reported in a number of other recent studies internationally(50-52). In the study by Eizadi-Mood et al.(51), although the kind of opioids (tramadol, opium or methadone) was not a predictive factor in the outcome of the patients with acute poisoning, it was reported that tramadol was the second most common studied opioid involved in poisoning (after methadone), and that the rate of suicide was higher in the tramadol group. A systematic review by Rostam-Abadi et al.(53) have further reported significant issues in Iran with tramadol abuse, dependence, poisonings, seizures and tramadol-related deaths in recent years. Finally, Alrashdi et al.(54) conducted a recent systematic review of case studies and case series specifically looking at tramadol-associated deaths, noting that many of these were unintentional.

It is possible that, in many of these jurisdictions, tramadol is more readily available than other more heavily-regulated prescription opioids (such as morphine and oxycodone) and consequently the patterns of usage and harm vary. Most of these studies are unable to contextualise these rates of harm in the context of utilisation, including patient population and clinical context.

In addition to this, questions have been raised as to whether tramadol, given its non-opioid pharmacologic effects, might plausibly confer risks to patients not typically immediately associated with opioids. It should be noted that, given tramadol's place in the therapeutic algorithm in many regions, including North America, such analyses are highly susceptible to residual confounding by indication (2019 report, page 24).

To this end, two recent UK studies examined effects of tramadol on cardiovascular risk. A population-based study by Wei et al.(55) in osteoarthritis patients reported the six-month risk of myocardial infarction was higher among tramadol initiators than that of naproxen, but was comparable to those of diclofenac or codeine. However, the effect was only relatively modest (Rate Difference = 1.9/1000 person-years), present in the short-term, and may be a consequence of channelling of patients with pre-existing cardiovascular risk away from non-steroidal anti-inflammatory drugs, given their known cardiovascular risk, as discussed in the 2019 report regarding Zeng et al(39). Additionally, another retrospective population-based cohort study found that short-term use of tramadol, compared with codeine, was not associated with an increased risk of cardiac events (myocardial infarction, unstable angina, ischaemic stroke, coronary revascularization, cardiovascular deaths and all-cause mortality) among patients with non-cancer pain(56).

The same phenomenon may extend more broadly to other outcomes in pharmacoepidemiological studies regarding tramadol. The association comparing tramadol and codeine with adverse clinical outcomes was also investigated in another recent population-based cohort study in Spain by Xie et al.(57) where it was reported tramadol was significantly associated with a higher risk of subsequent all-cause mortality, cardiovascular events, and fractures, when compared with codeine. The analyses were corrected with propensity score matching, which was robust across sensitivity analyses, and the possibility has to be entertained that a real effect exists, although its mechanism remains uncertain and contrary results have been previously found in similarly large data from the United States(58). Similarly contrasting data was seen in Korean populations, where a study by Yoo et al.(59) found that current use and past use of opioid (including tramadol) did not increase all-cause mortality after hip fracture in elderly patients over 65 years of age, whereas another Korean population-based case-crossover study found that tramadol use was associated with an increased mortality risk (aOR 1.77, 95% CI 1.67-1.87) in the adult population, noting that age, parenteral administration of tramadol, and cardiovascular, renal and hepatic disease were prominent risk factors(60).

Summary of peer-reviewed evidence surrounding tramadol

Real-world data comparing different prescription opioids are potentially helpful, with provisos. Ambulance data may represent health utilisation and multiple factors, but episodes which are assessed as involving extramedical use do capture harm in a more broad-based manner than more serious forms of harm. When these data are corrected for estimated numbers of doses used by the community, as appropriate for this report's analysis, rather than oral morphine equivalents, tramadol does not distinguish itself from other prescription opioids in either a positive or negative light. This reflects the context in which it is used, but suggests that that context is not dissimilar to other opioids in how frequently it necessitates ambulance callout. Notably, as well, more serious harm in the form of altered conscious state and transport to hospital were not more or less likely with tramadol compared to other harms, and further analysis suggested that emergency department presentations and subsequent admission were similar as well.

While these data could be affected by a number of different factors, may have been affected by residual confounding, and the sponsorship of this study by one of the manufacturers of one of the studied agents commercially distinguishing itself on safety should be noted, the fact that tramadol was unable to distinguish itself from other opioids is of note. To what extent this might be a product of restrictions such as scheduling is unclear, but data from this time largely preserved analogous scheduling settings to present, and largely preceded real-time prescription monitoring at all.

The relevance of many large pharmacoepidemiological studies, however, is less clear. As noted in the 2019 edition of this report, such data appear affected by residual confounding by indication, with implausible associations noted (such as an increased cancer risk in the first twelve months). This also applies to conclusions that might be made about implications of tramadol beyond classical opioid-related effects; while data regarding cardiovascular risk are appropriately analysed, it is still possible for confounding to remain.

Variations in context internationally also limit their applicability. While tramadol may have a case-fatality risk five times less than oxycodone or morphine in Ireland, such outcomes are an amalgam of pharmacological properties and clinical context, the latter of which varies between countries. Nevertheless, it should be noted that tramadol is frequently observed in intentional poisonings internationally, with all the caveats that varied regulation profiles might carry, and such poisoning reports have varying mortality associated with it.

In short, it is hard to make definitive conclusions about tramadol, but it would appear that the peer-reviewed literature finds it hard to distinguish tramadol from other prescription opioids. Given that context is critical, Australian data should be given greater weight, but these data, with analogous regulations and restrictions to the current time in Victoria, fail to distinguish tramadol from other opioids at every step between ambulance attendances for extramedical use to hospital admission following opioid-related poisoning.

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

5.1 Utilisation of medications to be examined in local data regarding harm

Given that metrics of harm need to be contextualised by use, this report first details changes in usage over the time which has elapsed since data from the last edition of the report (and therefore represents the usage to which subsequent metrics are normalised).

While not all data are always readily available, metrics have been estimated by using the methods established in Chapter 3.2, and full details of usage during this period are published in Appendix 2, including under co-payment calculations.

As in previous reports, overall utilisation of medications for Victoria is estimated on the basis of service reports accessible via PBS Item Reports on Medicare Statistics Online (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp) and the annual PBS under-co-payment report. It should be noted, from previous editions of the report and as noted in the peer-reviewed literature reviewed, that private scripts have minimal contribution to use of either pregabalin or tramadol, and many of the complications most relevant to estimates of codeine, which were published in previous editions of this report, are not relevant to the medications examined in this edition.

As articulated in Chapter 3.2 and in previous reports, prescription usage, rather than oral morphine equivalent or other standardised pharmacological measures, is considered to be the appropriate denominator given that this correlates with the burden of SafeScript.

Estimated overall utilisation by prescription usage is shown in Figure 5.1.1. Notably, since the last report, pregabalin utilisation has plateaued in keeping with maturity of use given current restrictions, and tramadol use has declined, likely due to increased attention and regulatory changes to opioid prescribing.

Usage of combinations of medications

On the basis of concerning trends from the peer-reviewed literature (detailed in Chapters 4.1), we have interrogated the combination of gabapentinoids and opioids, given the potential for synergistic harm, or the possible use of pregabalin as a surrogate marker which might flag high-risk opioid use. Such analysis was performed for both prescription medication-related deaths and poisoning calls, and compared to a relevant Schedule 4 medication comparator, selected on the basis similarity of context of use. The approach to analysis of combination data is more clearly outlined in Chapter 3.3, and selection of the comparator is outlined in the relevant sections of this chapter.

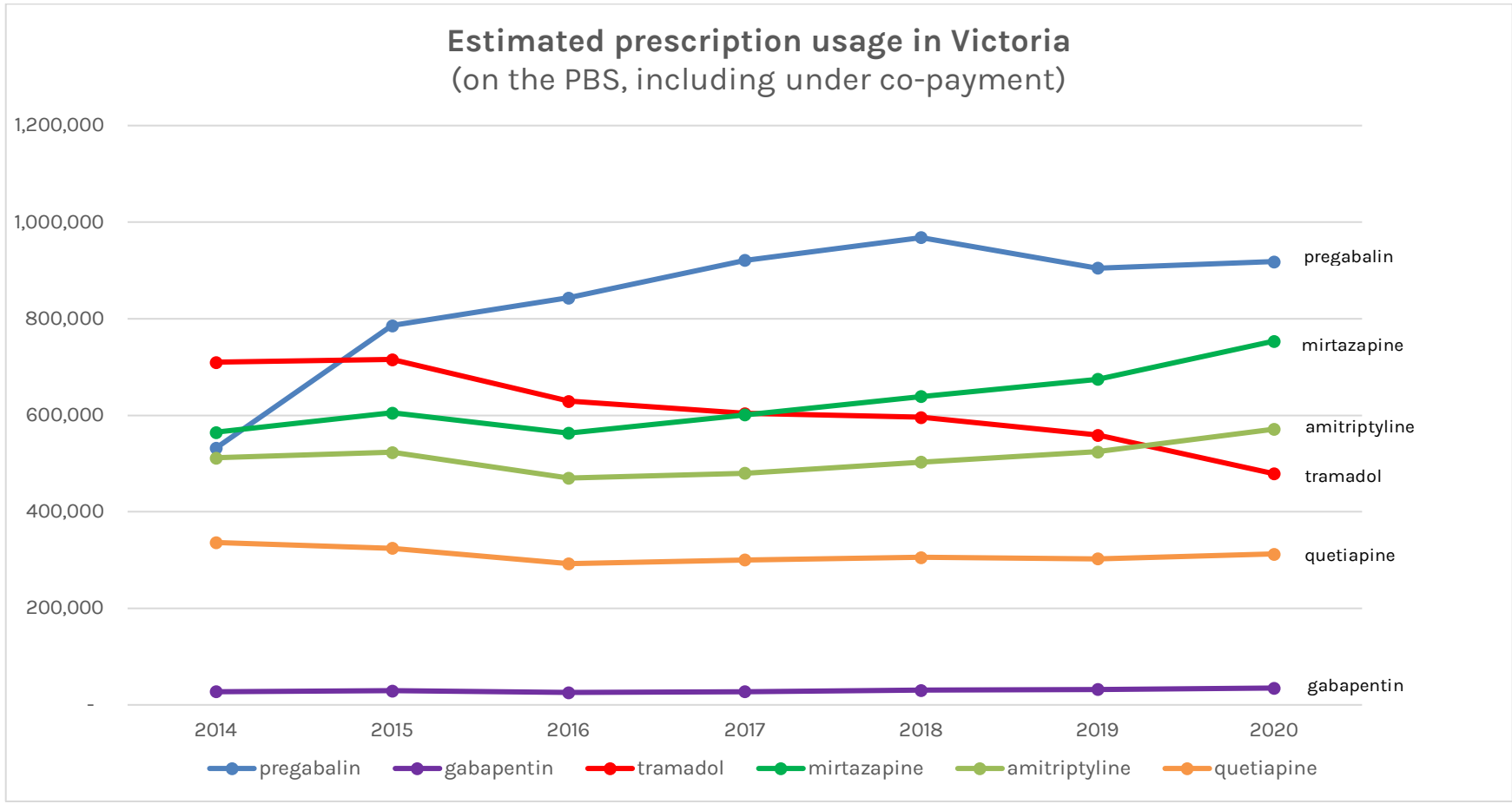

Figure 5.1.1. Estimated prescription usage (prescriptions/year) in Victoria (on the PBS, including under co-payment) of gabapentinoids and tramadol, and comparator Schedule 4 prescription drugs as utilized in Chapter 5.2. Estimations made based on PBS Online Statistics data and annual 'Report on the Collection of Under Co-payment Data' data.

5.2 Victorian Overdose Deaths Register (managed by the Coroners Prevention Unit, Coroners Court of Victoria)

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 (VODR) 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, although a consequent limitation is the inclusion of open cases, which disproportionately affects more recent data.

The authors gratefully acknowledge the generous contribution of Dr Jeremy Dwyer in this matter. This data source remains a resource unparalleled in Australia and data from it has been provided in the public interest. Most of the data has been compiled in a CCoV report(61).

It should be noted, however, that Dr Dwyer was not party to analysis or commentary in this report. It therefore should not be considered that this report or its recommendations are endorsed in any way by Dr Dwyer, the CPU, the CCoV, or any other of his affiliated organisations.

The authors also emphasise that the academic ownership of these data remains with the custodians of the data, and that the presence of these data in this report should not prejudice subsequent peer-reviewed publication by these custodians.

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 by applying the principles articulated in a consensus panel convened by the Substance Abuse and Mental Health Services Administration (SAMHSA)(62), 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(63) and in a report authored by Dwyer et al., co-written with Turning Point(64).

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 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.

These factors should be considered in the interpretation of these data but notably, compared to previous editions of this report, for the purposes of this report, causality is less important. As we have outlined previously, this report differs in that (a) causing harm outside of death may be sufficient for inclusion on SafeScript (b) given the maturity of use of the system, inclusion could be considered if a medication's presence is appropriate to flag review.

Deaths attributable to individual medications

Deaths over the last four complete calendar years have been collected in terms of attribution to individual medications. In order to understand the deaths attributable to individual medications in the context of their volume of use, normalised indices (fatal toxicity index: deaths per million prescriptions) were examined over the most recent period. The methodology for determining total prescriptions in Victoria are detailed in Chapter 3.2 and 5.1, and are displayed in full in Appendix 2.

For this analysis, apart from gabapentinoids and tramadol, other Schedule 4 medications were selected for comparison. Schedule 8 medications were not considered as candidate comparators given they are subject to different regulation which makes them difficult to compare to Schedule 4 medications such as pregabalin and tramadol. We also sought to consider, in the context of confounding by indication, medications which are often used in the same context, either in therapeutic use or in misuse, abuse, or misadventure. Given this, we included:

- quetiapine, as a medication already included in SafeScript, and frequently co-located in opioid-related misadventure;
- mirtazapine and amitriptyline, as medications not included on SafeScript and which have not been recently proposed to be considered for inclusion on SafeScript, but who had relatively high normalised death rates in the analysis included in the 2019 edition of the report.

These medications are presented alongside pregabalin and tramadol for the period 2015-2020 inclusive in Table 5.2.1 and Figure 5.2..1.

As in previous editions, this report urges caution in interpreting fatal toxicity indices for medications with relatively low numbers of attributable deaths, given that small fluctuations in absolute numbers of death can dramatically influence normalised indices and therefore have a wide margin of error. For this reason, cases attributed to gabapentin have not been listed in this edition of the report, although as previously it should be considered interchangeably with pregabalin, but even for the medications listed, caution should be taken in over-interpreting fluctuations from year-to-year.

These data nevertheless help to illustrate some trends evident in these updated data:

- Stabilised normalised indices of harm associated with pregabalin at a low-moderate level, substantially less than that for the SafeScript-included quetiapine and similar to that of mirtazapine and amitriptyline,
- low normalised indices of harm associated with tramadol overall, which remain stable over the study period, demonstrating that no net effect was seen in terms of a substitution effect of use of high-risk opioid use flowing from monitored medications to tramadol and leading to increased mortality associated with tramadol.

On overall normalised death rates alone, pregabalin and tramadol do not distinguish themselves from mirtazapine and amitriptyline, and sit substantially below quetiapine. Nevertheless, it is plausible that there are specific use cases where monitoring of pregabalin can provide important information to prescribers and dispensing pharmacists – particularly, as previously articulated:

- with combination toxicity with prescription opioids, and
- as a surrogate measure to flag high-risk opioid use.

Given these trends, and the observations from the peer-reviewed literature, further analyses were performed to examine this possibility.

	total deaths attributable (absolute number)						fatal toxicity index (per million prescriptions)					
	2015	*2016*	*2017*	*2018*	*2019*	*2020*	*2015*	*2016*	*2017*	*2018*	*2019*	*2020*
pregabalin	34	34	52	69	66	69	43.3	40.3	56.5	71.3	72.9	75.2
tramadol	32	26	32	35	37	28	44.7	41.3	53.0	58.8	66.2	58.5
quetiapine	49	57	74	53	50	53	150.9	194.8	246.4	173.5	165.3	169.5
mirtazapine	50	25	42	59	45	54	81.0	101.3	123.2	83.0	74.1	70.3
amitriptyline	28	34	47	40	41	32	95.5	53.2	87.6	117.4	85.9	94.6

Table 5.2.1. Deaths attributable to individual medications in Victoria as captured by the CCoV CPU VODR across medications selected for local data analysis, and normalised index of harm (fatal toxicity index: deaths per million prescriptions), 2015-2020 inclusive. Quetiapine, mirtazapine, and amitriptyline, shaded in light grey, represents Schedule 4 medication comparators to contextualise indices of harm. These were selected on indices from the last edition of the report, indicating SafeScript-included medications (quetiapine) and not included in SafeScript with upper-end metrics (mirtazapine, amitriptyline).

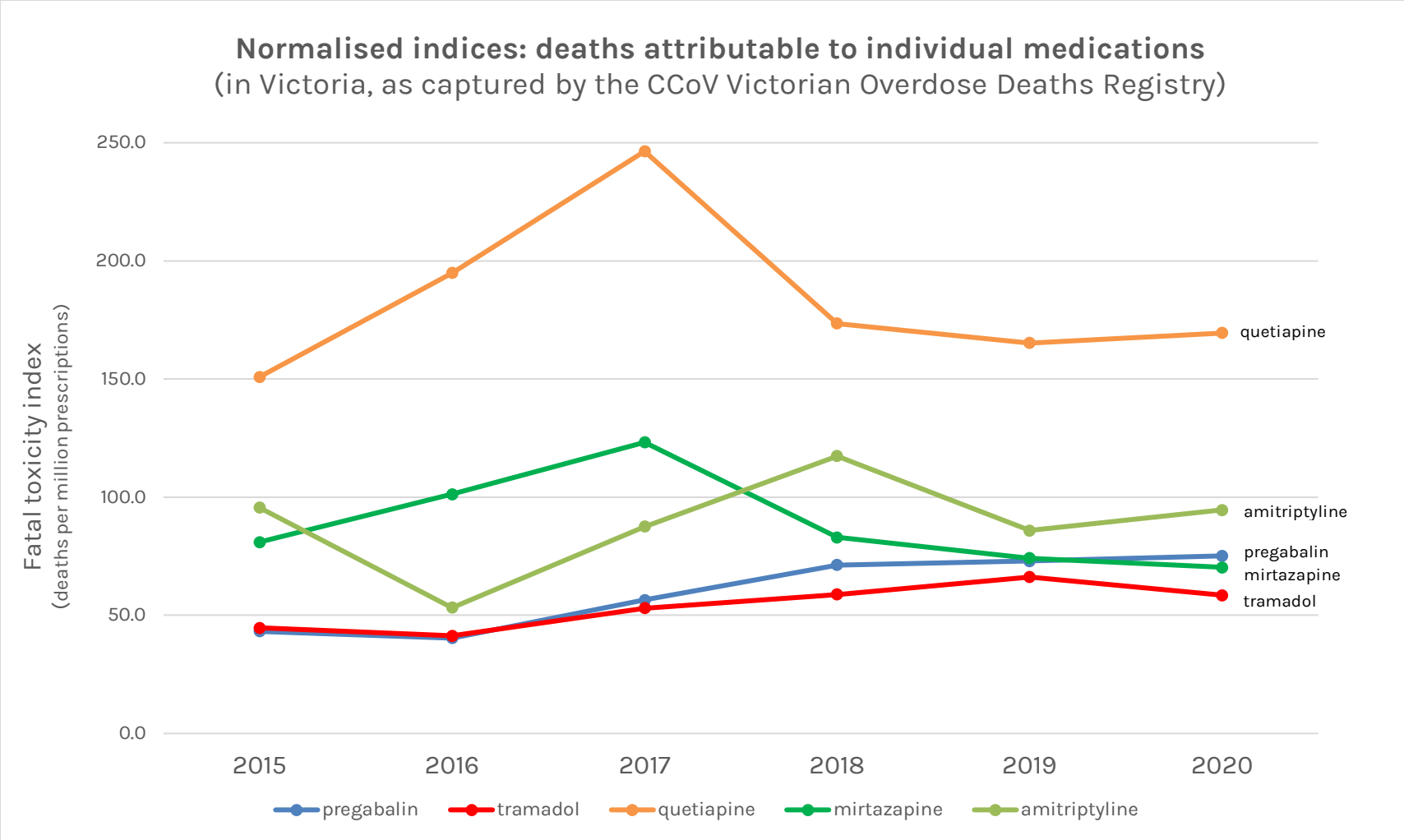

Figure 5.2.1. Normalised indices of harm (fatal toxicity index: deaths per million prescriptions) for deaths attributable to individual medications in Victoria by calendar years 2015-2020 inclusive, as captured by the CCoV CPU VODR for pregabalin and tramadol, compared to selected Schedule 4 medication comparators.

Proportion of pregabalin-attributed deaths where pharmaceutical opioids were also culpable

Given concerning peer-reviewed reports alluding to disproportionate harm being derived from subsets of use, further analysis regarding combination therapy was performed for pregabalin with pharmaceutical opioids. Quetiapine was selected as a comparator for the reasons previously articulated.

Given the potential for drug-drug interactions and also pregabalin as a surrogate marker of high-risk use, the combination of pregabalin and pharmaceutical opioids was of particular interest. The number of deaths is recorded in Table 5.2.2 and Figure 5.2.2. In terms of unadjusted numbers of deaths, it is clear that a large proportion of pregabalin-attributable deaths have involvement from pharmaceutical opioids. These data mirror those examined in Chapter 4.4. of the 2019 report, and other reports from the peer-reviewed literature(65).

A	*2015*	*2016*	*2017*	*2018*	*2019*	*2020*	Represented in diagram by
pregabalin without pharmaceutical opioids	10	8	8	17	13	13	b_h
pregabalin and pharmaceutical opioids	24	26	44	52	53	56	c_h
pharmaceutical opioids without pregabalin	161	157	154	155	154	134	a_h
pregabalin total	34	34	52	69	66	69	$b_h + c_h$
pharmaceutical opioid total	185	183	198	207	207	190	$a_h + c_h$
Proportion of pregabalin-attributable deaths with co-attribution to pharm. opioids	70.6%	76.5%	84.6%	75.4%	80.3%	81.2%	$\frac{c_h}{b_h + c_h}$

B	*2015*	*2016*	*2017*	*2018*	*2019*	*2020*	Represented in diagram by
quetiapine without pharmaceutical opioids	24	23	35	25	17	28	b_h
quetiapine and pharmaceutical opioids	25	34	39	28	33	25	c_h
pharmaceutical opioids without quetiapine	160	149	159	179	174	165	a_h
quetiapine total	49	57	74	53	50	53	$b_h + c_h$
pharmaceutical opioid total	185	183	198	207	207	190	$a_h + c_h$
Proportion of quetiapine-attributable deaths with co-attribution to pharm. opioids	51.0%	59.6%	52.7%	52.8%	66.0%	47.2%	$\frac{c_h}{b_h + c_h}$

Table 5.2.2. Deaths attributable to combinations of (A) pregabalin and pharmaceutical opioids during the period examined, and (B) a corresponding analysis for quetiapine. Data from the CCoV CPU VODR, specific to Victoria.

Notably, opioids are far more frequently co-attributed in pregabalin-related death than quetiapine is, despite both having the possibility of being an 'innocent bystander' in terms of culpability. Furthermore, as seen in Figure 5.2.3, pregabalin is considered co-attributable in a progressively increasing number of opioid-related deaths, whereas this has not been seen for quetiapine in data seen since the last edition of the report.

Culpability may not necessarily be inferred from such data, although this does seem probable, but an emerging and increasing trend of concern regarding deaths in patients receiving both pregabalin and prescription opioids appears clear from these data. Given the current question

of this report, if pregabalin represents an 'innocent bystander', it certainly is one whose presence is, relatively speaking, a harbinger of increased risk of death, and such a presence would be one worth noting.

Limitations on this interpretation should be considered as above. It is notable that, while overall utilisation and overall mortality as a consequence of pregabalin is stable, there is a trend of escalation which potentially indicates changes in utilisation and harm in this subpopulation of patients, and may lead to higher metrics in the future.

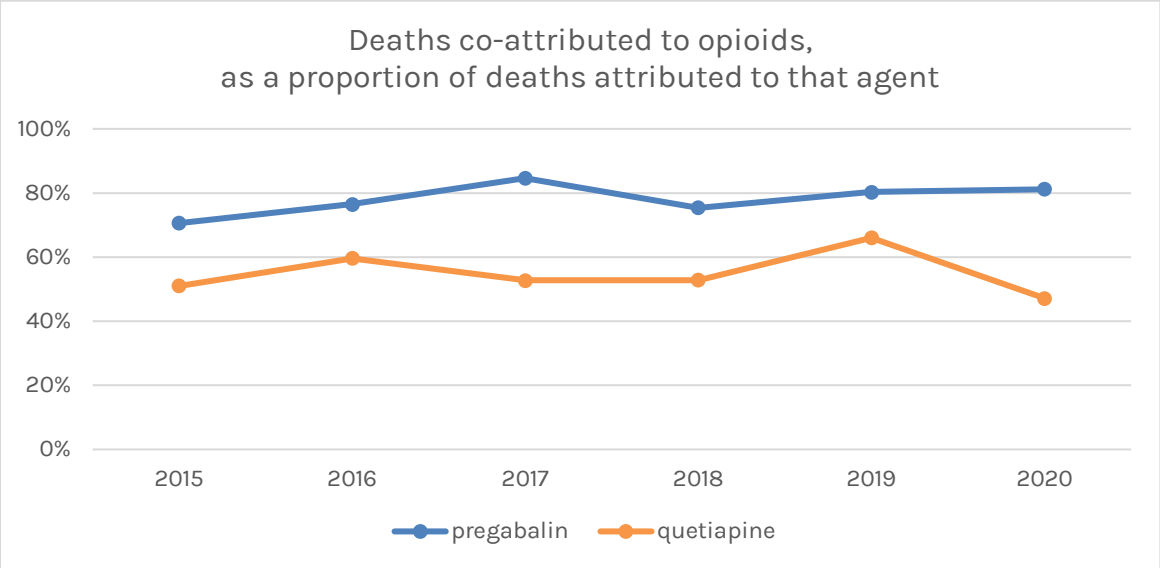

Figure 5.2.2. A comparison of the role of opioid co-attribution in pregabalin-related deaths and quetiapine-related deaths, 2015-2020 in Victoria (from CCoV VODR).

	2015	*2016*	*2017*	*2018*	*2019*	*2020*
pregabalin	13.0%	14.2%	22.2%	25.1%	25.6%	29.5%
quetiapine	13.5%	18.6%	19.7%	13.5%	15.9%	13.2%

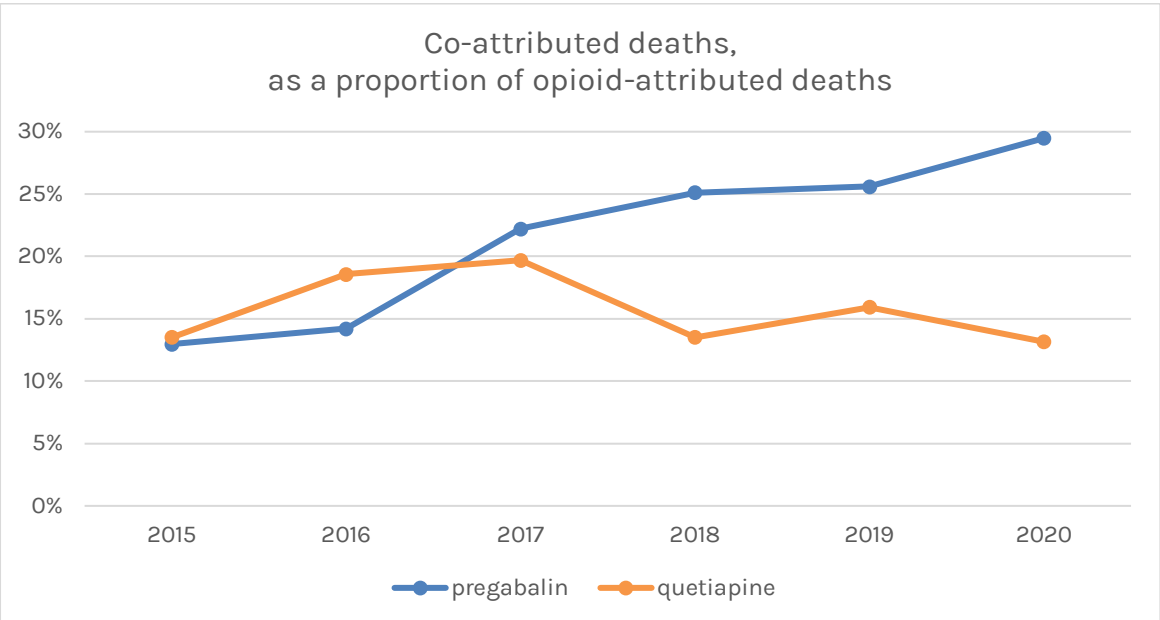

Figure 5.2.3. Co-attribution of prescription opioid-related deaths to pregabalin and quetiapine, 2015-2020 in Victoria (from CCoV VODR).

5.3 Victorian Poisons Information Centre

The Victorian Poisons Information Centre (VPIC) receives telephone calls with queries about poison exposures, animal/insect stings/bites and overdoses both intentional and unintentional in nature. 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 to 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. Interpretation of these data is limited by their self-reported nature, often from patients themselves. It should also be noted that VPIC fields calls overnight from the catchments of other Australian poisons information centres on a rotational basis for logistical reasons (for approximately 7.5 hours/week for all of Australia), and in this way Victorian calls are rotationally fielded by other poisons information centres (for approximately 67 hours/week). 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 (average one in 5.6 nights) roughly approximates the proportion of burden conferred by the VPIC catchment.

Provision of VPIC data

Relevant raw data has been graciously made available by A/Prof Rohan Elliott and Alice Norvill on behalf of VPIC for the purposes of this report, in the public interest. It should be noted, however, that VPIC itself was not party to analysis or commentary in this report. It therefore should not be considered that this report or its recommendations are endorsed in any way by VPIC or its affiliated organisations.

The authors also emphasise that the academic ownership of these data remains with the custodians of the data, and that the presence of these data in this report should not prejudice subsequent peer-reviewed publication by these custodians.

Relevance of VPIC data to this report

The main utility of the VPIC data for this report is to detect trends in drug related exposures within the Victorian population, and while it cannot show hard endpoints of death or hospitalization, it might detect emerging trends of harm earlier than metrics of overdose death might.

New medications may be subject to a form of reporting bias known as ‘notoriety bias’, where reporters are alert to new medications and thus are more likely to report adverse outcomes (or similarly, to be unaware of risks and therefore seek help). Reassuringly, all medications analysed in this report over the period examined were well known.

Note that, given that the importance of a phone call to this report is the potential toxicity rather than the call itself, all numbers represent an individual patient, and thus follow-up calls were excluded from the analysis. Calls where there was no known/suspect exposure (i.e. queries) were excluded, as were recalls about previous exposures.

Data prior to 2016 or earlier can be obtained from the Initial Report.

Progression of pharmaceutical-drug related PIC calls for gabapentinoids and tramadol

For this comparison, given the nature of poisonings (and, in particular, intentional poisonings) we thought it inappropriate to use mirtazapine and amitriptyline as comparator Schedule 4 medications. As a result, for the VPIC analysis we have used the highest-ranking medications from the last edition which were not anti-depressants, olanzapine and risperidone. We have retained quetiapine as the primary comparator, given its similar context of co-prescribing and co-administering use to pregabalin, particularly in the context of opioids. While no comparator from such observational data can make a perfect comparison, particularly given that these data are not corrected for demographic features, they nevertheless serve their primary purpose: being representative of use in the Victorian context.

Data regarding PIC calls for medications selected for analysis of local data are displayed in Figures 5.3.1. It should be noted that data from 2021 are estimates, with VPIC calls recorded until December 6, 2021, and utilisation statistics extrapolated from the first six months of 2021.

Notably, during the period 2017-2021, there is very little change in overall numbers of calls attributable to individual medications. Quetiapine demonstrates a normalised rate of poisoining calls almost always double that of risperidone, and while most calls for risperidone are not intentional, most calls for quetiapine are. Pregabalin and tramadol, in absolute terms, demonstrate low metrics of harm with respect to poisoning calls. Gabapentin correlates with higher metrics of harm with respect to poisoning calls, although a substantial proportion of these are not intentional.

Co-ingestion of pregabalin with prescription opioids

Considering the peer-reviewed descriptions of the concerning combination of prescription opioids and gabapentinoids, we have additionally performed an analysis of pregabalin co-ingestion interacting with opioid co-ingestion, corresponding to the analysis presented in Chapter 5.2 regarding Victorian Overdose Death Registry data and displayed in Figure 5.3.2. As for the comparison in Chapter 5.2, we have made a comparison to quetiapine, given its position as a Schedule 4 medication often found in a similar high-risk context.

In contrast to the analysis seen in Chapter 5.2, over the period 2017-2020 pregabalin's contribution to opioid-associated poisoning calls was static (Figure 5.3.2, frames A and C), in contrast to the climbing contribution of quetiapine. It is notable that this differing picture of co-contribution to opioid-related harm is reversed for the most serious harm, in the form of prescription medication-related death. This lack of concordance is in keeping with the trends seen in the peer-reviewed literature, as illustrated in Table 4.2.1, and suggests that opioid-gabapentinoid co-administration and poisoning occur at lower rates to death. This trend is of substantial importance to the aims of this report, and is explored further in Chapter 5.4.

Similarly, the presence of prescription opioids in poisoning calls regarding gabapentinoids had previously been elevated compared to quetiapine, but dropped over the course of this study period, and was similar in 2019-2021 (Figure 5.3.2, frames B and D). This is once again disconcordant with findings from Chapter 5.2, and suggests that any interaction between gabapentinoids and prescription opioids may not necessarily apply across all metrics of harm.

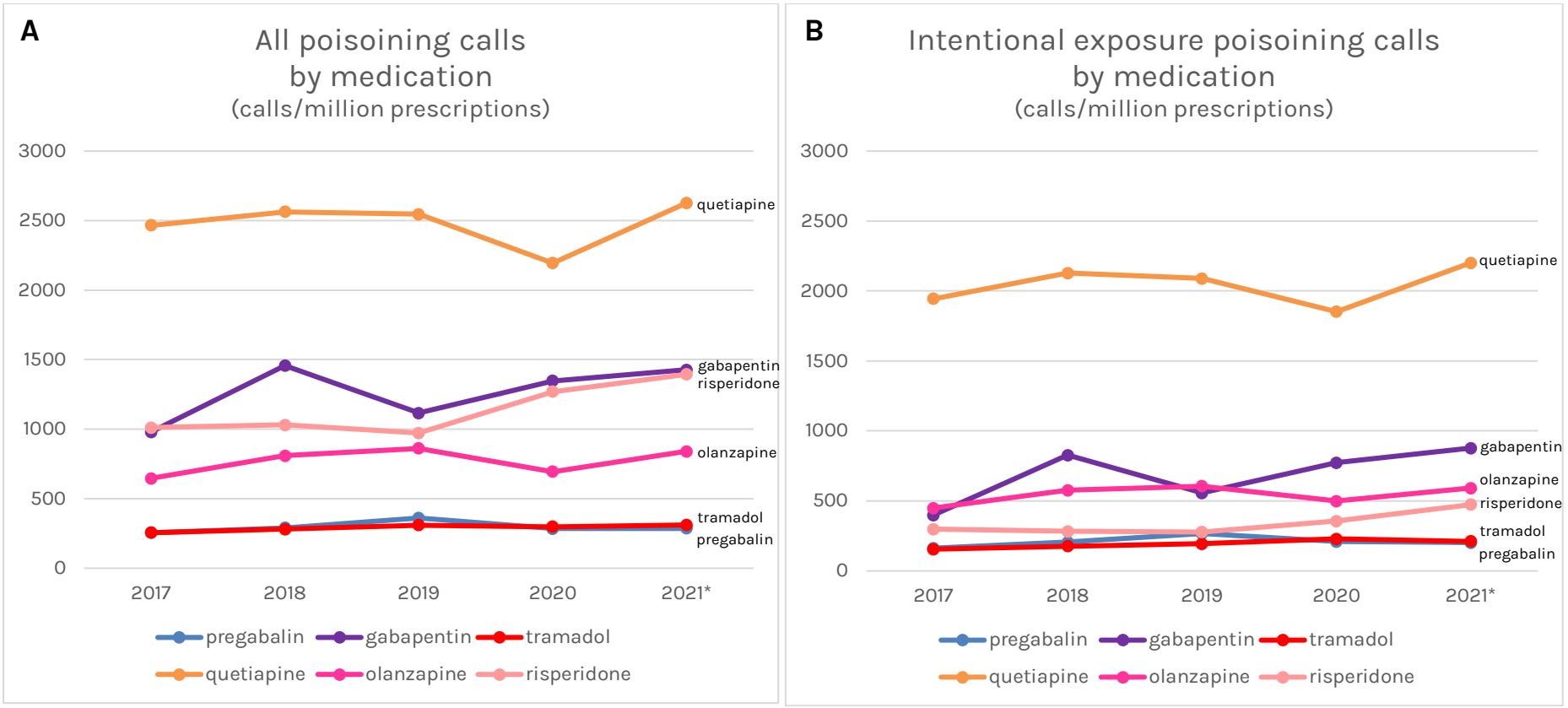

Figure 5.3.1. Calls to VPIC between 2017-2020, expressed relative to estimated Victorian usage as an incident toxicity index (calls per million prescriptions), for gabapentinoids, tramadol, and selected comparator Schedule 4 medications. Figures show (A) all calls received (B) intentional exposure (includes deliberate self-poisoning, intentional misuse, intentional recreational use, intentional other). Note that 2021 is extrapolated based on VPIC data to 6/12/2021 and utilisation data from 1/2021-6/2021 inclusive, extrapolated to an annual figure.

Figure 5.3.2. Co-ingestions involving gabapentinoids and opioids, with quetiapine as a comparator, looking at all exposures (A and B) and intentional exposures only (C and D). When looking at poisoning calls involving opioids, gabapentinoids have not been more commonly co-ingested over time, whereas quetiapine has (A and C). Opioids have become less frequently co-ingested when gabapentinoids are involved, in contrast to no change when quetiapine is involved (B and D).

5.4 Comparison of opioid-related death and poisoning data

It is reasonable to assume that a spectrum of harm occurs in a cascading manner, as we have previously described (2017 report, p6; 2019 report, p6). In this, we might see trends of poisonings earlier, and subsequently this might advance to harm at the most serious end, such as deaths, later.

In considering whether pregabalin might be associated with high-risk prescription opioid use (either in a culpable manner, or as a surrogate which might flag high-risk use) in a way that disproportionately biases towards more serious harm, we sought to see whether pregabalin was disproportionately represented in prescription opioid-related deaths compared to prescription opioid-related poisonings. A similar disparity has been illustrated in Table 4.1.1.

In order to illustrate that in a single analysis, we compared how often pregabalin was culpable in opioid-related deaths to how often pregabalin was co-ingested in opioid-related poisonings. We have represented this as a ratio:

$$HR(deaths{:}\,poisoinings) = \frac{proportion_{pregab\ in\ opioid\ deaths}}{proportion_{pregab\ in\ opioid\ poisoinings}} = \frac{deaths_{pregab+opioids}/deaths_{all\ opioids}}{poisonings_{pregab+opioids}/poisonings_{all\ opioids}}$$

With this ratio:

- one represents the point at which pregabalin contributes equally to both opioid-related deaths and poisonings,
- numbers more than one mean that pregabalin contributes to opioid-related deaths more than opioid-related poisonings (i.e. harm is more impactful),
- numbers less than one mean that pregabalin contributes to opioid-related deaths less than opioid-related poisonings (i.e. harm is less impactful).

We performed a similar analysis on the similar-context comparator Schedule 4 medication we have used, quetiapine. Results of this analysis are displayed as below (Figure 5.4.1).

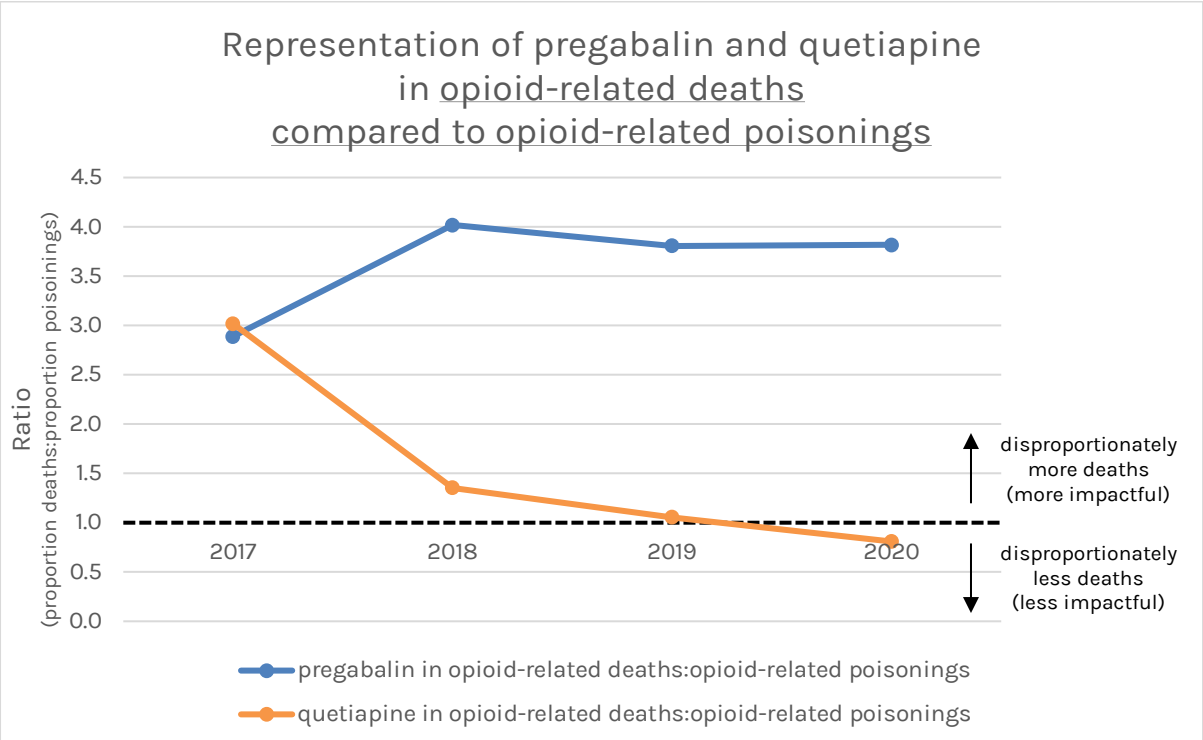

Figure 5.4.1. Representation of both pregabalin and quetiapine in prescription opioid-related deaths (CCoV VODR) compared to prescription opioid-related poisonings (VPIC), 2017-2020.

From this, it appears that persistently during the period 2018-2020, pregabalin is 3.8-4 times more likely to be represented in a prescription opioid-related death compared to prescription opioid-related poisonings. In contrast, quetiapine has progressively trended to a less impactful profile of harm, with a greater contribution to opioid-related poisonings than deaths in 2020.

It should be noted that a similar trend of similar magnitude is observed when considering intentional poisonings rather than all poisonings.

It is not clear why such changes in quetiapine have been observed. Speculatively, it is plausible that this may, at least in part, have been contributed to by SafeScript's impact in reducing prescription medication-related deaths compared to prescription medication-related poisonings, which may have a more stochastic element to them.

Overall, these data would suggest that, similar to the peer-reviewed data described in Chapter 4, pregabalin disproportionately is associated with opioid-related harm at the most severe end of the spectrum, in contrast to a Schedule 4 medicine used in similar opioid-related contexts, quetiapine. It should be noted that causality is hard to ascertain from this, given that even in individual cases that causality may be hard to determine, and that the context of harm in these situations is complex. Nevertheless, it suggests that flagging pregabalin may help to identify high-risk prescription opioid use which is most likely to proceed to the most serious harm, such as death.

5.5 Conclusions from this chapter

This analysis of local data varies from that in 2019, as the underlying question has changed. In 2017 and 2019, the fundamental question was different: was the local data relating to harm sufficient to prove that candidate medications were culpable in causing a disproportionate number of deaths. As previously mentioned, given the subsequent and pleasingly uneventful maturity of use of SafeScript, it is very reasonable that the consideration now becomes regarding whether gabapentinoids and tramadol are associated with any harm, and indeed whether including those medications on SafeScript (and making their checking compulsory by prescribers and dispensing pharmacists, as per the rules of SafeScript) is helpful in preventing prescription medication-related death.

With this in mind, we examined not just the overall trends amongst individual medications, but also the combination that was clearly flagged as of concern in the peer-reviewed literature: pharmaceutical opioids with gabapentinoids. In the data from the Victorian Overdose Death Registry, examining prescription medication-related deaths, overall pregabalin-related deaths have stabilised since the last edition of the report, both in real terms and when normalised for usage, where the previous slow increase in its fatal-toxicity index has plateaued at a rate which is hard to differentiate from other medications not currently monitored.

What is more evident, however, is a progressively strengthening relationship between gabapentinoids and prescription opioids, relating to prescription mediation-related deaths. Opioids have been progressively increasingly represented in pregabalin-related deaths in a way that is not seen with the comparator, quetiapine. Most notably, however, pregabalin is steadily increasingly contributing to opioid-related deaths while the comparator has remained stable, to the point where now 29.5% of opioid-related deaths had pregabalin co-attributed. While there may be some element of notoriety bias with this, it is clear that a substantial proportion of people who die as a consequence of prescription opioids might have had an additional opportunity to be flagged, or an opportunity to be flagged with additional emphasis, if pregabalin was to be monitored on SafeScript.

Such a relationship is not seen with poisoning calls from the Victorian Poisons Information Centre; in fact, the inverse occurs, with the comparator increasing in co-ingestions. While this might initially seem to some to contradict the result in deaths, it in fact emphasises the previous finding in line with the peer-reviewed literature: gabapentinoids are most likely to be seen with risk of the most serious harm. This is demonstrated in the ratio between deaths and poisonings, as illustrated in Figure 5.4.1: while quetiapine now favours less impactful forms of opioid-related harm over more impactful, pregabalin is persistently 3.8-4 times more strongly associated with opioid-related death over opioid-related poisoning. These data would support the monitoring of pregabalin, even if only to flag high-risk opioid use.

On the contrary, there is little to specifically support tramadol as more dangerous than previous editions of this report. Its normalised metrics have stabilised compared to previous editions of this report, and remain at low-moderate levels of deaths and poisonings. No comparisons to Schedule 8 opioids have been made in this report, given the differences in regulation, and comparisons to codeine are difficult given the a number of factors which affect the latter. While no local metrics of prescription medication-related harm clearly identify it as definitely warranting inclusion, this is not as exhaustive as to override cues from the peer-reviewed literature or logistical considerations.

A full discussion follows in Chapter 8, including a discussion regarding implications of inclusion.

Chapter 6. Updated characteristics of other prescription drug monitoring programs

6.1 Review of Australian state and territory RTPM systems and currently monitored medicines

Introduction

It is planned that Australia will eventually have a nationally implemented system, designed to monitor the prescribing and dispensing of controlled medicines with the aim of reducing their misuse in Australia(66). Whilst all Australian states and territories have agreed to participate in a national real time prescription monitoring solution, the RTPM systems of individual states and territories are at varied stages of development and implementation.

Although Commonwealth, state and territory agencies are working together to implement the RTPM system, each state or territory remains responsible for the management of their own RTPM system and the controlled medicines within its jurisdiction. Therefore, each Australian state or territory will implement their own local version of the national RTPM system, with core features and functionality to enable national consistency, and the list of controlled medicines and other high-risk medicines currently being monitored in each jurisdiction is determined individually by the states and territories.

The following section will provide a brief overview of the progress of current Australian state and territory RTPM systems, the medicines currently being monitored in each jurisdiction, as well as any processes or evidence that informed the inclusion of these monitored medicines. The information provided below is summarised content openly available from the various jurisdictions' Department of Health websites, as well as other references where available, but without utilising any knowledge that is not otherwise publicly available or evident.

Australian Capital Territory
(ACT Government Health)(67)

Current progress of RTPM system

ACT DAPIS Online Remote Access (DORA) was implemented by the ACT Government in March 2019 to reduce the growing harms associated with pharmaceutical abuse and misuse. DORA is an extension of the Drugs and Poisons Information System (DAPIS), which is used by the ACT Government Health Protection Service (HPS) as its prescription monitoring system. The use of DORA by health professionals is not mandatory.

The ACT Government is now working on a project to replace DORA in 2021 with the RTPM system, Canberra Script. The national system will provide enhanced features and functionality for health practitioners over ACT DORA. According to the ACT Department of Health website, Canberra Script will be implemented in select pilot sites from late 2021, ahead of full release in early 2022. The use of Canberra Script by practitioners will also only be voluntary at this stage.

Currently monitored medicines

In ACT, monitored medicines are all controlled medicines (medicines listed under Schedule 8 of the Commonwealth Poisons Standard) or a medicine declared by the ACT Minister for Health to be a monitored medicine. On 30 August 2021, the Minister for Health declared the following medicines as monitored medicines under the Medicines, Poisons and Therapeutic Goods Act 2008:

- codeine
- tramadol
- all benzodiazepines
- quetiapine
- zolpidem and zopiclone
- gabapentin and pregabalin

From 1 October 2021, the ACT Health Directorate will collect information on prescriptions of these medicines through the National Data Exchange. It is anticipated that Canberra Script will include information about all controlled (Schedule 8) medicines and some prescription only (Schedule 4) medicines that are associated with abuse or misuse (such as the declared list of monitored medicines above). Information will include all monitored medicines dispensed in the ACT, as well as those dispensed in any other state or territory for ACT patients.

Process for inclusion of monitored medicines

Currently monitored medicines, which include tramadol, gabapentin and pregabalin, were declared by the Minister for Health "due to evidence of harms including deaths associated with their abuse and misuse in the Australian community".

New South Wales

*(*NSW Government, 2021)(68)

Current progress of RTPM system

SafeScript NSW is the RTPM system used in NSW. The prescribing and dispensing data feed for monitored medicines in NSW commenced 7 April 2021. According to the NSW Department of Health website, prescribers and pharmacists in the Hunter New England and Central Coast regions were the first to be invited to access the system from late October 2021, as part of a phased state-wide rollout, with prescribers and pharmacists in other NSW areas to be invited to access SafeScript NSW in the first half of 2022. The use of SafeScript NSW is not mandatory.

Currently monitored medicines

The current list of monitored medicines include:

- opioids (including tramadol)
- benzodiazepines
- zolpidem and zopiclone
- dexamfetamine, lisdexamfetamine, methylphenidate
- ketamine, pregabalin, quetiapine
- all other Schedule 8 medicines not listed above

(A full list of monitored medicines is included in the NSW Poisons and Therapeutic Goods Regulation 2008 Appendix E*)*

Process for inclusion of monitored medicines

The list of medicines monitored by SafeScript NSW was considered by a panel of medical experts (academics, pharmacologists and experts in addiction medicine and pain management) based on which medicines have the potential to cause the most harm to the community in NSW. The panel also considered approaches in other states and territories when determining the monitored medicines list for NSW.

According to the NSW Department of Health website, the following detailed criteria were used to guide decision making when considering the inclusion of Schedule 4 medicines in the SafeScript NSW system:

1. **Evidence of harm** – for a medicine to be included there should be evidence of a pattern of harm in NSW, including non-prescribed use, dependence and fatal and non-fatal overdoses.
2. **Trends in prescribing** – for a medicine to be included there should be evidence of an increasing trend in prescribing rates, as well as non-prescribed use or abuse in an Australian or global context.
3. **Substitution effect** – a medicine or group of medicines should be included if there is a risk that regulation of another medicine may result in a displacement of use to other medicines or illicit substances.
4. **Chilling effect** – inclusion of medicines for monitoring in SafeScript NSW may discourage prescribing of monitored medicines when they are otherwise clinically appropriate, resulting in negative patient outcomes.
5. **Regulatory burden** – care must be taken to ensure that the information collected in SafeScript NSW should be sufficiently inclusive as to adequately perform its purpose in mitigating harm without adding to the significant regulatory burden that prescribers and pharmacists already face or diluting the impact of SafeScript NSW on the actions of prescribers and pharmacists.
6. **Utility of information for clinical care** - medicines should be considered for inclusion where the added visibility will provide clinicians greater confidence in assessing and managing the patient, leading to improved patient care. Vulnerable and complex patients in particular are at a higher risk of harm from these high-risk medicines due to polypharmacy and the multiplying effect of being on numerous medicines. This criterion provides for the monitoring of medicines that aren't inherently high-risk in their own right but may be meaningful to the health practitioner and assist them to form a more accurate overall picture of medicines use.
7. **Consistency with other jurisdictions** – consideration is given to the approaches of other states and territories in determining their lists of monitored medicines, so as to ensure co-ordinated approaches and minimise cross-border issues.

These criteria mirror that developed by Victoria and adopted by South Australia.

It is also stated that NSW Health will monitor usage trends of medicines that were considered but ultimately not included in the monitored medicines list, and any emerging evidence may warrant reconsideration of their inclusion in the SafeScript NSW system. The current list of monitored medicines includes tramadol and pregabalin, but not gabapentin.

Northern Territory

(NT Government, 2021)(69)

Current progress of RTPM system

NTScript is the proposed RTPM system to be used in NT. In July 2020, an agreement was signed between NT Health, the Commonwealth Department of Health and software provider FredIT for the NT to link to the Commonwealth's federated RTPM and to develop an RTPM system for the NT. However, the exact date for health practitioner access is not yet decided. It is planned that NTScript will continue the mandatory monitoring that has been in place since 1983 in the NT. The department website has indicated that it would not be possible to opt out as the use and supply of these "monitored of substances" is a major public health and safety concern, thus implying the likely mandatory nature of NTScript.

Currently monitored medicines

Schedule 8 (S8) Controlled Drugs have been monitored in the NT since 1983, through weekly pharmacy reports of dispensed S8 prescriptions. The implementation of real time prescription monitoring of S8 drugs was recommended by the NT Coroner in 2017. Initially, it is planned that NTScript RTPM will only monitor S8Controlled Drugs, consistent with current monitoring. However, it is proposed that at a later stage, monitoring will be extended to include specific S4 medicines (prescription only) as is the case in other states and territories. According to the NT Department of Health website, the list of additional S4 'Monitored Substances' will include:

- all benzodiazepines not in S8
- zolpidem and zopiclone
- quetiapine
- gabapentin and pregabalin
- codeine combination products
- tramadol

The date for inclusion of these S4 medicines is yet to be confirmed.

Process for inclusion of monitored medicines

According to the NT Department of Health website, "Monitored Substances" were determined based on "those medicines that were deemed to greatly increase risk to the patient due to likelihood of dose escalation, dependence, overdose, misuse and diversion". The proposed monitored substances list includes tramadol, pregabalin and gabapentin.

Queensland

(Queensland Government 2021)(70)

Current progress of RTPM system

QScript is Queensland's real-time prescription monitoring system. From 28 October 2021, relevant health practitioners are required to check QScript for patient records, based on the QLD *Medicines and Poisons Act 2019*. Currently, QScript does not contain record of all monitored medicines supplied in other states/territories. However, it is proposed that information about monitored medicines dispensing events occurring in other states and territories may be recorded and viewable in QScript once the national RTPM is implemented.

Currently monitored medicines

According to the QLD Department of Health website, QScript captures a comprehensive list of medicines that have a recognised therapeutic use but may also present a high risk of physical, mental and social harms. The *Medicines and Poisons Act 2019* refers to these medicines as 'monitored medicines' which includes:

- All Schedule 8 medicines
- The following Schedule 4 medicines:
    - all benzodiazepines
    - codeine
    - gabapentin and pregabalin
    - quetiapine
    - tramadol
    - zolpidem and zopiclone

Process for inclusion of monitored medicines

The QLD Department of Health website specifies that the list of monitored medicines, which includes tramadol, gabapentin and pregabalin, was been determined based on local and international research and incorporates the recommendations of a multi-disciplinary working party (Monitored Substances Steering Committee). Numerous factors were considered when determining whether a medicine was suitable for inclusion in the list, including the evidence of harm (on its own or in combination with other substances) and trends in prescribing, misuse, and abuse. Specifically, 'Monitored medicines' are medicines identified by Queensland Health as potentially presenting a 'high risk of harm to patients as a result of misuse, abuse, diversion, substance use disorder and/or overdose'. Ongoing research and trends in prescribing medicine will inform any future changes to the monitored medicines list.

South Australia

(Government of South Australia, 2021)(68)

Current progress of RTPM system

ScriptCheckSA is the RTPM system used in South Australia. ScriptCheckSA was released across SA on 31 March 2021. Although currently it is not mandatory, it is expected that in early 2022, it will be mandatory for prescribers and pharmacists to use ScriptCheckSA when prescribing or dispensing a monitored drug. This will allow for approximately 12 months of voluntary use during the transition period.

Currently monitored medicines

According to the SA Department of Health website, prescription medicines that cause the greatest harm to the South Australian community are monitored by ScriptCheckSA, irrespective of whether they receive a PBS subsidy or are private, non-PBS prescriptions. Monitored drugs include all Schedule 8 medicines (drugs of dependence) and Schedule 4 medicines that increase the risk of harm when co-prescribed with drugs of dependence, including:

- All Schedule 4 medicines that are benzodiazepines
- All S4 medicines that contain codeine
- gabapentin and pregabalin
- quetiapine
- tramadol
- zolpidem and zopiclone

Process for inclusion of monitored medicines

According to the SA Department of Health website, the above Schedule 4 medicines, including tramadol, pregabalin and gabapentin, have been included because evidence demonstrates their potential to increase harms associated with Schedule 8 medicines if co-prescribed. Both national and international evidence was considered, in particular the findings from the Victorian Austin Health literature review conducted in 2017 and 2019.

Furthermore, SA Health formed a Real-Time Prescription Monitoring (RTPM) Clinical Advice and Pathways Working Group (CAPWG) to guide the addition or removal of Schedule 4 medicines from the list of monitored drugs, whilst ensuring that a nationally consistent and evidence-based approach is applied, including the use of the following criteria:

1. Evidence of harms (misuse, abuse, addiction and fatal / non-fatal overdoses)
Consideration should be given to the severity of harm, the total burden of harm relative to the total volume of medicine prescribed and whether the harm associated was because of a medicine on its own or in combination with other high-risk medicines.

2. Trends in prescribing, misuse and abuse
A demonstrated increasing trend in misuse and abuse of the medicine in SA. Consideration should be given to interstate and international evidence to assist in predicting locally emerging trends of harm.

3. Potential for the 'substitution effect'
Where monitoring a particular medicine or medicine class is causing or can cause misuse or harm to be displaced to other medicines or illicit drugs.

4. Potential for the 'chilling effect'
Where monitoring a particular medicine or medicine class is resulting or could result in prescribers becoming reluctant to prescribe the medicine, thereby resulting in patients receiving sub-therapeutic treatment and poorer health outcomes.

5. Regulatory burden (including cost-benefit) and clinical utility
The addition of a monitored medicine in ScriptCheckSA is intended to provide benefits through more informed clinical decisions and safer patient care. However, monitoring a medicine should not add unnecessary or unreasonable regulatory burden on health practitioners or the Regulator (Drugs of Dependence Unit).
The benefit of monitoring a medicine should be considered in the context of:

- the potential increased demand for addiction medicine, pain management services, psychiatry and other specialist services
- the regulatory burden to users of ScriptCheckSA
- the social and economic benefits to individuals and the community (reduced deaths, hospital admissions, use of high-risk medicines)

6. Inter-jurisdictional approaches
Where appropriate, inclusion of medicines should align with other jurisdictions.

It is also stated that Schedule 8 medicines will always be monitored by ScriptCheckSA and other Schedule 4 medicines may be monitored if there is evidence of an emerging risk of harm when co-prescribed with drugs of dependence. SA's monitored drugs list will be periodically reviewed by the Department for Health and Wellbeing in consultation with an Expert Advisory Group.

Tasmania

(Tasmanian Government, 2021)(67)

Current progress of RTPM system

Tasmania current uses DAPIS Online Remote Access (DORA) as its RTPM. DORA is an extension of the Drugs and Poisons Information System (DAPIS), which is used by the Tasmanian Department of Health's Pharmaceutical Services Branch (PSB). DORA was first made available to prescribers and pharmacists in 2011. Tasmania was the first state to implement RTPM with DORA. While Tasmania has agreed to an implementation of the national RTPM system, details regarding the implementation and RTPM system is not yet made available. The use of DORA by health professionals is not mandatory.

Tasmania's Chief Pharmacist suggested that Tasmania's RTPM may have assisted in a reduction in individual patient risk and opioid-related harms in Tasmania, but the "extent of the reduction could not be determined"(71). Nevertheless, Boyles suggested that DORA has proved to be a valuable tool for many clinicians, but the changes seen in Tasmania in reducing opioid preventable deaths is also likely attributed to various expert clinician-led, clinical governance regulatory activities and improvements in the awareness of GPs and pharmacists initiatives during this period.

Currently monitored medicines

The list of monitored medicines in the current DORA system in Tasmania includes all S8 medicines and S4D opioids (codeine, tramadol, and dextropropoxyphene) (Personal communications). The list of monitored medicines was expanded from all S8 medicines to include the S4D opioids (codeine, tramadol, and dextropropoxyphene) from 1 February 2018.

Process for inclusion of monitored medicines

Information regarding criteria used to guide the inclusion of medicines required for RTPM monitoring was not available on the Tasmanian Department of Health website. Gabapentinoids are not currently monitored.

Victoria

(Victoria Government, 2021)(72)

Current progress of RTPM system

SafeScript is Victoria's RTPM system. After initial successful implementation in the Western Victoria Primary Health Network region, SafeScript was implemented across Victoria from 1 April 2019. From October 2018, SafeScript was available to Victorian medical practices and pharmacies on a voluntary opt-in basis; from April 2020, it has been mandatory to check SafeScript prior to writing or dispensing a prescription for monitored medicines (except in certain circumstances such as treating patients in hospitals, prisons, police jails, aged care and palliative care). This follows worldwide best practice, as mandatory systems adopted in other countries have shown to provide greater reduction in harms from high-risk prescription medicines.

One local research letter provided some initial insights into the impacts of SafeScript, based on a survey of people who inject drugs(73); further commentary follows in Chapter 6.4.

Currently monitored medicines

SafeScript monitors all prescriptions for monitored medicines regardless of whether they receive a PBS subsidy or are private, non-PBS prescriptions. Medicines that are currently monitored include:

- all Schedule 8 medicines
- benzodiazepines
- zolpidem and zopiclone
- quetiapine
- ketamine
- codeine containing products

Process for inclusion of monitored medicines

The VIC Department of Health website has provided extensive information regarding criteria used to guide the inclusion of medicines required for RTPM monitoring of prescription medicines that are considered as causing the greatest harm to the Victorian community, largely driven based on the latest international and local research and recommendations from an expert advisory group.

Specifically, it was stated that the inclusion of medicines were determined based on a study, conducted by Austin Health, of local and international research which informed recommendations from the SafeScript Expert Advisory Group, including an updated literature review conducted in the lead up to SafeScript becoming mandatory in April 2020. Copies of the initial literature review (2017), the updated review (2019) and the criteria for inclusion of additional medicines in SafeScript are available on the Department website.

The department will continue to closely observe data and review any new evidence of harm for the medicines considered in the 2019 review and indeed any medicine not currently monitored. A framework has been developed to guide future recommendations on the inclusion of additional Schedule 4 medicines in SafeScript. This will enable a consistent, transparent and evidence-based approach to be applied when a medicine is being considered for monitoring in SafeScript. It should be noted that the authors of the 2019 edition of the report helped advise the Victorian Government regarding this framework.

Briefly, the criteria for inclusion of additional Schedule 4 medicines will be based on the following:

7. Evidence of harms
8. Trends in prescribing, misuse and abuse
9. 'Substitution effect'
10. 'Chilling effect'
11. Regulatory burden and cost-benefit
12. Inter-jurisdictional approaches

Western Australia

(Government of Western Australia, 2021)(74)

Current progress of RTPM system

Western Australia currently operates a comprehensive prescription monitoring program (PMP) that has been in place for a number of years. This collects all dispensing data relating to Schedule 8 medicines only from community pharmacies; however the system is not real-time. Similar to the other States, WA has also agreed to an implementation of the national RTPM system, however details regarding the RTPM system are not yet available. Additionally, it is not clear whether the proposed RTPM system will be made mandatory or not.
A new controlled drugs database, the Electronic Recording and Reporting of Controlled Drugs (ERRCD) was implemented by the Department in February 2021. This database replaced the Monitoring of Drugs of Dependence System (MODDS) database and was a pre-requisite for implementation of RTPM. Steps toward RTPM in WA are outlined on the WA Department of Health website, with the final step to release the Health Practitioner Portal expected to be completed in early 2022.

Medicines to be monitored

The WA Department of Health website has flagged that the new RTPM system will aim to report on all S8 data, plus Schedule 4 reportable data, ie. medicines that have been prescribed by regulation, for example benzodiazepines, tramadol, and compound codeine products. However, the exact list of medicines to be monitored is not reported on the Department's website.

Process for inclusion of medicines to be monitored

The WA Department of Health conducted stakeholder consultations as part of the RTPM implementation process. Between April and June 2019, the WA Department of Health ran a series of stakeholder workshops for prescribers, dispensers and consumers. The workshops were used to inform policy and regulation when implementing RTPM in Western Australia, including discussions on medicines to include in RTPM.

From the workshop, it was proposed that listing should be dependent on factors such as:

- the current harm the medicine confers, e.g. morbidity and mortality;
- risk of abuse;
- risk of dependence; and
- evidence of increased abuse and misuse of the Schedule 4 medicine.

From the workshop, specific S4 medicines under consideration be reported include benzodiazepines as a clear priority for monitoring, followed by tramadol, non-Schedule 8 codeine-based products, and then gabapentinoids.

Table 6.1.1. Summary of RTPM programs for Australian States and Territories.

State	RTPM used/proposed	Mandatory use?	Inclusion	Justification made for their inclusion	Timing of their inclusion relative to other prescription drugs, and ongoing inclusions
ACT	Currently DAPIS/DORA; will move to CanberraScript (late 2021/early 2022)	No	All S8s plus selected monitored medicines: • codeine • tramadol • all benzodiazepines • quetiapine • zolpidem and zopiclone • gabapentin and pregabalin	Canberra Script will include information about controlled (schedule 8) medicines and some prescription only (schedule 4) medicines that are associated with abuse or misuse or evidence of harms in the Australian community	Only S8 included in DORA; however tramadol, gabapentin and pregabalin added to monitored medicines list from 1 Oct 2021
NSW	SafeScriptNSW (late 2021/early 2022)	No	• opioids (including tramadol) • benzodiazepines • zolpidem and zopiclone • dexamfetamine, lisdexamfetamine, methylphenidate • ketamine, pregabalin, quetiapine • all other Schedule 8 medicines not listed above	An expert panel of academics, pharmacologists and experts in addiction medicine and pain management was established to provide advice regarding monitored list in SafeScript NSW Criteria for inclusion: 1. Evidence of harm 2. Trends in prescribing, misuse and abuse 3. 'Substitution effect' 4. 'Chilling effect' 5. Regulatory burden and cost-benefit 6. Utility of information for clinical care 7. Consistency with other jurisdictions	NSW Health will monitor usage trends of medicines that were considered but ultimately not included in the monitored medicines list, and any emerging evidence may warrant reconsideration of their inclusion in the SafeScript NSW system.

NT	Implementing NTScript (launch?)	Yes	Initially NTScript RTPM will only monitor S8 substances. At a later stage, monitoring will be extended to include specific S4 medicines The additional monitored medicines will include: • all benzodiazepines not in S8 • zolpidem and zopiclone • quetiapine • gabapentin • pregabalin • codeine combination products • tramadol	"Monitored Substances" are those medicines that greatly increase risk to the patient due to likelihood of dose escalation, dependence, overdose, misuse and diversion.	Initially NTScript RTPM will only monitor S8 substances. At a later stage, monitoring will be extended to include specific S4 medicines. The date for inclusion of these S4 medicines is yet to be confirmed.
QLD	QScript (Active)	Yes	All S8 medicines The following S4 medicines: • benzodiazepines • codeine • gabapentin • pregabalin • quetiapine • tramadol • zolpidem • zopiclone	QScript captures a comprehensive list of medicines that have a recognised therapeutic use but may also present a high risk of physical, mental and social harms. The list of monitored medicines has been determined based on local and international research and incorporates the recommendations of a multi-disciplinary working party. Numerous factors were also considered when determining whether a medicine was suitable for inclusion in the list, including the evidence of harm (on its own or in combination with other	Ongoing research and trends in prescribing medicine will inform any future changes to the monitored medicines list.

				substances) and trends in prescribing, misuse, and abuse.	
SA	ScriptCheckSA (Active)	Yes	Monitored drugs include all Schedule 8 medicines (drugs of dependence) and Schedule 4 medicines that increase the risk of harm when co-prescribed with drugs of dependence, including: • all Schedule 4 medicines that are benzodiazepines, • all S4 medicines that contain Codeine, and • gabapentin • pregabalin • quetiapine • tramadol • zolpidem, and zopiclone	Prescription medicines that cause the greatest harm to the South Australian community are monitored by ScriptCheckSA, Real-Time Prescription Monitoring (RTPM) Clinical Advice and Pathways Working Group (CAPWG) reviewing national and international evidence, including the following criteria for inclusion: 1. Evidence of harms (misuse, abuse, addiction and fatal / non-fatal overdoses) 2. Trends in prescribing, misuse and abuse 3. Potential for the 'substitution effect' 4. Potential for the 'chilling effect' 5. Regulatory burden (including cost-benefit) and clinical utility 6. Inter-jurisdictional approaches	Other Schedule 4 medicines may be monitored if there is evidence of an emerging risk of harm when co-prescribed with drugs of dependence. SA's monitored drugs list will be periodically reviewed by the Department for Health and Wellbeing in consultation with an Expert Advisory Group
TAS	Currently using DORA (will implement national RTPM system when released – information not yet available)	No	Current monitored list: • all S8 medicines • S4D opioids (codeine, tramadol, and dextropropoxyphene)	Not available	The list of monitored medicines was expanded from all S8 medicines to include the S4D opioids (codeine, tramadol, and dextropropoxyphene) from 1 February 2018.

VIC	SafeScript (Active)	**Yes**	• All Schedule 8 medicines • benzodiazepines • zolpidem and zopiclone) • quetiapine • ketamine • codeine containing products	Austin Health literature review of local and international research Criteria for inclusion: 1.Evidence of harms 2.Trends in prescribing, misuse and abuse 3.'Substitution effect' 4.'Chilling effect' 5.Regulatory burden and cost-benefit 6.Inter-jurisdictional approaches	The department will continue to closely observe data and review any new evidence of harm for the medicines considered in the 2019 review and indeed any medicine not currently monitored.
WA	Currently using ERRCD (will implement national RTPM system when released – information not yet available)	Unclear	Current Prescription Monitoring Program (PMP) only monitors S8 The new RTPM system will aim to report on all S8 data + Schedule 4 reportable data – medicines that have been prescribed by regulation, for example benzodiazepines, tramadol, compound codeine products (Gabapentinoids are under consideration)	As per WA DoH RTPM workshop 2019: Listing dependent on factors such as: • the current harm the medicine confers, e.g. morbidity and mortality; • risk of abuse; • risk of dependence; and • evidence of increased abuse and misuse of the Schedule 4 medicine. Specific S4 meds to be reported: • considered benzodiazepines as a clear priority for monitoring, followed by tramadol, non-Schedule 8 codeine-based products, and then gabapentinoids	

Discussion

RTPM programs are useful tools that are effective in improving clinical decision-making when prescribing or dispensing high-risk medicines. However, it is critical that the use and implementation of RTPM is continually reviewed to assess its risks and benefits and evidence regarding its impacts on clinical practice and health outcomes. Whilst there is momentum towards the implementation of a national RTPM in recent years, different states and territories are currently at varied stages of development and implementation with their respective RTPMs. This creates a major challenge in attempting to draw clear conclusions and lessons from the program, due to the lack of consistency and harmonization between systems in different jurisdictions. Furthermore, it is still very early in the implementation of RTPM across Australia and progress is ongoing, with most jurisdictions having only implemented their respective RTPM in the last year or two, including updates to the list of medicines that are to be monitored. This presents additional limitations to conclusions that can be drawn to help inform changes (if any) to Victoria's SafeScript system. Nevertheless, exploring and comparing the similarities and differences between RTPM systems and monitored medicines in the different states and territories, in particular assessing interstate precedents and decision-making insights, is important to ensure the transparency, consistency and rigor of RTPM systems.

In general, there is great consistency between all the States and Territories in the current (or proposed) monitored medicines lists, based on the controlled substance or high-risk nature of those prescription medicines (such as measures of harms). Of particular interest for the context of this report is whether tramadol and/or the gabapentinoids (ie. pregabalin and gabapentin) are listed as monitored medicines by various other jurisdictions. As summarised above, these medicines have been or will be included in majority of the other states and territories' RTPM. ACT, NT, QLD and SA will monitor tramadol, pregabalin and gabapentin, while NSW will monitor tramadol and pregabalin, but not gabapentin. Tasmania, which does not currently have an RTPM, monitors tramadol but not gabapentinoids, while WA's RTPM system is still in development, but will consider the inclusion of S4 medicines including tramadol and gabapentinoids. In this context, it is timely for Victoria to also consider whether tramadol and gabapentinoids should be added to SafeScript's monitored medicines list, taking into account the implications of inclusion and currently available evidence.

A lack of a coordinated approach and uniformity between the RTPM systems of the states and territories may potentially lead to situations of cross-border accessing by drug-seeking individuals for medicines in jurisdictions with less restrictions (for example if a medicine is listed as a monitored medicine in New South Wales and South Australia, but not in Victoria). This concern has been identified by some states and territories and has been included as a consideration in their respective criteria for inclusion of monitored medicines. Implementation of national data sharing arrangements may reduce the risk of cross-border issues with safe supply of prescription medicines. Nevertheless, unintended consequence of inter-jurisdictional variability needs to be monitored closely.

In addition, there is variability between states and territories as to whether the use of RTPM should be or will be mandatory. Drug-seeking individuals may inappropriately access monitored medicines in jurisdictions where RTPM use is not mandatory. Various jurisdictions have indicated that mandatory systems adopted in other countries have shown to provide greater reduction in harms from high-risk prescription medicines, thus supporting the notion that RTPM should be made mandatory nationally.

A major limitation to understanding the need to monitor tramadol and/or gabapentinoids is that for many jurisdictions, a detailed explanation or justification as to how the list of monitored medicines has been determined by each state/territory is not freely available to be scrutinized. Details on respective jurisdictions' Department of Health websites is quite

limited in this respect, with most citing only that medicines were included as they were considered "most likely to cause harm". In many cases, it appears that additions to the monitored list may have been suggested based on interstate precedence, or from each jurisdiction's expert advisory group, taking into account a review of both national and international evidence, in particular the findings from the Victorian Austin Health literature reviews conducted in 2017 and 2019, which were produced to inform the Victoria RTPM program. It is important that the listing of monitored medicines is continually monitored and reviewed, including assessing emerging trends.

A final and perhaps most significant limitation to assessing the inclusion of monitored medicines is the paucity of clear direct evidence from the various RTPM systems and their impacts on measures of harms and of any unintended impacts of regulation. Given the early stages for RTPM implementation across Australia, studies investigating the impact of RTPM implementation on these measures are limited and the evidence is greatly lacking. The immaturity of inter-jurisdictional RTPM data and evidence limits the ability to extrapolate any program features for Victoria, in particular in the context of listing tramadol and/or gabapentinoids as a monitored medicines. As momentum for RTPM implementation gains, more data and evidence should become available to address these questions.

Conclusion

In conclusion, it is clear that more research and ongoing evaluations are needed to understand the impact of RTPM programs in Australia and to draw lessons from experiences in different state and territory jurisdictions. In particular, evidence is needed to inform the true impacts (intended or unintended), suitability and sustainability of RTPMs as Australia moves towards the implementation of a national RTPM, with particular reference to how this may affect SafeScript and its ongoing evolution.

6.2 Update of characteristics of prescription drug monitoring programs in the USA

Much of the current research and evidence of RTPM/PDMP comes from the United States of America (USA) as prescription drug monitoring programs (PDMP) have been in place extensively there and for a much longer period than in Australia. In recent years, there has been more changes and developments to their PDMP implementations and monitoring requirements, including more data on their impacts and research in that space. As such, much of the discussion in this report will be based on lessons from the US. Although there are obvious limitations and challenges whilst trying to extrapolate international lessons for Victoria, nevertheless it is of value to review some of the similarities and differences. The following section aims to provide an update from the 2019 Austin Health literature review on the operational PDMPs in the USA.

There are currently fifty-four operational PDMP in the USA. This includes the 50 US States, the District of Columbia, and the territories of Guam and Puerto Rico. Northern Mariana Islands started their PDMP in 2021 and has been added since the 2019 review.

One of the challenges with PDMPs in the United States is that there is substantial variability in how PDMPs are organised and operated between states and territories. For example, each state determines which agency houses the PDMP; which controlled substances must be reported; how often data are collected; and who is required to access the information. There is also variability between states with respect to whether or how information contained in the database is shared with other states.

The majority of PDMP characteristics have remained the largely same since the 2019 Austin Health literature review. However, a number of updates have been implemented for several states' PDMP. These changes include: some modifications to lists of monitored drugs; inclusion of Schedule 5 drugs to some of the monitored lists whereas previously only monitoring up to Schedule 4 was required; as well as some alterations to conditions for mandatory reporting. Fourteen states have now added gabapentin to their list of monitored drugs. There have also been updates in some states for the mandatory reporting of monitored drugs by the prescriber, or the dispenser, or both persons. All changes made to PDMPs since the 2019 Austin Health literature review are highlighted in Table 6.2.1.

In summary, mandatory reporting is currently required in 49 states. The majority of US PDMPs (54 in total) are engaged in some form of interstate data sharing, allowing the PDMPs from neighbouring states (and sometimes beyond) to review data entered from other PDMPs. Recent concerns with gabapentin has resulted in some states now taking action to track gabapentin use through prescription monitoring programs, and some states have reclassified it as a Schedule 5 controlled substance(75). Gabapentin is not currently listed as a Federal controlled substance under the Controlled Substances Act of 1970, however individual states are able to independently reclassify gabapentin under state pharmacy rules as a Schedule 5 drug. As of 20th November 2020, Alabama, Kentucky, Michigan, North Dakota, Tennessee, Virginia and West Virginia have classified gabapentin as a Schedule V controlled substance; Connecticut, District of Columbia, Indiana, Kansas, Massachusetts, Minnesota, Nebraska, New Jersey, Ohio, Oregon, Utah and Wyoming have mandated gabapentin reporting; and Delaware, New York and Wisconsin are states that are deliberating the mandated reporting of gabapentin and/or reclassification as a controlled substance.

Table 6.2.1. Characteristics of all active PDMPs in the USA and its Territories.
Adapted from: Prescription Drug Monitoring Program – Training and Technical Assistance Centre. State PDMP Profiles and Contacts [internet]. United States of America [cited 5/10/2021]. Available from http://www.pdmpassist.org/State

State	In operation since	Drugs monitored	Frequency of data trans-mission	Mandatory reporting by prescriber (P) or dispenser (D)	Conditions for mandatory reporting	Identification (ID) requirement	Data sharing
Alabama	2006	Sched 2-5 codeine cough syrups, anabolic steroids, butalbital, chlordiazepoxide and combinations, tianeptine and combinations (gabapentin is Sched 5 in AL)	Daily/Next business day	P only	Morphine milligram equivalent (MME) 30-90mg - check twice per year; MME >90mg - check with every prescription	ID of patient, person dropping off prescription and person picking up prescription	Yes
Alaska	2011	Sched 2-4	Daily/Next business day	P only	All prescriptions (only sch 2&3) for quantities lasting >3 days	ID of patient only	Yes
Arizona	2008	Sched 2-5	Daily/Next business day	P and D	All monitored drugs every time	No ID requirement	Yes
Arkansas	2013	Sched 2-5, nalbuphine, Tianeptine	Daily/Next business day	P only	Sched 2 or 3 opioids every time, first-time benzodiazepines in non-surgery/palliative circumstances. Nursing home residents excluded.	No ID requirement	Yes
California	1939	Sched 2-5	Daily/Next business day	P only	All first-time prescriptions and re-check every six months if treatment ongoing	No ID requirement	No

Colorado	2007	Sched 2-5	Daily/Next business day	P only	Prior to prescribing the second fill for an opioid	No ID requirement	Yes
Connecticut	2008	Sched 2-5 (mandated gabapentin reporting in CT)	Daily/Next business day	P only	All monitored drugs in quantities >3 days. Schedule 2-4 drugs for prolonged treatment requires re-checking every 3 months. Schedule 5 drugs requires re-checking annually	No ID requirement	Yes
District of Columbia	2016	Sched 2-5, cyclobenzaprine, butalbital, gabapentin	Daily/Next business day	P and D	Opioid or benzodiazepine for >7 consecutive days; for prolonged treatment requires re-checking every 3 months	No ID requirement	Yes
Delaware	2012	Sched 2-5 (reclassification of gabapentin under consideration in DE)	Daily/Next business day	P and D	All monitored drugs every time	No ID requirement	Yes
Florida	2011	Sched 2-5	Daily/Next business day	P and D	All monitored drugs every time	ID of person picking up prescription only	Yes
Georgia	2013	Sched 2-5	Daily/Next business day	P only	First prescription and re-check every 3 months if treatment ongoing	ID of patient only	Yes
Guam	2013	Sched 2-5	Within 14 days	P only	First prescription of monitored drugs, or preceding 12 months	ID of patient and person picking up prescription	Yes
Hawaii	1943	Sched 2-5	Within 7 days	P only	All monitored drugs every time	ID of patient only	Yes

Idaho	1967	Sched 2-5	Daily/Next business day	P only	First prescription of opioid analgesic or benzodiazepine listed in Sch 2-4, or preceding 12 months	No ID requirement	Yes
Illinois	1968	Sched 2-5	Daily/Next business day	P only	First prescription for monitored drugs unless the patient is palliative or has cancer, or if quantity supplied is <7 days	No ID requirement	Yes
Indiana	1998	Sched 2-5, ephedrine, pseudoephedrine, gabapentin	Daily/Next business day	P and D	First prescription for all monitored drugs, and 'periodically' while treatment continues	ID of patient only	Yes
Iowa	2009	Sched 2-5	Daily/Next business day	P only	Prior to prescribing an opioid. Additional requirements are specific to the individual prescribers licensure board	No ID requirement	Yes
Kansas	2011	Sched 2-4, butalbital, acetaminophen with butalbital, caffeine, pseudoephedrine, promethazine with codeine, gabapentin	Daily/Next business day	No mandatory reporting	N/A	No ID requirement	Yes
Kentucky	1999	Sched 2-5, gabapentin (gabapentin is Sched 5 in KY)	Daily/Next business day	P only	Prior to prescribing a sched 2 drug and re-check every 3 months. Additional requirements are specific to the individual prescribers licensure board	ID of patient only	Yes
Louisiana	2008	Sched 2-5, Ephedrine products (C-V in LA)	Daily/Next business day	P only	First opioid prescriptions and then every 90 days if treatment continues	ID of patient only	Yes

		Butalbital Naloxone hepatitis treatment medications Gabapentin					
Maine	2004	Sched 2-4	Daily/Next business day	P and D	Initial prescription of an opioid or benzodiazepine and every 90 days for ongoing treatment, or if first script in 12 months, or if interstate resident or paying by cash	ID of patient only	Yes
Maryland	2013	Sched 2-5	Daily/Next business day	P and D	New course of treatment with an opioid or benzodiazepine, and every 90 days if continuing. Any monitored drug if there is reason to believe the prescription is being filled for something other than a legitimate medical diagnosis	ID of patient only	Yes
Massachusetts	1994	Sched 2-5, gabapentin	Daily/Next business day	P only	All Sched 2 or 3 opioids, or when prescribing a benzodiazepine for the first time; and when prescribing schedule 4 or 5 controlled substance to a patient for the first time	ID of patient, person dropping off prescription and person picking up prescription	Yes
Michigan	1989	Sched 2-5 (gabapentin is Sched 5 in MI)	Daily/Next business day	P only	All monitored drugs with supply >3 days	ID of patient only	Yes
Minnesota	2010	Sched 2-5, gabapentin, butalbital, HGH, hCG, pseudoephedri	Daily/Next business day	P only	Before the prescriber issues an initial prescription order for a Schedule 2-4 opiate controlled substance to the patient; and at least once every three months for patients receiving an opiate for treatment of chronic pain	No ID requirement	Yes

		ne and Ephedrine			or participating in medically assisted treatment for an opioid addiction		
Mississippi	2005	Sched 2-5, Ephedrine and pseudoephedrine	Daily/Next business day	P and D	As regulated by each respective board, and reviewed every 6 months thereafter for any CS ; For pharmacists: prior to dispensing a prescription for a Schedule II opiate, a pharmacist shall review the prescription monitoring program if: a) the patient is a new customer to that pharmacy; or b) the patient has not had an opioid prescription at that pharmacy within six (6) months	ID of patient only	Yes
Missouri (St Louis County Only)	2017	Sched 2-4	Daily/Next business day	No mandatory reporting	N/A	No ID requirement	Yes
Montana	2012	Sched 2-5	Daily/Next business day	P only	Before a prescription for an opioid or a benzodiazepine with supply >7 days; every 3 months for chronic pain patients; Authority to enforce MPDR mandates will be managed through the State's professional licensing complaint process	ID of patient only	Yes
Nebraska	2011	Sched 2-5 All prescription drugs are monitored (mandated gabapentin reporting in NE)	Daily/Next business day	No mandatory reporting	N/A	ID of patient only	Yes

Nevada	1997	Sched 2-5	Daily/Next business day	P only	All monitored prescriptions at first prescribing and at least every 90 days if continuing	No ID requirement	Yes
New Hampshire	2014	Sched 2-4	Daily/Next business day	P only	All monitored drugs for first prescription and at least twice a year	No ID requirement	Yes
New Jersey	2011	Sched 2-5, gabapentin, HGH	Daily/Next business day	P and D	Prior to initial prescription for any schedule opioid or benzodiazepine and no less than quarterly thereafter. Dispensers - only if they suspect the patient is acquiring the medication for abuse, misuse or diversion	ID of person picking up prescription only	Yes
New Mexico	2005	Sched 2-5	Daily/Next business day	P and D	First prescription for Sched 2-5 CS when quantity is >4 days or if there is a gap in prescribing a CS for ≥30 days; and at least every 3 months if ongoing	No ID requirement	Yes
New York	1973	Sched 2-5, hCG (reclassification of gabapentin under consideration in NY)	Point of sale/within 24 hours	P only	All monitored drugs (including medical cannabis) unless the practitioner is administering a controlled substance, quantity <5 days, hospice, methadone programs, or consultation would adversely impact a patient's medical condition	No ID requirement	Yes
North Carolina	2007	Sched 2-5	Daily/Next business day	P and D	Initial prescription of monitored drug and every 3 months if ongoing treatment. Hospice/Palliative/Cancer pain management situations exempted	No ID requirement	Yes
North Dakota	2007	Sched 2-5, gabapentin (gabapentin is Sched 5 in ND)	Daily/Next business day	P and D	Opioid treatment programs must check monthly. Dispensers must check all initial prescriptions for controlled drugs and re-check at their own discretion	No ID requirement	Yes

Northern Mariana Islands	2021	Sched 2-5 All prescription drugs are monitored	Daily/Next business day	P and D	No information provided	ID of patient and person picking up prescription	Yes
Ohio	2006	Sched 2-5, gabapentin, medical marijuana	Daily/Next business day	P and D	First prescription for opioids and benzodiazepines and every 90 days if continuing. Dispensers must check for first prescription of a monitored drug and annually	No ID requirement	Yes
Oklahoma	1991	Sched 2-5	Point of Sale	P only	For prescriptions for opiates, benzodiazepines or carisoprodol if it has been 180 days since the last prescription	ID of patient and person picking up prescription	Yes
Oregon	2011	Sched 2-4, pseudoephedrine, gabapentin, naloxone	Within 3 days	P only	Before dispensing each prescription	No ID requirement	Yes
Pennsylvania	1973	Sched 2-5	Daily/Next business day	P and D	All initial prescriptions, all prescriptions for opioids or benzodiazepines, if there is a belief of abuse/diversion. Dispensers must check for all new patients, early refills, cash payments in place of insurance, multiple prescribers	No ID requirement	Yes
Puerto Rico	2018	Sched 2-5	Within 2 days	No mandatory reporting	N/A	ID of patient only	Yes
Rhode Island	1979	Sched 2-5	Daily/Next business day	P only	Initial opioid prescriptions and every 3 months, or every 12 months if the patient is continued on the opioid for a period of ≥ 6 months, or every 3 months if an intrathecal pump is used. Initial medical marijuana prescriptions need to be checked	ID of patient only	Yes

South Carolina	2008	Sched 2-4	Daily/Next business day	P only	Initial prescriptions for Sched 2 opioids with supply >5 days, and re-check every 90 days if ongoing	No ID requirement	Yes
South Dakota	2011	Sched 2-5	Daily/Next business day	No mandatory reporting	N/A	No ID requirement	Yes
Tennessee	2006	Sched 2-5, gabapentin (gabapentin is Sched 5 in TN)	Daily/Next business day	P and D	Initial prescriptions of monitored drugs and at least semi-annually if ongoing treatment	No ID requirement	Yes
Texas	1982	Sched 2-5	Daily/Next business day	P and D	All monitored drugs	No ID requirement	Yes
Utah	1996	Sched 2-5, butalbital, acetaminophen, gabapentin	Point of sale/within 24 hours	P and D	Initial prescriptions for Sched 2 or 3 opioids where duration is >3 days (unless post-surgical, then duration >30 days). Periodic checking is required, but timing is not specified	ID of patient only	Yes
Vermont	2009	Sched 2-4	Daily/Next business day	P and D	First time prescribing monitored drugs, with opioid quantity > 10 pills, nonpalliative long-term pain therapy of ≥90 days, replacement prescription; Must re-check at least every 12 months (every 6 months for buprenorphine). Dispensers must check for all new patients, early refills, cash payments and individual has prescription drug coverage on file, multiple prescribers	No ID requirement	Yes
Virginia	2003	Sched 2-5, naloxone (gabapentin is Sched 5 in VA)	Daily/Next business day	P only	All opioids with treatment lasting >7 days, and every 3 months if ongoing treatment	No ID requirement	Yes

Washington	2011	Sched 2-5	Daily/Next business day	P and D	Not specified	No ID requirement	Yes
West Virginia	1995	Sched 2-5, opioid antagonists, gabapentin (gabapentin is Sched 5 in WV)	Daily/Next business day	P and D	Initial prescriptions for Sched 2, opioids and benzodiazepines, and at least annually if continuing	ID of patient and person picking up prescription	Yes
Wisconsin	2013	Sched 2-5 (mandated gabapentin reporting under consideration in WI)	Daily/Next business day	P only	All monitored drugs with supply >3 days	ID of patient and person picking up prescription	Yes
Wyoming	2004	Sched 2-5, gabapentin	Daily/Next business day	P only	Initial prescriptions and every 3 months if continuing	ID of patient only	Yes

6.3 Review of international RTPM/PDMP experience and relevance to local systems

Introduction

The presence of RTPM/PDMPs has expanded rapidly in recent years, but literature directly examining the effectiveness and impacts of these monitoring programs have been scarce and variable. Furthermore, existing research on RTPM/PDMP implementations have exhibited mixed evidence about their strengths and weaknesses, effectiveness and specific intended and unintended impacts to clinical practice and outcomes. Given the significant paucity of local and national studies critically examining the impacts of RTPM programs in Australia, in particular from the other states and territories in Australia in the context of inconsistent implementation and harmonisation across the country, much can be learnt from a review of the precedents, lessons and experience from international RTPM/PDMP programs.

Impacts of PDMP implementation on prescribing/dispensing practices and reducing medication harms

Many of current studies assessing the impact of RTPM/PDMP predominately come from international experience, especially from the United States. The majority of studies that investigated the effects of RTPM/PDMP implementation focus around its impact on two main themes: changes to prescribing/dispensing practices and rates and changes to measures of harm. Most current studies on international RTPM/PDMP focus on the broad impacts of these monitoring systems or examined the effects on opioid use more generally, without reporting specific data for tramadol, or for gabapentinoids specifically. The intention of this section of the report is to summarise key findings for recent RTPM/PDMP studies.

It should be noted that many of the early studies examined outcomes regardless of the characteristics or robustness of the individual PDMPs in different states, and so neglected to differentiate those which were passive and not necessarily widely used, from those that were proactive in providing alerts, requiring mandatory use, and rapid or real-time. These latter characteristics have been shown to improve system effectiveness (2017 report, p127)(76-78).

Studies from the United States have demonstrated the impact of PDMP use on reducing problematic opioid prescription patterns. One study showed in New York State's PDMP mandate was associated with reduced measures of potentially problematic multiple prescriber and pharmacy episodes(79). Although this study analysed all Schedule II-IV opioid analgesic prescriptions, which would include tramadol, specific data on tramadol was not presented. The authors noted that their data only assessed patterns of filled prescriptions and did not look at patient outcomes such as opioid misuse or harms. PDMP implementation leading to a reduction in high-dose opioid prescription and overlapping opioid prescription days was also reported in another recent study from Colorado, USA(80). Additionally, that study also demonstrated that PDMP use significantly decreased overlapping opioid and benzodiazepine prescription days.

Extending on this, Winstanley et al. have reported mandated PDMP used in Ohio was an effective regulatory strategy in reducing the quantity of opioids and benzodiazepines dispensed(81). No harms reduction data was reported from that study.

Similar results were also reported in another recent study by Castillo-Carniglia et al. in California (USA), where proactive and mandatory PDMP resulted in a reduction in patients' mean daily opioid prescription dosage, and mean number of patients prescribed high-dose opioids and prescribers' mean daily dosage prescribed(82). However, the PDMP did not change rates of opioid prescribing and other high-risk prescribing patterns such as percentage of

days with overlapping prescriptions for opioids and benzodiazepines Tramadol was one of the opioids included as part of the overall analyses but specific data on tramadol was not reported. Mandatory use of PDMP in Kentucky and Ohio was also shown to reduce multiple provider episode rate, rates of opioid prescribing and of overlapping opioid prescriptions, as well as rate of overlapping opioid/benzodiazepine prescriptions(83). Additionally, comprehensive PDMP mandates in the US have been shown to be associated with reduced opioid prescription rates, opioid-related hospital events, opioid-related inpatient stay, opioid-related emergency department (ED) visit rates; thus resulting in savings of up to USD$155 million in Medicaid spending(84, 85).

A study using the 2004-2014 National Survey of Drug Use and Health (NSDUH) data from the USA reported PDMP implementation (both mandatory or otherwise) was associated with a reduction in receipt of pain relievers for non-medical use from multiple doctors, as well as a reduction in the odds of having a fake prescription or more than two doctors as a source of non-medical prescription analgesics(86). However, the study found no effect of PDMP status on various measures of non-medical prescription opioid use, such as abuse, dependence, and initiation.

Conversely, a systematic review reported that that PDMP has demonstrated advantages as the cornerstone in combating the abuse and misuse of scheduled drugs, as well as for monitoring substance abuse, reducing unnecessary prescribing, and reducing patients using multiple prescribers(87). These, in turn, has assisted in mitigating opioid misuse and help to reduce drug-poisoning deaths. Furthermore, PDMP implementation has reportedly increased healthcare practitioner work efficiencies by reducing the erroneous prescription of controlled drug, reducing errors or overuse of controlled drugs, and increasing the level of transparency in the records of a person using scheduled drugs.

The association between PDMP and drug overdoses was investigated in a systematic review(88). This review did not specifically assess tramadol or gabapentinoid use. The review reported only low-strength evidence associating PDMP implementation with a reduction in fatal overdoses; an association between PDMP implementation and nonfatal overdoses was less clear. Additionally, the authors concluded that mandatory PDMP use, frequency of reports and monitoring of non-scheduled drugs were also associated with a decrease in overdose deaths. The authors also contend that evidence that PDMP implementation either increases or decreases nonfatal or fatal overdoses is largely insufficient, but this would appear to be dependent on PDMP characteristics.

Benefits for PDMP implementation from the international experience extend beyond direct reductions in measures of prescriptions and harms. A mixed methods systematic review reported that implementation and use of PDMP can also positively influence healthcare providers' clinical decision-making by encouraging prescribers to adopting risk mitigation strategies (which helps facilitate better communication, discussions, and treatment agreements), encouraging better education and counselling for patients, as well as facilitating better care-coordination and communication with other clinicians & more efficient referrals(89).

Other studies identified that variations in the law between states, and lack of a coordinated and unified approach may have potentially influenced the effectiveness of PDMPs between states(83, 90). This would suggest that consistency and harmonization between states/territories is of importance to RTPM/PDMP implementation and are challenges that need to be overcome. A qualitative study identified a key to success in PDMP implementation lies in having a champion leading the process, providing ongoing education and feedback to PDMP users, as well as having inclusive stakeholder engagement(90). These are indeed relevant lessons for Australia also when making changes to our RTPM processes.

Impacts of PDMP implementation on opioid harms

As introduced above, the current literature on the international experience on RTPM/PDMP implementation presents mixed results on the effect of PDMPs on different measures of prescribing patterns and harms. In a retrospective cohort study of Oregon's (USA) PDMP use and opioid prescribing trends and overdose events, it was shown that although opioid prescribing declined statewide after PDMP implementation, PDMP use did not subsequently lead to fewer patients receiving high-dose prescriptions, overlapping opioid and benzodiazepine prescriptions, inappropriate prescriptions, prescriptions from multiple prescribers, or overdose events(91). However, patients of frequent PDMP users experienced significantly fewer opioid-related hospitalizations.

A systematic review looking at studies from US states reported variable and conflicting evidence of PDMP status and opioid related outcomes(92). Although tramadol was not specifically assessed, the authors concluded only limited evidence to support the overall associations between PDMPs in decreasing opioid-related consequences, but did back the role of PDMPs in improving opioid prescribing. In another systematic review looking at interventions such as PDMPs on opioid use and harms in the US and Canada, Ansari et al. reported although PDMPs are promising, there is little consensus on the effectiveness of PDMP, as shown by mixed results regarding its effects on opioid prescribing, opioid use and harms despite PDMP implementation(93). PDMP effects were stronger in regions where PDMP use was mandatory, with varying effect sizes. This is similar to another review where there was limited but inconsistent evidence that PDMP (in the US and Canada) reduced Schedule II opioid prescribing and dispensing, as well as multiple provider use(94). Taken together, Ansari et al. have concluded that effectiveness of interventions such as PDMP largely depends on its robustness and associated policy design(93).

Finally, it is of interest to note that in 2019, Lachance & Frey from the Canadian Agency for Drugs and Technologies in Health (CADTH) prepared a report specifically summarising the clinical evidence regarding the safety of prescription monitoring programs for optimising medication use and preventing harm, and evidence-based guidelines informing the use of such programs, in a bid to aid provinces and territories within Canada in deciding whether to commence, continue, and/or expand their prescription monitoring programs(95). Although that report did not specifically look at tramadol or gabapentinoids, the authors concluded that no relevant clinical evidence describing the safety of prescription monitoring programs for optimising medication use and preventing harm were identified. Furthermore, they also highlighted that it is unclear how generalisable the recommendations of the included publications are to the Canadian population or to the Canadian healthcare system as they were all conducted and/or produced in the United States. It was also noted that one of the major limitations was the paucity of evidence derived from the Canadian population and Canadian prescription monitoring programs, thus limiting the conclusion and lessons that can be made. It stands to reason that similar caveats will be required in interpreting such arguments in the Australian context.

International PDMP/RTPM experience and tramadol

There have been limited studies directly investigating the specific impacts of PDMP/RTPM implementation on tramadol prescribing, use and harms. The majority of studies investigated prescribing trends rather than direct measures of harms. The following section provides a summary of recent studies from the literature where specific data for RTPM/PDMP and its potential impacts on tramadol was clearly reported.

Although not as recent, Surratt et al. investigated the impact of their PDMP on opioid abuse and diversion in Florida (USA)(96). Although the study documented reductions in statewide opioid diversion rates following implementation of Florida's PDMP, there were no declines in

tramadol diversion rates during the study period. No other specific measures of harms were reported in this study.

In a recent retrospective cohort study of Massachusetts' mandatory PDMP check on opioid prescribing (including tramadol) from an urban tertiary emergency department, it was reported that mandated PDMP checks resulted in an immediate decrease in opioid prescribing (including tramadol). However the PDMP mandate did not change the rate of decline and the drop in opioid prescribing was not sustained(97).

Fulton-Kehoe et al. also investigated the potential impact on opioid prescribing trends in Washington State with the addition of tramadol to the PDMP in 2014(98). Although the study did not specifically report the influence PDMP had on tramadol prescribing explicitly, the study demonstrated that the addition of tramadol to the PMDP did not increase overall opioid prescribing trends but did affect the observed prevalence of all opioid metrics and of all opioid-prescribing trends. The study also found the prevalence of chronic opioids also appeared to increase substantially in 2014 with the addition of tramadol to the PDMP, as well as the prevalence of concurrent prescribing of opioids and sedatives. Fulton-Kehoe et al's study suggests that if tramadol is added to an RTPM system such as Victoria's SafeScript, care needs to be exercised when interpreting trends, prescribing metrics, and prevalence of opioid metrics.

International PDMP/RTPM experience and gabapentinoids

Similar to tramadol, there are also limited studies directly investigating the specific impact PDMP/RTPM implementation on gabapentinoid prescribing and harms. The following section provides a summary of recent studies from the literature where specific data for RTPM/PDMP and its potential impacts on gabapentinoids was clearly reported.

Pregabalin and gabapentin misuse and abuse is widespread in France(34). As a result, these drugs have received attention from the French Addictovigilance Network in recent years; however it should be noted that this is a reporting system for medication-related adverse events, and is not a RTPM/PDMP system. The authors reported how gabapentinoid addictovigilance data helped to make visible gabapentinoid related harms, and how they are used in the context of abuse. Although this study did not assess real-time prescription monitoring of gabapentinoids, the authors highlighted the importance of specific monitoring on substance use related disorders and the gabapentinoid misuse behaviours in a bid to monitor this in their country.

A further study assessed gabapentin dispensing patterns and potential misuse using data from the PDMP of Ohio, USA(99). Gabapentin was mandated to be reported to Ohio's PDMP as of December 1, 2016, despite not yet classified by the US federal government as a controlled substance across all states. Results from the study when gabapentin PDMP reporting was in place showed no evidence of gabapentin misuse. However, supratherapeutic dosing of gabapentin was observed, and half of the individuals were co-dispensed gabapentin and opioids, with supratherapeutic dosing being associated with those with opioid use disorder. The authors concluded that further studies are needed to explore the impact of PDMP implementation on gabapentin dispensing.

PDMP implementation and tighter opioid legislation has also been shown to indirectly impact gabapentin exposures through drug substitution effects. This was demonstrated in a study using poison control center data in Kentucky(100). The study reported an increase in gabapentin exposures (with the majority of cases intentional ingestions, specifically suspected suicide or self-harm intent, followed by misuse/abuse) coinciding with Kentucky's implementation of prescription opioid reform legislation and PDMP requirements for opioids. This study implies the possibility that stricter opioid restrictions have led to an increase in

gabapentin use as an alternative to opioids. Interestingly, the authors have also indicated Kentucky has since become the first state to schedule gabapentin in an effort to capture and analyse all associated prescribing information and to efficiently detect such trends.

International experience with tramadol regulation and monitoring

It is well recognised that opioid abuse and misuse are major public health issues and are documented to be responsible for increasing numbers of overdoses and fatalities worldwide. An expanding epidemic of both prescription and illicit opioid overdoses is currently being observed across many countries such as the United States of America (USA), United Kingdom (UK) and Canada. Of particular interest for the purpose of this report is tramadol.

Tramadol is a synthetic weak opioid analgesic with serotonergic effects. Its utilisation escalated rapidly globally in the early 2010s. In 2020, tramadol was available in 40 countries around the world including Australia, Canada, China, India, Japan, Russia, the USA, France, Germany, Switzerland and the UK(101). In Australia, tramadol currently remains as one of only two Schedule 4 opioids, together with codeine. Within the different states and territories in Australia, there is variability with monitoring requirements for tramadol, as well as different RTPM systems currently in place.

A brief review of tramadol's global monitoring and regulations are important to review the current status of tramadol internationally. A direct comparison of tramadol regulations, restrictions and prescription practices are more difficult due to the diversity of regulatory systems in force.

Tramadol regulation and monitoring in the USA

In 2014, the US Drug Enforcement Administration (DEA) changed the status of tramadol from an unscheduled to a scheduled medication. Currently, tramadol is a controlled substance (Schedule IV) according to the USA *Controlled Substances Act*. Due to this classification, it is a requirement that tramadol is monitored by all US PDMPs, particularly due to the well documented opioid epidemic in the USA. However, as discussed elsewhere in this report, there is variability between the different US states regarding their tramadol monitoring expectations and requirements, and studies directly assessing the impacts of PDMP monitoring on tramadol in the US and its associated harms reduction is scarce and the available evidence has been mixed.

Tramadol regulation and monitoring in the UK

In the UK, the *Misuse of Drugs Act 1971* and the *Misuse of Drugs Regulations 2001* were amended on 10 June 2014 to reclassify certain drugs, including tramadol. As a result, tramadol has been classified as a Schedule 3 controlled drug due to increasing recognition of its risk of harms. Specifically, in the UK, tramadol is a Class C controlled drug, which is schedule 3 under the *Misuse of Drugs Act 1971 (Ketamine etc.) (Amendment) Order 2014*. Thus, since 2014, tramadol has been subject to controlled drugs legislation and special prescription requirements for controlled drugs, but not safe custody or register records requirements(102, 103).

A recent paper that reported on two tramadol deaths case studies has reinforced that the UK coroners' repeated warnings of the dangers of tramadol, in particular of repeat prescriptions for tramadol(102). Further, it has been noted that there has been increasing fatal suspected adverse drug reactions to tramadol being reported over the last 7 years. This has led to calls to administer better evidence-based solutions, including the need to improve the repeat prescribing systems, and implement more timely monitoring systems in general.

Tramadol regulation and monitoring in Canada

There have also been many recent developments with the regulation of tramadol in Canada. It is recognised that the crisis of overdoses and deaths caused by opioids is of national concern in Canada, and as such, much attention has been placed on reviewing their use and evidence of harms in recent years, in particular on tramadol.

Tramadol has been marketed in Canada since 2005. It is regulated under the *Food and Drugs Act* (FDA) and is available by prescription only. Unlike most opioid analgesics, tramadol was not controlled under the *Controlled Drugs and Substances Act* (CDSA) or regulated under the *Narcotic Control Regulations* (NCR) previously. Due to its problematic use and harms and recent evidence, the Canadian government has proposed to put tighter restrictions on tramadol regulations(104).

As a result, following extensive consultations from 2019-2020, in 2021, a proposal by the Canadian Government has been put forward to amend regulations to Schedule I to the *Controlled Drugs and Substances Act* and the Schedule to the *Narcotic Control Regulations* to add tramadol(105). Controlling tramadol under the CDSA would align Canadian regulations with jurisdictions such as US and UK. Furthermore, the Department website also stated that changing the restrictions will make it subject to the same regulatory requirements already in place for other opioid analgesics in Canada, and therefore would strengthen surveillance of tramadol prescribing practices(105). On March 31, 2021, Health Canada confirmed a change in scheduling on March 31, 2022(104).

Various Canadian provinces have comprehensive prescription monitoring or prescription review programs. As identified in the Austin Health 2019 literature review, there are at least eight active PDMPs in Canada including the Provinces/Territories of Alberta and Yukon, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island and Saskatchewan. Federal legislation identifies controlled drugs and their precursors through Schedules 1-5, outlined in the *Controlled Drugs and Substances Act*, with each Province and Territory having a State-determined list of drugs requiring monitoring. Currently, tramadol is monitored by at least PDMPs of three Canadian provinces. We have been unable to locate additional information, updates or more recent publications relating to their PDMP since that last literature review. However, given the future addition of tramadol to schedule 1, it is likely that stricter monitoring requirements will be implemented also as part of this change.

6.4 Unintended consequences of RTPM/PDMP

Introduction

While the intention of RTPM/PDMP programs is to have positive impacts on health outcomes, it is also critical to identify and consider potential unintended consequences of RTPM/PDMP programs, both positive and negative. Although it is generally agreed that RTPM/PDMP systems are important clinical tools, it is recognised that it is possible for RTPM/PDMP systems to trigger a number of unintended consequences(88) that should be considered when assessing the true impact of RTPM/PDMP programs. If the unintended risks of RTPM/PDMP can be identified and addressed, this will allow for opportunities to maximise the benefits of these systems.

Although studies that directly measure actual or perceived potential unintended consequences are limited, evidence is emerging and a number of common themes and insights can be drawn from several recent systematic reviews and exploratory qualitative studies. Findings on unintended consequences of RTPM/PDMP have been mixed, and sometimes with contradictory results, and just as some have suggested positive benefits of RTPM/PDMPs might be due to other factors, unintended consequences should be viewed through the same lens.

Nevertheless, it is the intention of this section of the report to summarise some of these key reported findings, with the knowledge that these have not yet been systematically evaluated. If harmonisation between jurisdictions is a consideration, it warrants consideration as to what evaluation has occurred so far.

It is important to note that there is limited local data assessing the unintended consequences of Australian RTPM programs, largely due to the different status of RTPM implementation programs. RTPMs are also not yet mandatory across all jurisdictions, nor is there a consistent harmonised approach to inclusions to monitored medicines or the RTPM program/software utilised. This lack of local data is a major limitation drawing conclusions to inform the optimisation of Victoria's SafeScript RTPM, including the pros and cons of adding tramadol and/or gabapentinoids to the monitored medicines list.

Therefore, a review of potential unintended consequences of RTPM predominately comes from international experience, especially from the United States of America (USA). It is important to highlight that many of the suggested unintended consequences stem from the use of RTPM/PDMP programs more broadly, rather than specifically in relation to tramadol or gabapentinoids for the context of this report. Additionally, it should be noted that most studies assessed the impact of RTPM/PDMP programs on opioids, rather than on tramadol specifically, thus limiting the direct conclusions that can be made with the potential inclusion of tramadol to RTPM/PDMP programs. Finally, as previously emphasised, it is not merely the characteristics of any program that is important, but the context in which they are held and maintained.

Furthermore, it should also be highlighted that most of the RTPM/PDMP research has predominately focused on opioids, with significantly fewer studies investigating gabapentinoids and RTPM/PDMP. Given that opioids are already listed on SafeScript apart from tramadol, international lessons on the unintended consequences of inclusion of tramadol and/or gabapentinoids to the RTPM needs to be taken into context and its clinical significance critically considered.

Many of the lessons that can be drawn regarding the unintended consequences of RTPM/PDMP comes from qualitative research studies, which have been proposed by some to provide substantial insights and a more holistic assessment of RTPM/PDMP programs(106).

We feel that SafeScript has and continues to show a dedication to transparently adapting its system on the basis of data that many other programs have not demonstrated. However, there is a collective agreement that more research would be useful in answering this question, and that there is a current lack of data, as well as a lack of rigorous evaluations of RTPM/PDMP programs internationally to inform lessons on its potential impacts/unintended consequences.

Increased use and harms from illicit substances

One unintended consequence of RTPM programs is the increased use and harms for patients accessing illicit substances as a substitute to monitored medicines restricted under RTPM/PDMPs, noting that heroin overdose deaths reported to the Coroner since the implementation of SafeScript have decreased(61).

Several recent studies in the US have suggested an actual increase as well as perceived potential increases in illicit heroin or opioids or stimulant use as a result of tighter RTPM/PDMP implementation(93, 107-110). More stringent state PDMPs are associated with higher rates of heroin-related deaths, potentially due to decreases in prescription opioid availability(88, 110). Experience with stakeholders across three US states (Connecticut, Kentucky, and Wisconsin) also supported this view and noted an increase in heroin use as prescription drugs became harder to obtain due to PDMPs(107). In qualitative interviews, it has been suggested that restricting access to prescription opioids due to PDMP reports may lead to patients substituting heroin or other synthetic opioids such as fentanyl for their previously prescribed opioids(109). It should be noted that these conclusions are in the context of opioids more broadly rather than specifically tramadol, and that features in SafeScript and introduced in the Victorian system in general(111) are likely to at least partially mitigate any such effect.

In contrast, a study examining the impact of their PDMP using the 2004-2014 National Survey of Drug Use and Health (NSDUH) data from the USA reported PDMP use was not associated with an increase in heroin use or initiation, but was associated with an increase in number of days of heroin use in the past year(86). A few studies showing statistically non-significant decrease in heroin overdoses from PDMP implementation were also identified in a systematic review(88).

Given all opioids except tramadol are already currently listed on Victoria's RTPM program SafeScript, the concerns regarding the significance of substitution into illicit substances should tramadol and/or gabapentinoids be included as monitor substances is unclear. This is perhaps less likely to be of major significance but there are no local data to support this assertion.

Reduced access to care or refusal of treatment

Another significant negative unintended consequence identified in the literature is the impact of RTPM/PDMP monitoring as an access barrier for those with legitimate medical need for monitored medicines, thus leading to refusal to prescribe or treat, including abruptly stopping an opioid prescription or prescribing less restricted medications which may not be as appropriate(89). Furthermore, it has been suggested that perceived scrutiny from the RTPM/PDMP systems has resulted in some prescribers' and pharmacists' refusing to supply potentially high-risk medications despite appropriate clinical indication(106, 112), although there are no quantitative local data that speak to this being problematic in the Australian context.

In a study in the US, experience from the studied states with PDMP have identified prescriber's reluctance to prescribe opioids even when appropriate, resulting in under-prescribing and undertreatment of pain(107). Pain is of particular interest given its context for opioid analgesics included in RTPM/PDMP monitoring, as well as the implications of potential inclusion of tramadol and/or gabapentinoids and their significant roles in chronic pain management and the potential for reliance on these classes of medicines.

It has also been suggested that providers may use PDMP data to refuse treating patients, thus compromising healthcare access and leading to the "dumping" of patients, or not ensuring that they are appropriately followed up or transferred to other more appropriate care(107, 109). Furthermore, this study also reported the opinion that the PDMP and new opioid prescribing recommendations have become a reason for doctors to avoid treating problematic patients while also avoiding being marked as someone who prescribes excessive amounts of opioids(107). A similar theme was reported in a mixed methods systematic review and meta-analysis, where PDMP use can affect clinical decision-making and clinical care by influencing a healthcare provider's refusal to prescribe, treat or supply(89). Taken together this may result in a "chilling effect", whereby prescribers may become reluctant to prescribe monitored medicines. It should be noted that this is specifically a consideration articulated as criteria for consideration for SafeScript, and remains an important consideration particularly for tramadol.

One study, whose results so far only reported briefly as correspondence but whose baseline characteristics have recently been published(113), assessed the impact of SafeScript in a cohort of people who inject drugs, examining self-reporting of prescription access(73). In that study, Fetene et al. reported implementation of SafeScript led to refusal of prescriptions monitored by SafeScript, as well as withdrawal of prescriptions the patient already received, or refused dispensing of a prescribed medicine by a pharmacist. The authors highlighted that this has suggested there may be unmet treatment needs in patients denied prescriptions, citing risk of anxiety and depression in these patients and the fact that many of them report an intention not to seek medication from their doctors in the future. However, it is also worth noting that such changes to a patient's treatment may indeed be justified and appropriate and perhaps was in fact aided by SafeScript providing a clinical decision support system for prescribers and pharmacists to identify patients at risk(111).

It stands to reason that further, ongoing evaluation of SafeScript is justified, and in keeping with what Fetene et al. suggest, careful implementation is necessary, and caution should be taken to ensure those who are at risk of the 'chilling' effect do not suffer from unintended consequences of listing either tramadol or gabapentinoids.

Risk of stigmatisation

Another theme arising from the literature regarding potential unintended outcome of RTPM/PDMP systems is the increased risk of stigma or stigmatizing behaviours, for both patients and prescribers.

It has been suggested that PDMP has the potential to increase patient stigma or even influence prescriber attitudes and clinical decision making(89, 106, 114). This is significant and has the potential to affect clinical outcomes(89, 106). Experience from the US has shown that scrutinising RTPM/PDMP information can actually result in both increases and decreases in stigmatising clinical responses(89). In the context of a patient, PDMP patient histories may be stigmatising and may result in the non-treatment of a patient, even in legitimate and clinically appropriate cases. Other qualitative studies have supported these findings by highlighting the important need to recognise the unintended impact of PDMP in patient stigma, including the potential for prejudicial clinical decision-making based on clinicians' negative attitudes towards people identified by the system as 'high risk'(112). There also remains a risk that PDMP patient histories could also inadvertently be stigmatising leading to a situation whereby clinically permissible actions would incorrectly appear suspicious(89).

Additionally, it is possible that RTPM/PDMP information may result in prescriber stigmatisation(112); for example, without sufficient information or context to the reason for high or frequent opioid prescribing (e.g. clinical reasoning is not recorded in current RTPM/PDMP systems), RTPM/PDMP information may result in stigma or negative perceptions of higher prescribers, thus placing appropriate prescribers at risk of unfair judgement.

These factors are likely to be a consideration for patients and prescribers in general and are unlikely to be specific to gabapentinoids and tramadol. Having said this, any inclusion of these medications will increase the number of patients who might be subject to this.

Substitution to alternative medications

Although substitution to an alternative drug is another possible consequence of any pharmaceutical policy intervention, the data surrounding this as a consequence of RTPM/PDMPs is still evolving.

An example of this type of unintended consequence was demonstrated in a study which investigated gabapentin exposures using poison control center data in Kentucky(100). Specifically, that study reported an increase in gabapentin exposures coinciding with Kentucky's implementation of prescription opioid reform legislation, including the use of the state PDMP for all opioids. This suggest that prescribers could be using gabapentin as an alternative to strong opioids. In the context of SafeScript, monitoring of opioids, without the inclusion of gabapentinoids, theoretically has the potential to lead to substitution of gabapentinoids as an alternative to opioids, although this does not appear to have been the case as yet.

Another example of this effect was reported in a recent Saudi Arabian study where implementation of a regulation to restrict the use of pregabalin resulted in a decrease in the overall use of pregabalin but also led to a direct and temporarily increase in the use of gabapentin(115). The authors also reported that this restriction did not result in a worsening of conditions among patients treated with pregabalin and had not been associated with an increased use of tramadol as an alternative.

One study reported an increase in lower scheduled opioids, possibly as a consequence of PDMP(116); this is arguably a desired effect. Although the study was not explicitly examining the substitution of tramadol, this 2018 US study reported PDMP has led to a small increase in

prescribing for lower scheduled opioids (such as Schedule IV opioids which includes tramadol) as a substitute for higher-profile opioids such as oxycodone. Despite an increase in these lower scheduled opioids, PDMPs were not associated with changes for non-opioid analgesics or other opioids in Schedules II and III, thus indicating minimal substitution in that respect. Given that tramadol is the only opioid not yet listed in SafeScript, the potential for reverse substitution to other, possibly more potent, opioids if tramadol was included as a monitored medicine is unclear but warrants consideration.

Encourage using multiple prescribers across state lines

A review on curbing gabapentin misuse in the US has highlighted that PDMPs may result in unintentional harm by encouraging multiple prescribers across state lines to states where there are more lenient regulatory policies(117). Specifically, gabapentin was used as an example to illustrate this concept, given the current variable classification and mandatory reporting differences of gabapentin across different states in the US.

The authors identified that it is possible that actions taken by one state may negatively affect neighboring jurisdictions with no restrictions, as the health system may experience the effects of seeking multiple prescribers or an influx of patients in search of a more lenient policy, thus adding additional humanistic and economic costs(117, 118).

Similar activity has been anecdotally reported in Australia. However, it should also be noted that no specific studies that provided evidence investigating this type of practice or documenting its occurrence could be currently found in the literature. Nevertheless, such practice could inadvertently take place here in Australia if there is an absence of a unified approach among states and territories to listing drugs that should be monitored by RTPM systems.

Chapter 7. Informal scoping of the impacts of inclusion of gabapentinoids and tramadol on SafeScript

7.1 Introduction and methodology

A brief informal consultation process was undertaken to gain a working understanding of the themes of potential impacts of inclusion of gabapentinoids and tramadol on SafeScript on both health care providers and patients. To this end, this exercise was not intended to be definitive, but rather to inform the discussion within this edition of the report.

Relevant organisations, representing both those affected most directly by the implementation and also utilisation, were identified and invited to participate via email. A nominated representative from those organisations that responded then completed a semi-structured recorded interview using Microsoft Teams.

The following organisations were contacted and invited to participate in the informal scoping process:

- Australian Medical Association (AMA) Victoria
- The Royal Australian College of General Practitioners (RACGP) Victoria
- The Royal Australasian College of Physicians Chapter of Addiction Medicine (RACP AChAM) Victorian/Tasmanian Branch
- Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (FPM ANZCA) Victorian Regional Committee
- Australian and New Zealand Association of Neurologists (ANZAN)
- Rural Doctors Association of Victoria (RDAV)
- Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- Toxicology and Poisons Network Australasia (TAPNA)
- Australasian College of Emergency Medicine (ACEM) Victoria Faculty
- Victorian Addiction Inter-Hospital Liaison Association (VAILA)
- Pharmaceutical Society of Australia (PSA) Victoria
- Pharmacy Guild of Australia Victoria Branch
- The Society of Hospital Pharmacists of Australia (SHPA) Victorian Branch
- Victorian Poisons Information Centre (VPIC)
- Medical Software Industry Association (MSIA)
- ScriptWise
- Burnet Institute

Given the need for these consultations to be shaped by results from previous components of the report, requests for interviews were made during a challenging period of time in Victoria, with relatively short notice. This informal scoping exercise may therefore not be entirely inclusive of a full spectrum of view, including a complete capture of possible negative unintended consequences, and any formal regulatory impact assessment would need to determine this more fully. We apologise for any voices which might otherwise not be fully heard.

To allow capture of these consultations and their themes without contamination from data analysis or detailed review of the literature, the semi-structured interviews were performed by a separate author (AK). While the questions were developed on the basis of the findings of the rest of the report, they therefore stand without direct reference to the data and analysis presented in other sections of the report.

7.2 Interview outcomes and key themes

Of the organisations contacted, six representatives were interviewed:

- AMA Victoria (Dr Roderick McRae, President),
- TAPNA (Dr Zeff Koutsogiannis),
- VAILA (Dr Martyn Lloyd-Jones),
- PSA Victoria (John Jackson, President),
- Pharmacy Guild of Australia Victoria Branch (Angelo Pricolo),
- VPIC (Nicole O'Shea).

Impact on Patients and Patient Care

The considerations of the impact on patients and their care as a result of the addition of gabapentinoids and tramadol to SafeScript is complex. Clinicians recognise that the use of these medications, especially in combination with other medications, places patients at risk of interactions and additive sedative effects. However, the balance of the desire to improve appropriate rational prescribing to reduce harm associated with misuse is countered by the potential barriers associated with extra regulation.

Effective education and supports need to be in place to ensure this intention of harm reduction does not lead clinicians to compromise patient care by refusing to continue to prescribe or supply these medications for legitimate clinical indications.

"Generally, patients find it challenging for there to be more steps of regulation placed between their clinical need and their doctor's capacity. So from a patient perspective, I'm not sure that they would be keen for it to be included, either of these drugs. If you think of patient care from a clinician's point of view, where I think there's great concern, and this is the thing that undermines the use of SafeScript for these drugs and any other drugs that are already in there is what is classically called the 'chilling effect'. The idea that clinicians get worried about their responsibility in patient care, rather than the patient's actual situation. And listing drugs on SafeScript does lead to some clinicians running scared, refusing to supply and not necessarily providing adequate alternative therapies or withdrawal support services." – John Jackson, PSA Victoria

"There is one caveat, and it applies to any of the drugs listed on SafeScript, that some GPs are so concerned about getting into trouble, that they will avoid prescribing and avoid prescribing to patients who are identified on SafeScript and that, I think, is a problem. So that comes around education, and it comes around how we provide guidance to people who are prescribers. So, there is that risk which exists for all the agents currently listed by SafeScript and any others that could end up on SafeScript, that some doctors will just go, 'I can't prescribe that to you anymore or I'm not prescribing to you because I can see you've been using substance X and therefore, I'll get into trouble if I do', which is not the case. But unfortunately, sometimes it's perceived to be the case." – Dr Martyn Lloyd-Jones, VAILA

"There would be some time implications… The only thing in the back of my mind is that gabapentin could be for epilepsy. I would hate to affect someone's epilepsy control because we've added gabapentin to this list and then they lost their script, and they couldn't get more somehow." – Nicole O'Shea, VPIC

"Some patients will be quite annoyed… because it's designed to facilitate them not accidentally overdosing or letting it get into the streets. A good ambition." – Dr Roderick McRae, AMA Victoria

"I don't think the patient will be disadvantaged. Apart from they may not be able to access pregabalin when they shouldn't be accessing pregabalin, if they're seeking to use it in a non-medical or recreational way. As a clinician, when I look up SafeScript, it's nice to know if someone is on diazepam, oxycodone, and pregabalin, that that will ring alarm bells to me that that patient will be at risk of increasing sedation and they're that type of patient that is likely to use it in a non-medical way." – Dr Zeff Koutsogiannis, TAPNA

"I don't see it as being any different from the drugs that are already included on SafeScript." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

"When patients are being prescribed potent agents, whether its benzodiazepines or opioids, if you don't know what other potent or sedative or other agents that may interact with the ones that you're using, the risk to the patient is significant. Quite apart from not actually knowing what you're dealing with. So, there would be a benefit to patient care." – Dr Martyn Lloyd-Jones, VAILA

"In terms of the difference between the gabapentinoids and tramadol, there are definitely a smaller number of cases of tramadol use that are excessive. A lot of tramadol use, I think, is within clinical bounds. (With) gabapentinoids there definitely does seem to be a lot more widespread excessive use I think. I think the gabapentinoids need a high level of clinical consideration and judgment. And I don't think that's necessarily always applied. Is safe script the answer to that? I think it's a very blunt instrument for a delicate situation." – John Jackson, PSA Victoria

Identification of Patients at Risk of Harm From Medication Misuse

Identifying patients prone to medication misuse and associated harm from overdose was a common positive outcome raised during the consultation process. While many of these patients may already be identified as a result of the medications that are already monitored on SafeScript, that does not necessarily mean that their additive risk that results from also taking gabapentinoids and or tramadol, is appropriately addressed. As this group of patients usually have complex health needs resulting from chronic pain, mental health issues and substance use disorders, being able to identify any additional risks can help to improve patient outcomes. There may also be a new group of patients, whose medication misuse may not previously have been identified and had previously slipped through the cracks of our healthcare system. This will provide opportunity for intervention to address their medication misuse.

The pharmacists interviewed appeared to be of the opinion that the group of patients that would be identified may be more significant than what was expressed by the doctors interviewed. This may be a result of the mandatory SafeScript use requirements for pharmacists working in all settings, compared with the different requirements currently in place for prescribers (i.e. the non-mandatory requirements for those working in hospital settings).

"You may find a different group of people just because it's quite a different group of drugs (gabapentinoids). I suspect you'd probably see more misuse then." – Nicole O'Shea, VPIC

"The whole point of this is that, I think, as pharmacists, we recognize that there are some people with drug use problems that are slipping through the cracks, and this isn't the main cohort, and that's probably why it wasn't included initially, but it definitely represents a group of people. We're well aware that it's pretty rare that just one drug is responsible for a fatal overdose, and these two groups of drugs, tramadol and the gabapentinoids, are over-represented in overdoses. Even though that may not be the single drug involved. And so, what this is going to do is more often pick up instances where at risk people will be highlighted. I

think that this is just another drug which is going to lower the threshold for overdose, so if we can pick it up more often, then there's more chances to intervene." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

"Particularly with pregabalin, because it's so widely prescribed and widely prescribed not for it's appropriate indication." – Dr Martyn Lloyd-Jones, VAILA

"This identifies the patient at risk of the drug that's being checked, the gabapentinoid or the tramadol potentially. Those patients might have already been detected at risk from a benzo or opioid and that risk managed, but it doesn't mean that the risk associated with concurrent use of the gabapentinoid has been managed. So you know that this will expand the likelihood or risk of harm being detected." – John Jackson, PSA Victoria

"I think the return will be low because those patients who are likely to get these (gabapentinoids and tramadol) are also likely to be on everything there. So I don't know that we're going to identify that many other people, because they're probably already identified, but we won't be able to identify the consumption of the medications themselves." – Dr Roderick McRae, AMA Victoria

"It's hard to know, because the people that are at risk are also the people that are on benzodiazepines and opioids and this (pregabalin) is just another drug that can make them sedated. The deaths are small numbers, but they are increasing in the last ten years. If we're looking at a population of people that have got chronic pain, mental health issues, substance use disorder and injecting drug users or recreational drug users, then pregabalin should be on that list, because that's the population that we're going to be capturing I think." – Zeff Koutsogiannis, TAPNA

Clinician's Perspective on the Addition of Gabapentinoids and Tramadol

Clinicians recognise the clinical benefits of increased monitoring, with the primary emphasis largely on gabapentinoids, while more caution, including the possibility of unintended effects, was raised regarding tramadol. However, other factors may influence clinician's perspectives on the utility of the addition of these medications: concerns around integration with other systems and access challenges.

Importantly there is concern that, while SafeScript can identify at risk patients, a computer-generated process does not adequately address the clinical needs of these patients. It is important that there are also adequate supports available in the Victorian healthcare system to treat and address the clinical care of these patients. There is also the possibility that in adding these medications to SafeScript, that other medications may in turn be prescribed or used more frequently and this will have flow on effects for the health system. It can also be said that this has already occurred with pregabalin particularly, and this is one reason given to justify its inclusion on SafeScript.

Some interview participants also discussed the importance of national harmonisation between real time prescription monitoring programs and felt that this is also an important consideration when medications are being considered for addition to SafeScript.

"I think it would be regarded as tedious, but it's probably appropriate. So if you have tapentadol and the opiates and everything else, it's logical that they should be included." – Dr Roderick McRae, AMA Victoria

"I actually think that pharmacists are probably surprised that it (gabapentinoids) wasn't included in the first place." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

"Since its inception in 2005, and since coming on the PBS in 2013, we've seen an increasing prescription and use of pregabalin, a lot of it off label and if you look at some of the literature, in terms of people who've got chronic pain, substance use disorders, mental health disorders, they tend to be the ones that suffer the most with being on pregabalin because they mix their benzodiazepines with their opioids and there's a lot of non-accidental harm that occurs with that. And there's also from a toxicology point of view, anecdotally, we see a lot of intravenous drug use population that also use pregabalin as well. Either as a recreational, non-medical use, but also as a sort of a comedown drug type of thing. For pregabalin, there is also a dependence and a withdrawal aspect to it. So, people who are on large doses can have a withdrawal syndrome from it. So any drug that can give you a physical withdrawal should probably be on that list." – Dr Zeff Koutsogiannis, TAPNA

"From a clinical point of view, it would be better for there to be greater monitoring of the gabapentinoids. The advantage of greater clinical monitoring may well be undermined by some of the other concerns that some members have with SafeScript. The more we add drugs to this process, the more an automated computer-generated report is going to intervene in clinical care. And so, I'm not shy of having more drugs there, just as long as the system, the model has appropriate checks and balances and supports around it." – John Jackson, PSA Victoria

"I think for clinicians, it's essential, particularly those of us who work in the areas of addiction or chronic pain. All my colleagues in addiction medicine and certainly colleagues I work alongside in pain management, acute and chronic, are to some extent quite horrified about the fact that these drugs (gabapentinoids) are not included because we do see wide use of them and inappropriate prescribing and sometimes inappropriate use." – Dr Martyn Lloyd-Jones, VAILA

"Tramadol needs to be metabolised to get the opioid effects mainly and the enzymes in your liver that do that are the same enzymes in the liver that convert codeine to morphine. So there are people who don't metabolize it at all and don't get anything from it, but there are people who are ultra-metabolizers and get quite a substantial opioid effect from it. If tapentadol is included in it, I don't see why tramadol shouldn't be. It doesn't make sense at all to me." – Dr Zeff Koutsogiannis, TAPNA

"With the introduction of tapentadol, tramadol is perhaps less widely prescribed, but nonetheless, it's still a significant drug. I perceive tramadol is a drug that's less misused than pregabalin. That's probably because of the effect being slightly different. It obviously has opioid activity, but, it perhaps has slightly less sedative activity. I think one of the problems is that if some of these other agents are less prescribed or less used and then more people potentially might be exposed to tramadol and because it's perhaps not such a potent agent, they (people) might take more of it. We're then more likely to see other risks associated with that, and because it has a significant interaction with a number of other agents, I think it is important to include it.
I think one of the things we have to be aware of, which doesn't fit in with the way the statistics inform decision making, but when you make certain drugs, perhaps harder to obtain or harder to prescribe, there is a squeeze effect so that other substances become more prescribed and more easy to obtain. And we saw that with pregabalin. It's just so, I think, obvious to those of us who work in addiction and with patients who have problematic substance use that not including the substances that are open to misuse is problematic." – Dr Martyn Lloyd-Jones, VAILA

"What this would have to recognize is the risk that putting tramadol into SafeScript may well just create a diversion to the use of some of the other drugs that are now available in that class." – John Jackson, PSA Victoria

"We've now seen SafeScript roll into the other States. If there is going to be a computer enabled management program here, it should be universal across the country. I'd also argue that having had SafeScript now here in Victoria for a couple of years, rather than just going through a review process to see whether we add more drugs to it, we actually need to do a very detailed assessment as to whether this achieves its intended objectives at a cost to all that is acceptable." – John Jackson, PSA Victoria

Impact on Workflow

In terms of usage of the SafeScript program, interview participants believed the increase burden on their workflow would be marginal and the clinical benefits would outweigh this inconvenience. However, issues raised included the poor integration between other prescribing and dispensing systems in hospital settings, lack of renumeration and the flow on clinical consequences once an at-risk patient is identified.

"I think that now that the system is up and running, and we're all much more comfortable with it, I think that probably the biggest burden in the past for most pharmacists has, and most clinicians, I suppose, has been just the access to the program (and) the teething stuff around the authentication and getting through to the actual program. But I think that, the addition of a couple of drugs now is really just refining its use and overall, in the bigger scheme of things... I mean, obviously if you add more drugs, there are more times you're going to hit on it, but overall, I don't think that it's a big increase burden. But yes, obviously it has to be a percentage increase because there are more drugs to access." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

"You could say there will be a small additional burden, at the same time that can result in us saving, because if you know somebody is on other agents, it will mean that you're prescribing is hopefully more appropriate and better and potentially less problematic. So I think there are some small time costs, but I don't perceive in the scheme of things that should be perceived as a reason. I think the more information clinicians have, the better it is for their patients." – Dr Martyn Lloyd-Jones, VAILA

"The amount of opioids and benzodiazepines that are out there, I think the pregabalin scripts will pale into low numbers compared to those. So, if the clinician is happy to prescribe oxycodone and go through the SafeScript process, there's no reason why they can't do that for pregabalin, I would have thought." – Dr Zeff Koutsogiannis, TAPNA

"A lot of the hospitals have an electronic medical record which doesn't facilitate or integrate well with SafeScript. That would be the single biggest benefit. I've either got three screens in front of me, or I've got to log off one, come back on to the other, log back in to check. Is it prohibitive? Probably not. Will it be annoying? Mildly. To be honest, I'm not sure how many people routinely do it. Ultimately the issue for the Practitioner is busyness. So type, log on, check. I'm not getting paid for doing this. Now I've got to have this conversation that I'm not getting paid for and I don't want to have, so the wilful blindness comes in and someone else can worry about it." – Dr Roderick McRae, AMA Victoria

"I think because it's fairly well established in workflow, I don't think it would be significant. I don't know that hospitals have been set up great as yet, but I don't know that adding these is going to fix that or make that any worse. I think that we need to be getting SafeScript better aligned with the pharmacy dispensing programs and the electronic scripts." – Nicole O'Shea, VPIC

"If this process is successful, and it's premised on the basis that there are people who are being prescribed either within the one practice, or through multiple practices, an excessive

amount of a drug that's now listed on SafeScript. If this has been successful, some clinician has to step in and address that. That takes time. And if it's done properly, it takes considerable time. If you're going to find a pain clinic, if you're going to commence a person on a withdrawal program, if you're going to contact other clinics. All of that takes time. And when did the government recognise the impact on practitioners of SafeScript and recompense them for the work that it involves? Never." – John Jackson, PSA Victoria

"It's quite frustrating as a pharmacist when you jump on to SafeScript and have a look at the history, the number of times that you see that the Medical Practitioner that wrote the script hasn't checked SafeScript and I think that is extremely disappointing. Even being able to check that modifies my behaviour, in terms of what my next step is. So, it's still a huge advantage even if they're not using it, just if the pharmacists are, but that's not how it was designed. That's not what the regulations say, and it's disappointing that we continue to find that." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

Effect on Usage of Gabapentinoids and Tramadol

By identifying inappropriate prescribing, it is hoped that the addition of these medications to SafeScript would lead to higher levels of rational prescribing; in turn, this may then see an overall change in prescribing practices. However, this impact should be monitored, including for the risk of unintended consequences from monitoring tramadol.

"I think that we would understand that a lot of patients have prescribed these agents (gabapentinoids) for not approved indications. It may or may not influence it (usage), but it will at least alert prescribers if they see the patients are on a whole bunch of other medications, that they didn't know." – Dr Martyn Lloyd-Jones, VAILA

"If pregabalin is flagged as a drug that can potentiate other medications, and there's a red flag there, then it may alter behaviour. But if there's no consequences, then it will make no difference." – Dr Zeff Koutsogiannis, TAPNA

"We know not all of the changes that it will create are necessarily going to be good ones, but I still hope that it does make some changes. We hope that it's more appropriate prescribing and it's not just, 'I can't see you because you're misusing this drug'." – Angelo Pricolo, Pharmacy Guild of Australia Victoria Branch

"I hope that we capture those misuse people and look at how they can be better managed. A lot of these people my perspective are very poorly managed by GPs and get themselves into strife. They just put keep putting up the doses and then it takes three years to get into a pain clinic and it creates this vicious circle. Or it's poor prescribing or poor support for our GPs. So if we can solve that problem, I actually think that's something because to me the pregabalin problem is probably more misuse. There would be some abuse with pregabalin, but gabapentin is probably more of a misuse then an actual abuse problem." – Nicole O'Shea, VPIC

"I perceive that tramadol is often used where an opioid medication is wanted, but where somebody doesn't want to prescribe a pure Mu agonist. I don't think it's going to lead to an increase in tramadol use, but I don't know that it would necessarily lead to a significant reduction." – Dr Martyn Lloyd-Jones, VAILA

"If you put tramadol on, the prescriber may avoid putting themselves into a medico-legal risk situation, they will avoid the patient having to go through some kind of withdrawal program that's not available by transferring them to one of the similar drugs out of that class." – John Jackson, PSA Victoria

Chapter 8. Findings and discussion

Critical to the interpretation of this edition of the report, particularly with respect to previous editions of the report, is its scope with respect to the question it addresses. Previous editions of this report were intended to inform decisions about SafeScript in its infancy. There, the evidence had to answer whether medications could, with a reasonable level of certainty in the Victorian context, meet a threshold with two components: first, being culpable rather than merely an 'innocent bystander', and secondly, being responsible for death. It was critical at that time, for the acceptability and uptake of SafeScript as the culture of its use was being built in Victoria, that each Schedule 4 medication on it could be clearly justified as being responsible for mortality, and that the use of SafeScript for that medication was necessary for saving Victorian lives.

While we accept that some have discussed the complexities in evaluating real-time prescription monitoring services(RTPMs)(106) and that potential negative impacts of RTPMs must be fully evaluated(73), we believe that SafeScript has been successful in navigating treacherous waters with a holistic and balanced approach which is unlikely to tire out quickly. It appears there is largely a clear culture of good-spirited use, before and after the most challenging of times for healthcare in Victoria during the COVID-19 pandemic. In an environment which has stretched healthcare resourcing, conferred a sustained stress on frontline healthcare workers which might be sensitive to increases in administrative burden, and has provided societal-level triggers to disorders within the fields of addiction medicine, mental health, and pain, SafeScript is still universally seen as useful and necessary. While there will always be critical, divergent, and vocal opinions from others on what could or should be done, SafeScript has established itself not by accident but through careful planning, execution, and respect of the evidence and the independent interpretation of it. It is not surprising that other states have followed its lead.

It is understandable, however, that SafeScript needs to consider adaption as use of the system matures. The passage of time brings not only changes in use, its context, and risk, but the opportunity to build on existing approaches in a stagewise way, which may not have been appropriate or even possible from the beginning. It is therefore understandable that SafeScript might now consider changing those two components of the threshold. Harm that we seek to prevent may not just be from deaths, but in other forms as well, with economic, societal, and health consequences. In addition, monitoring prescriptions might give important information about not just those medications themselves, but about medications not on the prescription at hand. A real-time prescription monitoring service has arguably its greatest utility when revealing that which is unexpected by way of what is on the prescription being checked, and often the unexpected takes the form of another medication.

The analyses in this report therefore seek to determine not just culpability, but the possibility that the risk of prescription medication-related harm in general may be better identified by mandatory monitoring of a certain medication, irrespective of whether that medication is the one which is culpable for the harm. Given this, there is no longer a need to determine culpability as such; the 'innocent bystander' frequently at the scene should trigger further enquiries.

Additionally, this report has also considered the role of harms outside death, including peer-reviewed descriptions of ambulance attendances, emergency department presentations, and addiction. This was captured in previous reports, but through the lens of candidate identification and evolution of concern, rather than with respect to informing immediate action. While it cannot be assumed that different harms hold equal weight, they all warrant consideration for inclusion in a system which may now have the capacity to support the weight of addressing medications which create harm other than death.

As such, this report brings a different view even to evidence previously reported. Even in the context of static trends, different interpretation might apply. Of course, no trend is truly static, and even stable metrics may be an amalgam of multiple factors moving in different directions. Stability in the context of other factors changing – such as regulation or monitoring of relevant medications – is equally as important.

Gabapentinoids were already of some concern in the 2019 report; although overall metrics of death at that time were not remarkable, there was substantial concern about the combination of opioids with gabapentinoids in the peer-reviewed literature, particularly as to whether gabapentinoids might potentiate opioid-related harm. While the local data could not answer this open question, analyses examining the combination did raise the possibility that pregabalin could be considered for inclusion on SafeScript.

Given that the goalposts have moved, the high-risk misuse that is associated with gabapentinoids is relevant irrespective of its impact on death, as are intentional poisonings noted internationally. In line with gabapentinoids' known pharmacological properties, road traffic accidents and violent crime remain questions, but so too does any actual benefit regarding its opioid-sparing potential in non-neuropathic pain. While pregabalin and gabapentin are medications with not insignificant utility, and like many medications probably with benefit that exists beyond its narrow on-label indication, it is clearer that misuse and abuse of gabapentinoids extends across jurisdictions and settings, suggesting that beyond just societal context and trends it might be a medication which predisposes to this.

Of course, this does not speak to the risk of death, and this remains an open question. In Victorian data regarding overdose deaths, metrics for pregabalin have not followed an increasing trend from 2018 but have in fact remained stable, both in absolute and normalised terms. This may well correspond with maturity of overall use of pregabalin following the dramatic rise in its utilisation following PBS Streamline listing, and simultaneous clinical interest in its use.

However, we are blessed with a system which appears capable of managing to monitor not just medications which are themselves culpable, but might act as surrogates to flag high-risk situations, and it appears gabapentinoids do just that with prescription opioids. Opioids have been particularly present in pregabalin-attributable deaths. Pregabalin flags non-prescribed pharmaceutical opioid use in people who inject drugs. Most damningly, in well-executed Australian pharmacoepidemiological data, the initiation of persistently high pregabalin use appears to be associated with often substantial increases in prescription opioid use. In local data we see the increasing presence of pregabalin in opioid-related deaths in a way which does not occur in a comparator. In fact, it seems to be the highest risk opioid-related harm that pregabalin finds itself present at, in a way not seen with less impactful harm or in utilisation.

Questions about culpability will be tied into context of harm until data emerges to directly answer this, and we once again echo the sentiments of the 2016 PBAC DUSC report highlighting the need for a systematic approach in understanding contextual mechanisms of harm. In this respect, this edition of the report adds no great insights to that which was noted in 2019, but what is clear is that gabapentinoids, 'innocent bystander' or not, have a presence worth noting, and monitoring them might reveal more about the potential for high-risk prescription medication use than would otherwise be known by end-user clinicians.

It bears briefly noting that, as discussed previously and in this edition of the report at length, pregabalin and gabapentin should be included or excluded from SafeScript as a single entity. Data from regulation in Saudi Arabia perfectly demonstrates what we postulated, that any

pharmaceutical policy intervention on one gabapentinoid in isolation will merely lead to substitution to the other.

While precedents in other jurisdictions alone are not a good justification for inclusion of any medication, gabapentinoids are being increasingly monitored in other international jurisdictions, and are currently planned to be monitored in every Australian jurisdiction apart from Tasmania and Western Australia. The monitoring of gabapentinoids globally is still in its infancy, and lessons are difficult to draw from the international experience, but unintentional harms will have to be anticipated if gabapentinoids are to be monitored. In particular, monitoring for 'chilling effect' remains a risk, potentially leaving patients in pain. We are conscious that pregabalin has higher volumes in Victoria than any medication with local data analysed in this edition of the report, and its mandatory monitoring is likely to confer an administrative burden whose impact should be assessed formally. Nevertheless, there may also be substantial efficiency benefits realised by frontline clinicians in identifying pregabalin and other prescribing trends in patients who might otherwise be prescribed pregabalin. Ultimately, there seem to be multidimensional clinical gains to be made with the addition of gabapentinoids to SafeScript, and for a system whose use appears sufficiently mature to support it, gabapentinoids should remain a priority.

In the corresponding point of the 2019 report, we stated, of tramadol that "There are now a plethora of studies regarding tramadol-related misuse, abuse and addiction, although translation to tramadol-related death is less certain". This remains at least as true as before, two years later. Tramadol-related pharmacoepidemiological studies internationally seem prone to residual confounding by indication, and studies new in this edition, published in prominent journals, retain similar issues. Some, but not all, of this relates to the prescribing context which tramadol is frequently found, and often when death data are interrogated, tramadol distinguishes itself from other opioids. While we have avoided such comparisons on local data as we feel differences in regulation make this an invalid comparison, in Ireland, tramadol was found to have a case-fatality risk five times less than oxycodone or morphine. In local overdose death data, tramadol displays normalised metrics which are consistently less than the other Schedule 4 medications we analysed, and it also ranks lowly with the corresponding measures for poisoning calls. These data are in keeping with what has been seen in previous editions of this report, and on this front little has changed. It is plausible that increases in harm which would otherwise have occurred have actually been mitigated by regulatory changes and reduced prescription quantities introduced across many prescription opioids on June 1, 2020, but even prior to this, those metrics of harm did not show any clear cause for concern.

What is clearer is the non-death related harm associated with tramadol appears to be similar to that of other prescription opioids within the Australian context. In two corresponding peer-reviewed papers examining the Victorian context, tramadol was not distinguished from other prescription medications with respect to data from ambulance attendances for extramedical prescription opioid use, including conscious state and progression to hospital, and emergency department presentations for prescription opioid-related poisonings, including progression to inpatient admission. To some extent, these metrics primarily represent healthcare utilisation, but also correlate to firmer metrics of harm, and bear consideration when contemplating the inclusion of tramadol on SafeScript.

It is notable that all other Australian jurisdictions plan to monitor tramadol, and all except the Northern Territory are either doing that now or plan on doing so when their current plans are first implemented. This is in keeping with greater international scrutiny of tramadol, albeit in contexts which are not necessarily relevant to Victoria. We emphasise that, despite plans for a national approach, each state is on its own journey as far as real-time prescription monitoring is concerned, and each has a responsibility to its own jurisdictions to build towards a situation where SafeScript is relevant to its people; indeed, many other states diverge from

other ones based on expert advice that they have received from their local experts with variable transparency, although harmonisation seems likely at some point in the future as jurisdictions iterate their systems. It is less clear that asynchronous monitoring would lead to clinically concerning behaviour across the NSW or South Australian state borders with Victoria, but as Australia eventually moves towards a national system, this warrants consideration.

It is notable that discussions in the informal scoping consultation gravitated away from tramadol and toward gabapentinoids, and that the issues raised around tramadol did highlight unintended consequences as an issue. It also revealed that stakeholders often can see a pathway to acceptability for clinicians but are equally conscious of the burden of additional identified patients that monitoring these two commonly prescribed medications would bring. How this would be managed is key. For any medication, but particularly for tramadol given its current position in clinical use, acceptability may be contingent on support in clinically managing these patients – including for all the flow-on effects of at-risk patient identification, including adequate resourcing for substance abuse and pain management services to respond to increased demand – and in streamlining of SafeScript workflows. Plausibly, the thinking behind medication selection may need to be clearly articulated, and broader educational efforts taken. While the balance of convenience is likely to be understood by many, it is also important that changes in workflow do not become a precipitant lightning rod for other concerns end users might have regarding SafeScript's workflow and function.

If tramadol was to be included on SafeScript, what risks would exist? Unintended consequences of RTPMs are coming under emerging scrutiny, as reflected in the informal consultation, and SafeScript has an obligation to ensure that, beyond the balance of convenience that would be required to justify the added administrative burden on prescribers, no other harm emerges from such a change. In many ways, it can be argued that tramadol offers a 'lesser of evils' option – an opioid which appears to have more limited potential for mortality compared to its therapeutic alternatives, whose imperfect pharmacological properties, inter-individual pharmacokinetic variability aside, might actually buffer the risk in practice of the most serious harm, while providing an outlet for higher-risk opioid prescribing. This remains purely speculative, as do many of the potential unintended consequences, but they are worth considering in turn.

Might monitoring of tramadol lead prescribers to feel that it is of similar safety to oxycodone and morphine, and that they might as well prescribe what actually are riskier prescription opioids, leading to a reverse 'substitution effect'? Is it possible that patients, without an unmonitored prescription opioid to turn to, might access illicit opioids instead, as has been observed in the United States – and if so, how well could the broader Victorian healthcare system absorb this risk? Could this put patients suffering from pain at risk of a 'chilling' effect, where they might not receive appropriate prescriptions of a weak opioid with potential (albeit limited) benefits for nociplastic pain? Might the same pain patients be refused access to care as a consequence, as has been observed in the United States but not yet definitively in Australia? Might monitoring all prescription opioids lead to stigmatisation of pain patients, marginalising already vulnerable patients and turning them away from licit, conventional approaches?

These concerns might sound alarmist, and they may well be. It is plausible that regulatory changes already taken in June 2020 might have been firmer in precipitating these unintended consequences, diluting any further risk from monitoring tramadol. Nevertheless, these questions have been reasonably raised, with plausibility suggested from local and international sources, and may buffer any enthusiasm for mandatorily monitoring tramadol. Plausibly these risks could be buffered by making these 'monitored poisons' rather than 'monitored supply poisons' and thus making checks of them optional, but this brings its own logistical challenges which are outside the scope of this report.

The questions surrounding tramadol remain open and cannot be answered more definitively in this report. If tramadol is to be included, without the same clinical imperative as gabapentinoids, with potential risks identified, and given the inability to reverse such a decision, appropriate evaluation, mitigation, and support will be required, in what will independently be challenging times for the Victorian healthcare system. Sophisticated assessment of risk will be required, as missteps may still endanger the end user acceptance of SafeScript, which SafeScript's overall impact is almost entirely contingent on. Of course, SafeScript should never stand in isolation, and we reiterate that its presence does not abrogate the need for investment in other measures against prescription medication-related harm; if anything, SafeScript highlights the need for such measures. Unlike gabapentinoids, where a strong clinical imperative exists, decisions regarding tramadol's selection for SafeScript, and the timing of implementation, may eventually represent an exercise in priority setting and appetite for risk.

References

1. Liew DF, Joules E, Booth J, Garrett K, Frauman AG. Evidence to inform the inclusion of Schedule 4 prescription medications on a real-time prescription monitoring system. Austin Health; 2017 28/07/2017.
2. Liew DFL SE, Wilsdon T, McMaster C, Garrett K, Frauman AG. Evidence to inform the inclusion of additional Schedule 4 prescription medications on the Victorian real-time prescription monitoring system: an updated report. Medicines Optimisation Service, Austin Health; 2019.
3. Islam MM, McRae IS. An inevitable wave of prescription drug monitoring programs in the context of prescription opioids: pros, cons and tensions. BMC Pharmacology and Toxicology. 2014;15(1):46.
4. Scheduling Policy Framework for Medicines and Chemicals. 2015.
5. Pharmaceutical Benefits: Fees, Patient Contributions and Safety Net Thresholds: Pharmaceutical Benefits Scheme; [updated 26/05/2019. Available from: http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee.
6. Prescription Shopping Programme: Department of Human Services, Australian Government; [updated 22/02/2019. Available from: https://www.humanservices.gov.au/organisations/health-professionals/services/medicare/prescription-shopping-programme.
7. Cairns R SA, Ryan N, Pearson S-A, Buckley NA. Monitoring emerging prescription-drug related harms: a comment on Cairns et al. (2018)-in reply. Addiction (Abingdon, England). 2019;114(3):572-3.
8. 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.
9. Reclassification of pregabalin and gabapentin to Schedule 3 drugs from 1 April 2019: GOV.UK; [updated 02/03/2019. Available from: https://www.gov.uk/government/news/reclassification-of-pregabalin-and-gabapentin-to-schedule-3-drugs-from-1-april-2019.
10. Drugs ACotMo. Advice on the anticonvulsant drugs Pregabalin and Gabapentin: GOV.UK; 2016 [Available from: https://www.gov.uk/government/publications/advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin.
11. Pregabalin and gabapentin to be controlled as class C drugs: GOV.UK; 2018 [updated 15/8/2019. Available from: https://www.gov.uk/government/news/pregabalin-and-gabapentin-to-be-controlled-as-class-c-drugs.
12. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, Van Den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLOS Medicine. 2017;14(10):e1002396.
13. Gomes T, Greaves S, van den Brink W, Antoniou T, Mamdani MM, Paterson JM, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case–Control Study. Annals of Internal Medicine. 2018;169(10):732-4.
14. Throckmorton DC, Woodcock J. Combined Gabapentinoid and Opioid Use: The Consequences of Shifting Prescribing Trends. Annals of Internal Medicine. 2018;169(10):727.
15. sub-committee Du. Pregabalin: 24 month predicted versus actual analysis. Pharmaceutical Benefits Scheme; 2015 04/03/2016.
16. Cairns R, Schaffer AL, Ryan N, Pearson SA, Buckley NA. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. Addiction. 2019;114(6):1026-34.
17. Crossin R, Scott D, Arunogiri S, Smith K, Dietze PM, Lubman DI. Pregabalin misuse-related ambulance attendances in Victoria, 2012-2017: characteristics of patients and attendances. Med J Aust. 2019;210(2):75-9.
18. Darke S, Duflou J, Peacock A, Farrell M, Lappin J. Characteristics of fatal gabapentinoid-related poisoning in Australia, 2000-2020. Clin Toxicol (Phila). 2021:1-7.
19. Lyndon A, Audrey S, Wells C, Burnell ES, Ingle S, Hill R, et al. Risk to heroin users of polydrug use of pregabalin or gabapentin. Addiction. 2017;112(9):1580-9.
20. Sutherland R, Dietze PM, Gisev N, Bruno R, Campbell G, Memedovic S, et al. Patterns and correlates of prescribed and non-prescribed pregabalin use among a sample of people who inject drugs in Australia. Drug Alcohol Rev. 2020;39(5):568-74.

21. Schaffer AL, Brett J, Buckley NA, Pearson SA. Trajectories of pregabalin use and their association with longitudinal changes in opioid and benzodiazepine use. Pain. 2021.
22. Evoy KE, Covvey JR, Peckham AM, Ochs L, Hultgren KE. Reports of gabapentin and pregabalin abuse, misuse, dependence, or overdose: An analysis of the Food And Drug Administration Adverse Events Reporting System (FAERS). Res Social Adm Pharm. 2019;15(8):953-8.
23. Nahar LK, Murphy KG, Paterson S. Misuse and Mortality Related to Gabapentin and Pregabalin are Being Under-Estimated: A Two-Year Post-Mortem Population Study. J Anal Toxicol. 2019;43(7):564-70.
24. Chen TC, Knaggs RD, Chen LC. Association between opioid-related deaths and prescribed opioid dose and psychotropic medicines in England: a case-crossover study. Br J Anaesth. 2021;127(5):789-97.
25. Rahman A, Kane J, Montastruc F, Renoux C. Trends in new prescription of gabapentinoids and of coprescription with opioids in the 4 nations of the UK, 1993-2017. Br J Clin Pharmacol. 2021;87(8):3349-53.
26. Chen TC, Knaggs RD, Chen LC. Association between opioid-related deaths and persistent opioid prescribing in primary care in England: A nested case-control study. Br J Clin Pharmacol. 2021.
27. Minhaj FS, Rappaport SH, Foster J, Gashlin LZ. Predictors of Serious Opioid-Related Adverse Drug Events in Hospitalized Patients. J Patient Saf. 2021;17(8):e1585-e8.
28. Torrance N, Veluchamy A, Zhou Y, Fletcher EH, Moir E, Hebert HL, et al. Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland. Br J Anaesth. 2020;125(2):159-67.
29. Macleod J, Steer C, Tilling K, Cornish R, Marsden J, Millar T, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. PLoS Med. 2019;16(11):e1002965.
30. Kriikku P, Ojanperä I. Pregabalin and gabapentin in non-opioid poisoning deaths. Forensic Sci Int. 2021;324:110830.
31. Mariottini C, Kriikku P, Ojanperä I. Concomitant drugs with buprenorphine user deaths. Drug Alcohol Depend. 2021;218:108345.
32. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. Bmj. 2019;365:l2147.
33. Daly C, Griffin E, Ashcroft DM, Webb RT, Perry IJ, Arensman E. Intentional Drug Overdose Involving Pregabalin and Gabapentin: Findings from the National Self-Harm Registry Ireland, 2007-2015. Clin Drug Investig. 2018;38(4):373-80.
34. Tambon M, Ponté C, Jouanjus E, Fouilhé N, Micallef J, Lapeyre-Mestre M. Gabapentinoid Abuse in France: Evidence on Health Consequences and New Points of Vigilance. Front Psychiatry. 2021;12:639780.
35. Chan WL, Dargan PI, Haynes CM, Green JL, Black JC, Dart RC, et al. Misuse of prescription medicines is as prevalent as the use of recreational drugs and novel psychoactive substances in Singapore: an unrecognised public health issue? Singapore Med J. 2020.
36. Kurdi A. Opioids and Gabapentinoids Utilisation and Their Related-Mortality Trends in the United Kingdom Primary Care Setting, 2010-2019: A Cross-National, Population-Based Comparison Study. Front Pharmacol. 2021;12:732345.
37. Horne AW, Vincent K, Hewitt CA, Middleton LJ, Koscielniak M, Szubert W, et al. Gabapentin for chronic pelvic pain in women (GaPP2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2020;396(10255):909-17.
38. Murphy DL, Lebin JA, Severtson SG, Olsen HA, Dasgupta N, Dart RC. Comparative Rates of Mortality and Serious Adverse Effects Among Commonly Prescribed Opioid Analgesics. Drug Saf. 2018;41(8):787-95.
39. Zeng C, Dubreuil M, LaRochelle MR, Lu N, Wei J, Choi HK, et al. Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis. Jama. 2019;321(10):969-82.
40. Nielsen S, Crossin R, Middleton M, Lam T, Wilson J, Scott D, et al. Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Victoria, Australia from 2013 to 2018. Addiction. 2020;115(6):1075-87.

41. Nielsen S, Gisev N, Bruno R, Hall W, Cohen M, Larance B, et al. Defined daily doses (DDD) do not accurately reflect opioid doses used in contemporary chronic pain treatment. Pharmacoepidemiol Drug Saf. 2017;26(5):587-91.
42. Lam T, Hayman J, Berecki-Gisolf J, Sanfilippo P, Lubman DI, Nielsen S. Pharmaceutical opioid poisonings in Victoria, Australia: Rates and characteristics of a decade of emergency department presentations among nine pharmaceutical opioids. Addiction. 2021.
43. Choi NG, Choi BY, DiNitto DM, Marti CN, Baker SD. Opioid poisoning cases aged 50+ in the 2015-2020 National Poisoning Data System: suspected suicides versus unintentional poisoning and other intentional misuse/abuse. Drug Chem Toxicol. 2021:1-12.
44. Veronin MA, Schumaker RP, Dixit RR, Elath H. Opioids and frequency counts in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database: a quantitative view of the epidemic. Drug Healthc Patient Saf. 2019;11:65-70.
45. Champagne-Langabeer T, Madu R, Giri S, Stotts AL, Langabeer JR. Opioid prescribing patterns and overdose deaths in Texas. Subst Abus. 2021;42(2):161-7.
46. Hawton K, Ferrey A, Casey D, Wells C, Fuller A, Bankhead C, et al. Relative toxicity of analgesics commonly used for intentional self-poisoning: A study of case fatality based on fatal and non-fatal overdoses. J Affect Disord. 2019;246:814-9.
47. Daly C, Griffin E, Corcoran P, Webb RT, Ashcroft DM, Perry IJ, et al. A national case fatality study of drugs taken in intentional overdose. Int J Drug Policy. 2020;76:102609.
48. Chung CP, Callahan ST, Cooper WO, Dupont WD, Murray KT, Franklin AD, et al. Individual short-acting opioids and the risk of opioid-related adverse events in adolescents. Pharmacoepidemiol Drug Saf. 2019;28(11):1448-56.
49. Caré W, Langrand J, Vodovar D, Deveaux M, Alvarez JC, Mégarbane B, et al. Trends in severe opioid-related poisonings and fatalities reported to the Paris poison control center - a 10-year retrospective observational study. Fundam Clin Pharmacol. 2020;34(4):495-503.
50. Akhgari M, Sardari-Iravani F, Ghadipasha M. Trends in Poly Drug Use-associated Deaths based on Confirmed Analytical Toxicology Results in Tehran, Iran, in 2011-2016. Addict Health. 2021;13(1):18-28.
51. Eizadi-Mood N, Haghshenas E, Sabzghabaee AM, Yaraghi A, Farajzadegan Z. Common Opioids Involved in Drug Poisoning Presenting to the Emergency Department: A Cross-sectional Study. J Res Pharm Pract. 2020;9(4):202-7.
52. Gholami N, McDonald R, Farnaghi F, Hosseini Yazdi M, Zamani N, Hassanian-Moghaddam H. Fatal Outcome in Acutely Poisoned Children With Hospitalization: A 10-Year Retrospective Study From Tehran, Iran. Pediatr Emerg Care. 2021.
53. Rostam-Abadi Y, Gholami J, Amin-Esmaeili M, Safarcherati A, Mojtabai R, Ghadirzadeh MR, et al. Tramadol use and public health consequences in Iran: a systematic review and meta-analysis. Addiction. 2020;115(12):2213-42.
54. Alrashdi S, Paudyal V, Elnaem MH, Cheema E. Causes, Nature and Toxicology of Tramadol-Associated Deaths Reported in the Peer-Reviewed Literature: A Systematic Review of Case Studies and Case Series. Drugs & Therapy Perspectives. 2021;37(9):422-32.
55. Wei J, Wood MJ, Dubreuil M, Tomasson G, LaRochelle MR, Zeng C, et al. Association of tramadol with risk of myocardial infarction among patients with osteoarthritis. Osteoarthritis Cartilage. 2020;28(2):137-45.
56. Ou LB, Azoulay L, Reynier P, Platt RW, Yoon S, Grad R, et al. Tramadol versus codeine and the short-term risk of cardiovascular events in patients with non-cancer pain: A population-based cohort study. Br J Clin Pharmacol. 2021.
57. Xie J, Strauss VY, Martinez-Laguna D, Carbonell-Abella C, Diez-Perez A, Nogues X, et al. Association of Tramadol vs Codeine Prescription Dispensation With Mortality and Other Adverse Clinical Outcomes. Jama. 2021;326(15):1504-15.
58. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, et al. The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med. 2010;170(22):1979-86.
59. Yoo JI, Jang SY, Cha Y, Park CH, Kim JT, Oh S, et al. Effect of Opioids on All-cause Mortality and Sustained Opioid Use in Elderly Patients with Hip Fracture: a Korea Nationwide Cohort Study. J Korean Med Sci. 2021;36(19):e127.
60. Jeong S, Tchoe HJ, Li J, Shin JY. All-Cause Mortality Associated with Tramadol Use: A Case-Crossover Study. Drug Saf. 2019;42(6):785-96.
61. J D. Victorian overdose deaths, 2011-2020. Coroners Court of Victoria; 2021.

62. 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.
63. 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.
64. Dwyer J, Ogeil RP, Bugeja L, Heilbronn C, Lloyd B. Victorian Overdose Deaths: The Role of Pharmaceutical Drugs and Drug Combinations. Turning Point; 2016.
65. Cairns R, Buckley NA, Schaffer AL, Pearson SA, Ryan N. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. Addiction. 2018.
66. National Real Time Prescription Monitoring (RTPM): Australian Government Department of Health; [Available from: https://www.health.gov.au/initiatives-and-programs/national-real-time-prescription-monitoring-rtpm.
67. Real Time Prescription Monitoring: Department of Health, Tasmanian Government; [Available from: https://www.dhhs.tas.gov.au/psbtas/real_time_prescription_monitoring.
68. SafeScript NSW: NSW Government; [Available from: https://www.safescript.health.nsw.gov.au/health-practitioners/about-safescript-nsw/what-is-safescript-nsw.
69. NT Health. Medicines and poisons.: NT Health; [Available from: https://health.nt.gov.au/professionals/medicines-and-poisons-control2/ntscript-information-for-health-professionals.
70. Real-time prescription monitoring of monitored medicines Queensland Health; [Available from: https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/real-time-reporting.
71. Boyles P. Real-time prescription monitoring: lessons from Tasmania. Aust Prescr. 2019;42(2):48-9.
72. SafeScript – For prescribers and pharmacists: Department of Health, Victoria Government; [Available from: https://www.health.vic.gov.au/safescript.
73. Fetene DM, Higgs P, Nielsen S, Djordjevic F, Dietze P. The impact of Victoria's real time prescription monitoring system (SafeScript) in a cohort of people who inject drugs. Med J Aust. 2021;214(5):234-.e1.
74. Real Time Prescription Monitoring (Western Australia): Government of Western Australia, Department of Health; [Available from: https://ww2.health.wa.gov.au/Articles/N_R/Prescription-monitoring-in-Western-Australia.
75. Campbell LS, Coomer TN, Jacob GK, Lenz RJ. Gabapentin controlled substance status. J Am Pharm Assoc (2003). 2021;61(4):e218-e24.
76. Cerda M, Ponicki WR, Smith N, Rivera-Aguirre A, Davis CS, Marshall BDL, et al. Measuring Relationships Between Proactive Reporting State-level Prescription Drug Monitoring Programs and County-level Fatal Prescription Opioid Overdoses. Epidemiology. 2020;31(1):32-42.
77. Puac-Polanco V, Chihuri S, Fink DS, Cerda M, Keyes KM, Li G. Prescription Drug Monitoring Programs and Prescription Opioid-Related Outcomes in the United States. Epidemiol Rev. 2020;42(1):134-53.
78. Wang LX. The complementarity of drug monitoring programs and health IT for reducing opioid-related mortality and morbidity. Health Econ. 2021;30(9):2026-46.
79. Bachhuber MA, Tuazon E, Nolan ML, Kunins HV, Paone D. Impact of a prescription drug monitoring program use mandate on potentially problematic patterns of opioid analgesic prescriptions in New York City. Pharmacoepidemiol Drug Saf. 2019;28(5):734-9.
80. Calcaterra SL, Butler M, Olson K, Blum J. The Impact of a PDMP-EHR Data Integration Combined With Clinical Decision Support on Opioid and Benzodiazepine Prescribing Across Clinicians in a Metropolitan Area. J Addict Med. 2021.
81. Winstanley EL, Zhang Y, Mashni R, Schnee S, Penm J, Boone J, et al. Mandatory review of a prescription drug monitoring program and impact on opioid and benzodiazepine dispensing. Drug Alcohol Depend. 2018;188:169-74.
82. Castillo-Carniglia A, González-Santa Cruz A, Cerdá M, Delcher C, Shev AB, Wintemute GJ, et al. Changes in opioid prescribing after implementation of mandatory registration and proactive reports within California's prescription drug monitoring program. Drug Alcohol Depend. 2021;218:108405.

83. Strickler GK, Zhang K, Halpin JF, Bohnert ASB, Baldwin GT, Kreiner PW. Effects of mandatory prescription drug monitoring program (PDMP) use laws on prescriber registration and use and on risky prescribing. Drug Alcohol Depend. 2019;199:1-9.
84. Wen H, Hockenberry JM, Jeng PJ, Bao Y. Prescription Drug Monitoring Program Mandates: Impact On Opioid Prescribing And Related Hospital Use. Health Aff (Millwood). 2019;38(9):1550-6.
85. Wen K, Johnson P, Jeng PJ, Schackman BR, Bao Y. State Policies for Prescription Drug Monitoring Programs and Adverse Opioid-related Hospital Events. Med Care. 2020;58(7):610-6.
86. 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. Addict Behav. 2017;69:65-77.
87. Alogaili F, Abdul Ghani N, Ahmad Kharman Shah N. Prescription drug monitoring programs in the US: A systematic literature review on its strength and weakness. J Infect Public Health. 2020;13(10):1456-61.
88. Fink DS, Schleimer JP, Sarvet A, Grover KK, Delcher C, Castillo-Carniglia A, et al. Association Between Prescription Drug Monitoring Programs and Nonfatal and Fatal Drug Overdoses: A Systematic Review. Ann Intern Med. 2018;168(11):783-90.
89. Picco L, Lam T, Haines S, Nielsen S. How prescription drug monitoring programs influence clinical decision-making: A mixed methods systematic review and meta-analysis. Drug Alcohol Depend. 2021;228:109090.
90. Whitmore CC, White MN, Buntin MB, Fry CE, Calamari K, Patrick SW. State laws and policies to reduce opioid-related harm: A qualitative assessment of PDMPs and naloxone programs in ten U.S. States. Prev Med Rep. 2019;13:249-55.
91. Deyo RA, Hallvik SE, Hildebran C, Marino M, Springer R, Irvine JM, et al. Association of Prescription Drug Monitoring Program Use With Opioid Prescribing and Health Outcomes: A Comparison of Program Users and Nonusers. J Pain. 2018;19(2):166-77.
92. Rhodes E, Wilson M, Robinson A, Hayden JA, Asbridge M. The effectiveness of prescription drug monitoring programs at reducing opioid-related harms and consequences: a systematic review. BMC Health Serv Res. 2019;19(1):784.
93. Ansari B, Tote KM, Rosenberg ES, Martin EG. A Rapid Review of the Impact of Systems-Level Policies and Interventions on Population-Level Outcomes Related to the Opioid Epidemic, United States and Canada, 2014-2018. Public Health Rep. 2020;135(1_suppl):100s-27s.
94. Wilson MN, Hayden JA, Rhodes E, Robinson A, Asbridge M. Effectiveness of Prescription Monitoring Programs in Reducing Opioid Prescribing, Dispensing, and Use Outcomes: A Systematic Review. J Pain. 2019;20(12):1383-93.
95. Lachance C, Frey N. CADTH Rapid Response Reports. Prescription Monitoring Programs for Optimizing Medication Use and Preventing Harm: A Review of Safety and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health
Copyright © 2019 Canadian Agency for Drugs and Technologies in Health.; 2019.
96. 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.
97. Watson CJ, Ganetsky M, Burke RC, Dizitzer Y, Leventhal EL, Boyle KL. Impact of a Mandatory Prescription Drug Monitoring Program Check on Emergency Department Opioid Prescribing Rates. J Med Toxicol. 2021;17(3):265-70.
98. Fulton-Kehoe D, Lofy KH, Le V, Sterling R, Sears JM, Franklin G. Opioid-Prescribing Metrics in Washington State: Trends and Challenges. J Public Health Manag Pract. 2020;26(3):214-21.
99. Zhang Y, Castracane AR, Winstanley EL. Assessment of gabapentin misuse using prescription drug monitoring program data. Subst Abus. 2021;42(4):454-9.
100. Faryar KA, Webb AN, Bhandari B, Price TG, Bosse GM. Trending gabapentin exposures in Kentucky after legislation requiring use of the state prescription drug monitoring program for all opioid prescriptions(). Clin Toxicol (Phila). 2019;57(6):398-403.
101. Roulet L, Rollason V, Desmeules J, Piguet V. Tapentadol Versus Tramadol: A Narrative and Comparative Review of Their Pharmacological, Efficacy and Safety Profiles in Adult Patients. Drugs. 2021;81(11):1257-72.
102. Cox AR, Ferner R. Tramadol: repeated prescriptions and repeated warnings. BMJ Evid Based Med. 2021;26(6):e17.
103. The misuse of drugs act 1971 (ketamine etc.) (Amendment).

104. Regulations Amending the Narcotic Control Regulations (Tramadol): SOR/2021-43. Government of Canada.
105. Forward Regulatory Plan 2020-2022: Regulations amending Schedule I to the Controlled Drugs and Substances Act and the Schedule to the Narcotic Control Regulations to add tramadol and related substances. Government of Canada.
106. Haines S, Prathivadi P. Evaluation of Australian prescription drug monitoring programs need a holistic approach. Aust J Prim Health. 2021;27(5):354-6.
107. Dickson-Gomez J, Christenson E, Weeks M, Galletly C, Wogen J, Spector A, et al. Effects of Implementation and Enforcement Differences in Prescription Drug Monitoring Programs in 3 States: Connecticut, Kentucky, and Wisconsin. Subst Abuse. 2021;15:1178221821992349.
108. Kim B. Must-access prescription drug monitoring programs and the opioid overdose epidemic: The unintended consequences. J Health Econ. 2021;75:102408.
109. Yuanhong Lai A, Smith KC, Vernick JS, Davis CS, Caleb Alexander G, Rutkow L. Perceived Unintended Consequences of Prescription Drug Monitoring Programs. Subst Use Misuse. 2019;54(2):345-9.
110. Meadowcroft D, Whitacre B. Do prescription drug monitoring programs encourage prescription - or illicit - opioid abuse? Subst Abus. 2021;42(1):65-75.
111. Dobbin M. The impact of Victoria's real time prescription monitoring system (SafeScript) on a cohort of people who inject drugs. Med J Aust. 2021;214(5):234-.e1.
112. Haines S, Savic M, Picco L, Nielsen S, Carter A. Unintended consequences of using real time prescription monitoring systems. Med J Aust. 2020;213(3):142-.e1.
113. Van Den Boom W, Quiroga MdM, O'Keefe D, Kumar D, Hill PL, Scott N, et al. Cohort Profile: The Melbourne Injecting Drug User Cohort Study (SuperMIX). International Journal of Epidemiology. 2021.
114. Antoniou T, Ala-Leppilampi K, Shearer D, Parsons JA, Tadrous M, Gomes T. "Like being put on an ice floe and shoved away": A qualitative study of the impacts of opioid-related policy changes on people who take opioids. Int J Drug Policy. 2019;66:15-22.
115. Althunian TA, Alomran M, Alsagri G, Alrasheed M, Alshammari TM, editors. The impact of regulatory restrictions on the use of pregabalin: An interrupted time-series. PHARMACOEPIDEMIOLOGY AND DRUG SAFETY; 2021: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
116. Yarbrough CR. Prescription Drug Monitoring Programs Produce a Limited Impact on Painkiller Prescribing in Medicare Part D. Health Serv Res. 2018;53(2):671-89.
117. Peckham AM, Ananickal MJ, Sclar DA. Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance. Risk Manag Healthc Policy. 2018;11:109-16.
118. Peckham AM, Fairman KA, Sclar DA. Policies to mitigate nonmedical use of prescription medications: how should emerging evidence of gabapentin misuse be addressed? Expert Opin Drug Saf. 2018;17(5):519-23.

Appendix 1. Search strategy for peer reviewed literature

Standard peer-reviewed literature databases were searched: Embase, Ovid MEDLINE(R) ALL (covers content from MEDLINE Epub Ahead of Print and has parity with PubMed), and PsycINFO. The search was restricted to articles written in English that were predominately published between 2019-2021. All types of articles were included. This literature search was not conducted strictly as a systematic review due to a limited available timeframe. Search terms were prioritised in order to return manageable numbers of articles to answer the research questions in the timeframe provided. Google Scholar was searched using relevant terms to supplement the structured literature search.

The following describes the search strategy that was used to support review of the peer-reviewed literature. Given the specific scope of this report and the research question it seeks to address, a targeted literature search with keywords was employed to obtain the most relevant evidence to inform the writing of relevant sections of this report.

The individual medicines in question (ie. tramadol or pregabalin or gabapentin) and, where relevant, medicine classes (opioid or gabapentinoid) were used as the primary search terms. For the updated review of the peer-reviewed literature on local and international RTPMs, the search terms included: "RTPM", "real time prescription monitoring", "PDMP", and "prescription drug monitoring program". As an extension when assessing the literature on RTPMs/PDMPs, the following search terms were also included for the relevant sections of this report: "trend", "consequence", "unintended", "unintentional", "impact", and "precedence". For the updated review the peer-reviewed literature of harms, the search terms included: "harm", "risk", "overdose", "death", "addiction", "misuse", "abuse", and "safety". For all of the above searches, the Boolean operators OR and AND were used to combine the search terms.

Titles and abstracts were initially screened and papers that were potentially relevant underwent a full-text review. During the subsequent stage of screening articles in full text form, articles were also scanned for relevant references to include in this review where appropriate to answer the research question, with a focus on the recent articles and/or studies.

Appendix 2. Calculations regarding prescriptions attributable to medications

Estimations for prescription numbers, inclusive of under co-payment prescriptions

The following pages include the following metrics which were used to estimate total prescriptions for examined medications, as reported in Chapter 4.3:

- Victorian PBS/RPBS prescriptions, as obtained from PBS Online Statistics (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp),
- National PBS/RPBS prescriptions, as obtained from PBS Online Statistics,
- National under co-payment prescriptions from the PBS/RPBS, as obtained from annual 'Report on the Collection of Under Co-payment Data' reporting (http://www.pbs.gov.au/info/statistics/under-co-payment/ucp-data-report),
- National total prescriptions, derived as the sum of the two previous metrics,
- A correction factor designed as a multiplier to PBS/RPBS data for subgroups, derived from the division of national total prescriptions by national PBS/RPBS prescriptions,
- Victorian total prescriptions by financial year, derived using baseline data from PBS Online Statistics,
- Victorian PBS/RPBS prescriptions by calendar year, as obtained from PBS Online Statistics, and
- Victorian total prescriptions estimated by calendar year, derived as the average product of the correction factor for the two related financial years, and the Victorian PBS/RPBS prescriptions by calendar year.

It should be noted that 2021 calendar year estimations were extrapolated from the first six months of 2021, and therefore may be less accurate. As a consequence, these are marked with an asterix and shaded in grey.

Utilisation for candidate medications for inclusion

Victoria - PBS/RPBS FY	pregabalin	gabapentin	tramadol
2013/2014	365,373	23,609	457,005
2014/2015	608,135	23,293	476,405
2015/2016	758,081	22,900	466,993
2016/2017	854,603	22,946	440,178
2017/2018	890,821	24,784	418,110
2018/2019	828,155	26,204	403,081
2019/2020	743,436	27,393	376,554
2020/2021	746,369	30,117	297,963

National - PBS/RPBS	pregabalin	gabapentin	tramadol
2013/2014	1,665,548	115,253	1,940,533
2014/2015	2,621,839	107,826	2,009,721
2015/2016	3,258,071	103,001	2,014,473
2016/2017	3,613,737	99,389	1,913,184
2017/2018	3,745,304	101,639	1,844,266
2018/2019	3,615,936	106,979	1,838,163
2019/2020	3,319,882	107,536	1,741,661
2020/2021	3,308,361	112,156	1,351,203

National - under copay	pregabalin	gabapentin	tramadol
2013/2014	56512	4089	715685
2014/2015	101868	11606	769070
2015/2016	138824	13937	765215
2016/2017	170143	15736	773654
2017/2018	200604	17498	797825
2018/2019	476,587	19,271	819,443
2019/2020	711,384	22,000	761,426
2020/2021	782,451	23,568	528,934

National - total corrected	pregabalin	gabapentin	tramadol
2013/2014	1,722,060	119,342	2,656,218
2014/2015	2,723,707	119,432	2,778,791
2015/2016	3,396,895	116,938	2,779,688
2016/2017	3,783,880	115,125	2,686,838
2017/2018	3,945,908	119,137	2,642,091
2018/2019	4,092,523	126,250	2,657,606
2019/2020	4,031,266	129,536	2,503,087
2020/2021	4,090,812	135,724	1,880,137

National - correction factor	pregabalin	gabapentin	tramadol
2013/2014	1.033929974	1.035478469	1.368808467
2014/2015	1.038853644	1.107636377	1.382675008
2015/2016	1.042609262	1.135309366	1.379858653
2016/2017	1.047082286	1.15832738	1.404380342
2017/2018	1.053561473	1.172158325	1.432597575
2018/2019	1.131801835	1.180138158	1.445794524
2019/2020	1.214279905	1.204582651	1.437183815
2020/2021	1.236507141	1.210135882	1.391454134

Victoria - total corrected FY	pregabalin	gabapentin	tramadol
2013/2014	377,770	24,447	625,552
2014/2015	631,763	25,800	658,713
2015/2016	790,382	25,999	644,384
2016/2017	894,840	26,579	618,177
2017/2018	938,535	29,051	598,983
2018/2019	937,307	30,924	582,772
2019/2020	902,739	32,997	541,177
2020/2021	922,891	36,446	414,602

Victoria - PBS/RPBS CY	pregabalin	gabapentin	tramadol
2014	512,999	25,755	515,781
2015	755,058	25,788	518,073
2016	806,905	22,470	451,712
2017	876,797	23,640	425,457
2018	885,792	25,673	413,702
2019	771,536	27,067	387,789
2020	749,261	28,900	338,593

Victoria - total corrected CY	pregabalin	gabapentin	tramadol
2014	531,668	27,598	709,581
2015	785,813	28,921	715,597
2016	843,091	25,769	628,837
2017	920,919	27,546	603,506
2018	967,889	30,195	595,398
2019	905,043	32,274	558,994
2020	918,140	34,893	478,879
2021*	922,891	36,446	414,602

Utilisation for comparators in Chapter 5.2 and 5.3.

Victoria - PBS/RPBS FY	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	379,822	319,713	300,208	298,073	153,029
2014/2015	415,964	336,305	285,482	296,176	152,692
2015/2016	427,321	332,490	274,536	275,333	141,944
2016/2017	438,408	327,320	261,447	263,797	146,590
2017/2018	460,867	327,434	259,534	258,289	144,322
2018/2019	478,964	338,821	253,279	250,466	135,584
2019/2020	515,551	350,463	253,201	254,361	119,312
2020/2021	567,374	377,361	258,514	264,629	98,809

National - PBS/RPBS	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	1,475,936	1,447,439	1,030,427	1,039,950	573,198
2014/2015	1,603,319	1,498,566	971,984	1,018,390	566,511
2015/2016	1,699,174	1,517,124	953,442	960,351	539,085
2016/2017	1,749,591	1,487,448	903,414	919,604	552,465
2017/2018	1,832,595	1,488,630	895,710	898,700	530,642
2018/2019	1,959,076	1,585,405	907,170	902,511	514,422
2019/2020	2,080,982	1,634,678	921,148	912,525	451,519
2020/2021	2,268,527	1,758,647	931,205	942,261	366,813

National - under copay	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	431,602	587,005	27076	12,428	29,597
2014/2015	487,104	622,213	47057	62,633	38,320
2015/2016	523,582	641,019	69636	121,530	45,956
2016/2017	570161	674161	120254	142543	47567
2017/2018	638,456	732,889	163226	164,007	49,728
2018/2019	700,663	817,268	177,647	173,430	50,452
2019/2020	774,549	889,071	188,217	178,854	50,248
2020/2021	819,286	941,218	186,416	176,792	48,545

National - total corrected	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	1,907,538	2,034,444	1,057,503	1,052,378	602,795
2014/2015	2,090,423	2,120,779	1,019,041	1,081,023	604,831
2015/2016	2,222,756	2,158,143	1,023,078	1,081,881	585,041
2016/2017	2,319,752	2,161,609	1,023,668	1,062,147	600,032
2017/2018	2,471,051	2,221,519	1,058,936	1,062,707	580,370
2018/2019	2,659,739	2,402,673	1,084,817	1,075,941	564,874
2019/2020	2,855,531	2,523,749	1,109,365	1,091,379	501,767
2020/2021	3,087,813	2,699,865	1,117,621	1,119,053	415,358

National - correction factor	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	1.292425959	1.405547315	1.026276485	1.011950575	1.051634863
2014/2015	1.303809785	1.415205603	1.048413348	1.061501979	1.067642111
2015/2016	1.308139131	1.422522483	1.07303643	1.126547481	1.085248152
2016/2017	1.325882449	1.453233323	1.133110623	1.155004763	1.086099572
2017/2018	1.348389033	1.492324486	1.182230856	1.182493602	1.093712899
2018/2019	1.357649729	1.515494779	1.195825479	1.192163863	1.098075121
2019/2020	1.372203604	1.543881425	1.204328729	1.195999014	1.111286568
2020/2021	1.361153295	1.535194385	1.200187929	1.187625297	1.132342638

Victoria - total corrected FY	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2013/2014	490,892	449,372	308,096	301,635	160,931
2014/2015	542,338	475,941	299,303	314,391	163,020
2015/2016	558,995	472,975	294,587	310,176	154,044
2016/2017	581,277	475,672	296,248	304,687	159,211
2017/2018	621,428	488,638	306,829	305,425	157,847
2018/2019	650,265	513,481	302,877	298,597	148,881
2019/2020	707,441	541,073	304,937	304,216	132,590
2020/2021	772,283	579,322	310,265	314,280	111,886

Victoria - PBS/RPBS CY	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2014	435,051	362,643	324,240	330,365	168,543
2015	463,370	368,879	306,056	311,921	161,583
2016	427,425	326,774	265,209	265,677	143,120
2017	449,193	325,710	259,454	260,639	144,390
2018	472,223	334,306	256,839	253,978	141,745
2019	494,179	342,573	252,064	251,853	130,284
2020	551,365	370,937	260,021	262,314	105,255

Victoria - total corrected CY	mirtazapine	amitriptyline	quetiapine	olanzapine	risperidone
2014	564,747	511,463	336,349	342,498	178,595
2015	605,149	523,389	324,641	341,249	173,935
2016	562,923	469,861	292,545	303,078	155,382
2017	600,632	479,699	300,362	304,622	157,372
2018	638,927	502,766	305,389	301,555	155,337
2019	674,518	524,030	302,496	300,733	143,922
2020	753,539	571,072	312,612	312,629	118,077
2021*	772,283	579,322	310,265	314,280	111,886

Medicines Optimisation Service
Austin Health
Melbourne, Australia

December 2021