Australian Government

Department of Health

Therapeutic Goods Administration

Prescription strong (Schedule 8) opioid use and misuse in Australia – options for a regulatory response

Consultation paper

Version 1.0, January 2018

TGA Health Safety Regulation

Contents

Commentary on the consultation paper:

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General points

The paper claims to focus on "use and misuse," but predominantly discusses misuse and overdoses. Overdoses are experienced by a minority of users and many overdoses do not always occur in the context of "misuse." The term "misuse" is one which we intuitively recognise but for this paper, it requires careful definition (1).

Introduction

Purpose and scope

Purpose

Several overseas jurisdictions are already facing 'crises' in the widespread misuse of prescribed opioids and evidence shows Australia trending down a similar path. At the same time, it is important to recognise that strong opioids play a critical role in managing severe acute pain following trauma and major surgery and pain experienced in many forms of cancer and some other conditions as well as opioid dependency. Any regulatory response must not unduly restrict informed, rational prescribing of opioids for these indications.

This paper will examine the issues around prescription opioid use and misuse in Australia and explore options for a regulatory response to any issues identified, although some areas that have a direct interaction with areas of regulation are addressed. It is noted at the outset that use, and misuse, of opioids is affected by a wider range of factors beyond regulation, but regulation as it relates to demand from patients and supply from prescribers can play an important role in underpinning appropriate use and minimising misuse.

Substances in scope

At present prescription opioids are scheduled as follows:

Schedule 4 (S4) – Prescription Only Medicine

Codeine (after February 2018), dihydrocodeine, pholcodeine, dextromethorphan in moderate doses (except in low-dose cough preparations), dextropropoxyphene (at low doses), diphenoxylate at moderate doses, and tramadol.

Schedule 8 (S8) – Controlled Drug

Buprenorphine, fentanyl, hydromorphone, methadone, morphone, oxycodone, talpentadol and pethidine.

Other opioids in S8 include: acetyldihydrocodeine, acetylmorphines, benzylmorphine, dextropropoxyphene (at high doses), dihydromorphine, diphenoxylate (at high doses),

dihydrocodeine, hydromorphinol, levorphanol, methyldihydromorphine, morphine methobromide, morphine-N-oxide, norcodeine, normethadone and oxymorphone.

It is proposed that the focus of this consultation should be on the higher-risk S8 opioids, although some S4 opioids, such as tramadol, may also be considered.

Background

In 2014, almost 3 million people in Australia were prescribed at least one opioid under the Pharmaceutical Benefits Scheme (PBS) or Repatriation PBS (RPBS). Since the end of 2009, there has been a general increase in prescriptions, from about 10 million annually to 14 million annually. Analysis of utilisation by oral morphine equivalents, to adjust for potency, results in an increase in Defined Daily Doses (DDDs) over the period 2009 to 2014 from about 15-20 DDDs per 1000 population per day to about 30-35 DDDs per 1000 population per day. Although codeine is the most widely prescribed opioid by number of prescriptions, in terms of DDDs oxycodone is the most highly used opioid, followed by tramadol. A recent paper from the National Drug and Alcohol Research Centre argued that estimates based on PBS/RPBS data were underestimates because a proportion of prescriptions for opioids were below the reimbursement threshold.[1]

Levels of prescription opioid overdose, including accidental overdose are at record levels in Australia and internationally. One of the contributing factors has been significant 'indication creep' – their use in a range of types of chronic non-cancer pain, despite limited evidence of efficacy or safety for opioids in many of those patients.[2] Use in chronic pain is also driven by the inconsistent efficacy of alternative medicines in chronic pain such as non-steroidal anti-inflammatory drugs (NSAIDs), gabapentoids, antidepressants and muscle relaxants; opioid analgesics are often used when pain is refractory to these other treatments.[3] Judicious prescribing for some patients with chronic non-cancer pain has been described as an appropriate option.[4,5] by expert opinion based on short-term trials in selected patients. New evidence from a one-year randomised controlled trial indicates opioid worsen outcomes (Krebs et al 2017 s174-175 https://link.springer.com/article/10.1007/s11606-017-4028-8 - full paper in press due out March 6)

One major source of the problem has been described as "concern that patients with chronic pain are inappropriately being moved up the WHO 'analgesic ladder', originally developed for cancer pain, without considering alternatives to medication…".[6]

Australia currently ranks eighth internationally on the numbers of defined daily doses of prescription opioids per million population (at about 40% the level of the USA).[7] In the USA, opioid analgesics are now the most commonly prescribed class of medications.[8]

The National Coronial Information Service (NCIS) fact sheet *Opioid related deaths in Australia (2007-2011)* stated that for this five-year period there were 4102 deaths involving opioid drugs, although in three-quarters of cases opioids were one of multiple drugs detected.[9] Heroin was

[1] Gisev N et al;. Pharmacoepidemiol. Drug Saf (2017); doi: 10.1002/pds 4329
[2] Becker WC and Fiellin DA, BMJ (2017); 357: J3115
[3] Kroenke and Cheville A, JAMA (2017); doi: 10.1001/jama2017.4884
[4] Reuben DB et al, Ann Intern Med (2015); 162, 295-300
[5] Dowell D et al, JAMA (2016); 315: 1624-1645
[6] Foy et al, BMJ Open (2016); 6(5): e010276)
[7] Humphreys, K, Lancet (2017); 390: 437
[8] Centers for Disease Control and Prevention: www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm
[9] www.ncis.org.au/wp-content/uploads/2014/08/NCIS-Fact-sheet_Opioid-Related-Deaths-in-Australia-2007-2011.pdf

implicated in 1127 of the deaths, while pharmaceutical opioids were implicated in 2975 deaths (or 73% of the total). The majority of deaths involving opioids were deemed unintentional (71.2%), while almost one-sixth were due to an act of intentional self-harm (15.8%).

More recent statistics are available from the *Australia's Annual Overdose Report 2017*, released by the Penington Institute.[10] Some headline statistics include:

- There were 2023 drug related deaths in Australia in 2015, with 1489 being deemed as accidental (not suicide or homicide). In 2001 there were 1313 drug related accidental deaths. Most but not all of these were due to opioids.
- Opioid deaths increased by 60% in 2011-2015 compared with 2001-2005. Accidental death from oxycodone, morphine or codeine is responsible for most opioid-related deaths.

Pharmaceutical opioid deaths in Australia now exceed heroin deaths by a significant margin – by 2-2.5 times – the reverse of what was seen in the 1990s. Between 2011 and 2015 there were 2145 deaths associated with oxycodone, morphine, codeine, fentanyl, tramadol and/or pethidine compared with 985 due to heroin. Pharmaceutical opioid deaths particularly dominate in the over 30 age group.

The National Drug and Alcohol Research centre has put out some slightly different figures:

- There are 19,000 overdose deaths (not limited to accidental overdose) annually in the USA associated with prescription opioids and 670 annually (2013 figures) due to accidental overdose with opioids in Australia (70% of these from prescription opioids).[11] The opioid 'crisis' has led to calls for concerted action by clinicians, specialist colleges, government policymakers and regulators in a number of countries, including Australia.

A recent article in the BMJ stated that 'the opioid crisis is the latest self-inflicted wound in public health'.[12]

National Pharmaceutical Drug Misuse Framework for Action (2012-2015)

Within the context of the National Drug Strategy 2010-2015, the National Pharmaceutical Drug Misuse Framework for Action identifies national priorities and provides a guide for actions to minimise the harms to individuals, families and communities from pharmaceutical drug use and misuse. (Here a definition of misuse is needed).

The Framework aims to reduce the misuse of pharmaceutical drugs and associated harms, and improve the quality use of medicines without stigmatising patients or limiting accessibility of medicines for therapeutic use for endorsed or evidence-based indications.

The goals of the Framework are:

- to reduce the misuse of pharmaceutical drugs and associated harms in Australia
- to enhance the quality use of pharmaceutical drugs without stigmatisation or limiting their accessibility for therapeutic use.

Many of the priority areas and proposed actions are still valid. Changes to regulation are only part of the wide range of possible measures and may be less important than changing both prescribing behaviours and patient expectations of receiving opioid analgesia for non-cancer chronic pain. There were, however, a number of possible regulatory actions identified in the

[10] www.penington.org.au/australias-annual-overdose-report-2017/
[11] Roxburgh A and Burns L (2017) NDARC report, https://ndarc.med.unsw.edu.au
[12] Makary MA, Overton HN and Wang P BMJ (2017); 358: 98-99

framework that if implemented could reduce excessive or inappropriate (unsanctioned) opioid prescription or use. These included:

- real time on-line prescription monitoring and should be embedded with "My Health Record"
- medication labelling reforms
- better financial and geographical access to treatment for opioid dependence
- access to tamper-resistant medications to reduce intra-nasal and intra-venous use
- exploring opportunities to improve access to non-opioid adjuvant medications for pain conditions
- where possible, enhancing the range of medication pack sizes and/or dispensing options for PBS medications.
- Patient education
- Medical Benefits Scheme (MBS)Remuneration cues
- Mandating prescribers document guideline implementation as part of the opioid approval process.
- Disciplinary actions for illegal or unethical prescribing and targeted education for higher volume prescribers.

Re "real time on-line prescription monitoring," this should be embedded with the e-health project, "My Health Record."

Re: better access to tamper-resistant medications. It should be noted that this reduces intra-nasal and intra-venous use but not oral route, the preferred route of 72-97% of those who misuse opioids (2).

The Opioids Roundtable

In May 2015, an Opioids Roundtable was held in Canberra as part of the Post-market Review of Authority Required Pharmaceutical Benefits Scheme Listings. The Review aimed to improve patient safety and care by reducing administrative burden for health professionals, and with regard to PBS listed opioids, to continue to manage the risks of use, misuse and diversion. While the focus was on PBS listings and restrictions for opioids, discussion was held in a broader context and covered a range of issues associated with opioid use. Key points regarding chronic pain care included:

- Regulation of opioids should support and encourage best clinical practice and the quality use of medicines.

Psychosocial factors influence a patient's experience of pain, (in acute pain) their chance of developing chronic pain and their risk of opioid misuse. Psychosocial factors should be regularly, A discussion about identifying "vulnerabilities" is optimistic as "risk assessment tools" have not been shown to aid the identification or prevention of such specific opioid-related problems. Rather, they reflect how the fear of providing opioids to addicts or of creating addicts is a major barrier to providing opioid analgesics (3).

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- Patients should be managed under a comprehensive treatment plan that considers psychosocial factors and includes multimodal strategies for pain management.
- Better system pathways and linkages between health professionals are needed to facilitate this shared care approach.

"All patients with chronic non-cancer pain should undergo a trial treatment period of 1-3 months to assess their responsiveness to opioid therapy." This is based on expert opinion from the palliative care model and is non-evidence based. Opioids are hard to stop and may cause neurotoxic effects resulting in worse pain and related outcomes. Their initiation in chronic pain (CP) of musculoskeletal origin has now been shown in a randomised controlled trial to be associated with worse outcomes over twelve months (4). The non-initiation group also had less medication-related adverse reactions and emergency department visits. This paper is in press to be released March 6, 2018. In opioid-naïve patients, an initial prescription of opioids for over a week has been associated with a doubling of the proportion still using opioids one year later (6% to 13%) (5). This observation may be explained by the pre-clinical evidence that brief exposure to opioids after a nerve injury initiates prolonged chronic neuropathic pain and, potentially, neuroinflammation across the CNS (6). For these reasons the initiation of opioids on a "trial basis" may contribute to pain and other opioid-related harms, and should be rejected. Data are needed to inform best practice and support evidence-based decision making. This is assuming that CP care involves opioids and now may be unethical with evidence from the Krebs RCT trial (4).

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Although it is important to reduce the regulatory burden on clinicians, any relaxation of regulatory control should not make it easier for patients to obtain, and thereby potentially misuse or be harmed by, opioids. Assumes that reducing regulatory burdens on prescribing opioids in CP is a good thing. Is this evidence-based? We do need better regulatory support. It is possible to access a print-out of a complete list of past PBS prescriptions. However, many clinicians would be unaware of this facility or would be unable to locate the required documents at: https://www.humanservices.gov.au/sites/default/files/documents/2690-0611en.pdf . It may take over half a year to receive this useful print out.

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- An online authority system should include prompts to encourage quality use of opioids, and mandatory data fields to assist with data collection and inform policy development.
- It is unlikely that the current 12-month review is effective, as this time frame is too long to ensure quality use of opioids.

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Real-time prescription monitoring systems are an excellent tool to identify those patients who see many doctors and those clinicians who are higher prescribers. These are an excellent method of identifying those patients who see many doctors and those clinicians who are higher prescribers. However, these groups are not the only ones being harmed or causing harm, and may in fact not even be responsible for the majority of harms.

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- Prescribers and their patients may benefit from more education and training about pain care and opioid management.

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Can some of the problems with opioids potentially be addressed – at least in part – through regulatory measures?

There seem to be six, interrelated main outcomes and/or drivers of opioid-related harms:

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- overdose resulting in morbidity or mortality
- tolerance, requiring higher doses of product being required to achieve analgesia, but with accompanying increases in adverse effects (including potential addiction)
- addiction, including following tolerance and through use at prescribed rather than excessive levels
- deliberate abuse, encompassing use of high doses of immediate release opioids and manipulation of 'abuse deterrent' dose forms
- overuse or inappropriate use

diversion of legally-prescribed product to others for abuse purposes.

Add the following to the six, interrelated main outcomes and/or drivers of the problems:

- Opioids seem to be prescribed for large numbers of people outside the treatment of severe short-lived pain during acute painful events and at the end of life (7)
- Opioids used in the short-term may chronicify and increase pain (as per dot point 5)
- Opioids may delay functional recovery and return to work (8)
- Opioid use is associated with depression and sleep abnormalities (9, 10)
- There is little awareness that pain presentations are being altered iatrogenically by the pharmaceuticals themselves. Behaviours and affective changes may include, heightened distress, and an "unshakable belief in the supremacy of opioids" (11).
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At the highest level, regulatory approaches may have greater impact on unsanctioned (including excessive) opioid use while educational approaches may impact more on inappropriate prescribing of opioids.

An analysis of the TGA's role and powers under the *Therapeutic Goods Act 1989* and Regulations indicates that the TGA could implement particular measures that relate to the indications for opioid products (that is the approved circumstances in which the medicine can be prescribed), the pack sizes available, and ensuring comprehensive information in the Product Information (PI) and Consumer Medicines Information (CMI) regarding the risk of dependence, addiction and the potential for misuse or abuse. Because the policy purpose of the medicines scheduling framework is around controls on 'access' and appropriate safety labelling, it is also possible that scheduling controls could be useful (particularly greater use of conditions, in particular appendices to the poisons standard).

The role of regulation in addressing the opioid 'crisis' has come under the spotlight, particularly in the USA. The US National Academies of Science, Engineering and Medicine was commissioned to lead a major study 'Pain management and the Opioid Epidemic: balancing societal and

individual benefits and risks of prescription opioid use'.[13] Of the six chapters of the report, one is dedicated to reviewing current opioid approval and monitoring approaches by the US Food and Drug Administration (FDA). Senior leaders at FDA have also recently expressed the view 'simply reinforcing opioid related activities that are within FDA's traditional regulatory scope will not suffice to stem the tide'.[14]

Apart from possible TGA regulatory action, consideration should be given to the wider control mechanisms available in the Australian health care system. The states and territories have an important regulatory function in the prescribing and supply of controlled drugs, and other medicines that have an abuse potential. For example, they currently specify reporting requirements, and issue permits to prescribers to allow them to prescribe controlled drugs, such as S8 opioids. State and territory systems for the approval are also currently evolving to provide additional support and guidance to prescribers of opioids. Some states and territories are currently reviewing authority requirements to prescribe opioids, particularly around knowledge, practice and documentation requirements around use in chronic pain, patient education and informed consent and patient treatment agreements. (see notes)

The Australian Government has recently (Tanya Plibersek announced funding for this in 2012) extended funding to implement a national real-time prescription monitoring solution using the Electronic Recording and Reporting of Controlled Drugs (ERRCD) system for reportable S8 (and selected S4) medicines. Real-time reporting and alerts will assist doctors and pharmacists to identify patients who are at risk of those harms related to dependence, misuse or abuse of controlled medicines, and patients who may be diverting these medicines. It will limit 'doctor shopping', through provision of alerts to doctors and pharmacists if patients they have prescribed/supplied controlled drugs to have received multiple supplies of these monitored medicines from other practitioners.

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ERCCD will also provide state and territory regulators with usage data to assist with statistical analysis to detect non-compliance and provide opportunities for active intervention where these are identified. States and territories are the implementers of the ERRCD system. Given the responsibility of states and territories as regulators of controlled drug prescribing and monitoring, they are responsible for the implementation of the ERRCD within their jurisdictional boundaries consistent with what best represents the requirements of the jurisdiction to meet their local drugs and poisons regulatory responsibilities. Effective follow-up, education and on-going monitoring will be crucial to the success of the ERCCD. The involvement of health professionals in the effective implementation of real-time prescription monitoring will also be critical.

Through education programs, clinicians are being increasingly reminded to avoid prescribing opioids for chronic non-cancer pain, to be cautious about simply continuing earlier prescriptions, and to plan an exit strategy for opioids for each patient from the start. However, there is little funding for medical education research to determine if this is effective. A review of the suitability of the regulations around S8 opioids would align with the intent of the recent review and regulatory action by the TGA around rescheduling codeine-containing products, but potentially go further than scheduling-related issues.

The regulatory powers and role of regulators differ between countries. For example, both the US FDA and European Medicines Agency (EMA) have a regulatory role over the medicines supply chain that the TGA does not. Therefore aspects of management of medicines distribution and diversion in the supply chain are difficult for the TGA to enforce. Matters that the TGA can take into consideration when deciding whether to register a product may be different to those of FDA

[13] National Academies of Science, Engineering and Medicine (2017) doi:10.117226/24781.
[14] NEJM 374:15 14 April 2016.

States and territories, as regulators of the prescribing and pharmacy supply of prescription medicines, are responsible for the reporting and monitoring of prescription medicines within their jurisdiction, consistent with their respective drugs and poisons regulations. This responsibility includes determining which medicines are considered as reportable within their jurisdiction.

Australians would be better served if there was a consistency of rules and regulations around opioid prescribing and definitions of dependency both Federally and around the States and Territories (12, 13).

There needs to be more effective communication between Federal and State authorities as well as relevant criminal justice agencies. The proposed real-time, on-line monitoring system needs to be integrated with the “My Health Record” project.

Regulatory options for consideration

The TGA seeks feedback on the range of options presented below. It should be emphasised that regulatory responses will only potentially be part of a broader process to address the problems with excessive or inappropriate use of opioids. Changes in prescriber behaviour and changes in community expectations about the use of opioids in management of chronic non-cancer pain will have greater impact on appropriate prescription and unsanctioned use of opioids, although regulation has an important role to play.

For example, a major driver of increases in opioid prescriptions in Australia in recent years has been management of pain associated with osteoarthritis, although there is a lack of evidence for their use. Notwithstanding this, in the financial year 2015-16, 1.1 million PBS opioid prescriptions were dispensed for managing pain associated with osteoarthritis, a figure which has been forecast to grow to approximately 3 million by 2030.[15]

The widespread use of opioids brings with it the likelihood that many Australians – perhaps more than half a million – are currently dependent on opioids yet receive ongoing prescription. The implications of restricting availability of opioids on the clinical management of dependent individuals need to be addressed within a wider health systems context. Management of concurrent pain and addiction, particularly in general practice is challenging.

While different options are presented below these are not considered to be mutually exclusive and the strategy relies on the use of multiple levers to reduce prescribing and to reduce the risk of misuse, abuse and diversion (in other words, unsanctioned use) of S8 opioids. It is suggested (not sure why) that there is a need to be careful about adding extra layers of regulatory control to an already complex regime that encompasses both State and Commonwealth laws. Thus both the clinical impact and potential regulatory burden of any additional measure/s will need to be carefully monitored.

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The focus of the paper is on powers available under the Commonwealth *Therapeutic Goods Act 1989* and regulations, but where these powers and the potential options below interact with other schemes, references to the PBS, states and territories and education of health professionals are made.

We note all of these options revolve around the use of opioids and should rather focus on holistic pain care in general.

A few additional points:

The TGA could consider the risk of chronic pain (CP) as one factor in considering the introduction of new pharmaceuticals and devices. This is because some life-saving or life-prolonging therapies come with the risk of chronic suffering.

The TGA should promote the regular use of a brief multidimensional pain outcome measure. The P.E.G. scale takes only seconds and covers “Pain intensity,” “interference with Enjoyment of life” and “interference with General activity” (14). The PEG scale should be accessible through drop-down options in electronic health

[15] Ackerman IN, Zomer E, Gilmartin-Thomas JF-M and Liew D, Osteoarthritis and Cartilage (2017) doi http://dx.doi.org/10.1016/j.joca.2017.11.001.

records (EHRs) and able to be monitored in the same way as GPs currently do for cardiovascular risk factors.

The TGA should recommend using the accreditation process and "Practice Incentive Payment" (PIP) scheme to encourage practice based strategies.

We have been advised that GP Mental Health Treatment Plans ("Better Access to Mental Health Care") does not accept CP as a criterion for psychological service subsidies. While many CP patients have mental health co-morbidities, not all do, and the TGA should recommend that these patients should also be able to access mental health specialists to aid the CP care.

The TGA should ensure the PBS subsidies correlate with evidence. Thus, subsidies for opioids provided for the indication of CP could be switched onto opioid substitution therapy (OST) and safe non-opioid therapies (e.g. topical lignocaine). This is particularly pertinent following the up-scheduling of codeine. The TGA could well suggest to the PBS that they remove their subsidies for opioids outside active cancer treatment, palliative care, and end-of-life care.

The TGA should recommend that GP EHRs include appropriate clinical prompts and assessments.

The TGA should facilitate the ease by which GPs may refer CP patients to multi-disciplinary care providers.

The TGA should discuss with Medicare whether the current funding model of general practice should be reconsidered. It is currently based on productivity, so practicing 6-minute medicine is disproportionately rewarded. This equates to a quick script or a quick referral for all problems, particularly concerning given the association of CP with complex, multi-morbidity. This could better remunerate the provision of a broad range of analgesic approaches by GPs.

The TGA should ban the promotion of "trials" of opioids for CP indications. At least one pharmaceutical company selling opioid analgesics is recommending their use in trials for patients already on codeine. Mundipharma is not a current member of Medicines Australia. Medicines Australia is the self-regulating body tasked to ensure balance and accuracy in pharmaceutical advertising. Non-universal membership undermines such aims.

The TGA should encourage the collating of, or developing of, patient education materials about pain and treatment treatments. Making these accessible through GP EHRs or via community education.

The TGA should highlight the risks of the co-consumption of benzodiazepines and the relative risks of higher doses of opioids.

The TGA should increase awareness of the potential risks from misuse of the gabapentinoids (15).

As an indirect measure to improve CP care, we need to stop treating addiction treatment services with the same prejudice people naturally have for addicts. This is happening at a clinical level with few medical practitioners identified as authorised methadone prescribers. It is also apparent at a regulatory level, with OST not being PBS subsidised and with OST being seen as a responsibility of the States and Territories. Many people with opioid or other drug problems need to be able to access both therapies directed at their psychopharmacological problems as well as holistic pain care.

We need to address the way that urine toxicology is funded to align with clinical needs (16).

We should consider establishing a Controlled Substance Review Group to assist clinicians deal with challenging CP cases (17).

Authors of research papers and education presenters are required to declare conflicts of Interest. One of us recently had to call the police due to the aggression from a chaotic CP patient armed with a letter from his pain physician which described tapentadol as being non-addictive and not causative of tolerance and hyperalgesia. This pain physician regularly writes or presents in support of this opioid. We call for conflicts of Interest statement included in letters to colleagues where relevant.

We call on the TGA to mandate pharmacists to collect all unused opiates upon the death of a patient within 24 hours. This needs to be incorporated into "real time care." Many opioid misusers know palliative care patients have been liberally supplied with opioid analgesics and so target such situations in order to access the drugs.

We call on the TGA to ban pharmaceutical companies from all TGA & PBS hearings relating to the assessments of any of the mentioned addictive S8 or S4 drugs. We believe that their clear conflicts of interest & pressure appear to have hindered

objective assessments in the past. It is imperative that when their submissions are considered by the TGA/ PBS panels, this is done without the bias of conflicted industry in attendance.

We advocate for pharmaceutical companies that market opioid analgesics to be "blind taxed." These funds could be directed to the relevant colleges & the NPS to be utilised for practitioner education.

Option 1: Consider the pack sizes for Schedule 8 opioids

For consideration

- **The option**: Require sponsors to register and make available for supply both smaller (such as maximum three-day) pack sizes for treatment of patients with acute pain and suitable pack sizes (14 or 28-day) for treatment of people with chronic pain due to malignancy.
- **Potential implementation**: If agreed, these changes may be able to be implemented using powers through either or both the scheduling and/or the registration process.

While opioids are effective in acute pain, there are many cases of patients who after dental or minor surgery that may (only) require 1-3 days of analgesia, are nonetheless being prescribed 20 or 28 unit-dose packs of high dose-codeine or oxycodone. There is evidence that continued use of strong opioids for two weeks can lead to dependence and requests for further prescriptions to 'address the pain'.

A study from the US Center for Disease Control supports the concerns about excessive pack sizes for the management of acute pain where it was found that opioid naïve patients who filled a prescription for over a 30-day supply of opioids had a 29.9% chance of using opioids for one year or more.[16]

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Most opioids are listed on the PBS as Restricted Benefits for the treatment of moderate to severe disabling pain, with quantities limited to about 14 days of treatment. Prescribers may telephone the Department of Human Services to obtain an authority to prescribe larger quantities and/or repeats for patients who need long-term medication. For patients who require more than 12 months of treatment, another practitioner must review the patient before further authorities may be granted by the Department of Human Services.

This proposal would implement a system where there are both smaller (such as maximum three-day) pack sizes for treatment of patients with acute pain and suitable pack sizes for treatment of people with chronic pain due to malignancy (and in cases of chronic non-cancer pain, where opioid prescribing is unavoidable) where shorter courses would be a major inconvenience at a difficult time in their lives. However, this would require clearer delineation of

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[16] Shah A, Hayes CJ and Martin BC MMWR Morbity and Mortality Weekly Reports 66 (2016) 265-269 doi: 10.15585/mmwr.mm6610a1

indications for both long-term and short-term use to enable two different pack sizes to be indicated. The CMI for post-operative opioid analgesia could include information about de-escalation of opioid doses and moving to non-opioid pain relief medication.

Changes to the PBS listing could also be considered. Currently, apart from fentanyl lozenges and similar formulations, the indication for opioids is chronic severe disabling pain which is unresponsive to non-opioid analgesics, rather than acute post-surgical pain or cancer-related pain. This would require consultation with the Pharmaceutical Benefits Advisory Committee (PBAC). We should also include the indication of respiratory failure and dyspnoea.

This approach is consistent with the recommendations of the US FDA Commissioner who has asked that changes in pack size be considered in conjunction with health professional groups to develop standards for prescribing (and dispensing) opioids in different clinical settings, including certain cases of chronic non-cancer pain. In the USA, a number of the electronic prescribing software systems set 30 tablets as the default setting (similar to the default settings in clinical prescribing software in Australia), even though this is excessive for most post-operative pain regimens.[17] FDA is considering approval of new forms of packaging for opioids such as blister packs containing a limited number of tablets, or packaging that can track the number of doses taken.

While most oral solid dose forms of S8 opioids are packed in quantities of 20 or 28 units, there is currently nothing to stop a doctor writing a prescription for a lesser amount and to dispense quantities less than those contained in the manufacturers packaging. While some hospitals routinely use this approach for suitable patients, it is not widely done. Impacts on secure storage space in hospital and community pharmacies and on whether prescribers choose to prescribe smaller packs under the PBS or as private prescriptions would need to be considered.

We agree with this proposal to tailor the size of the pack to the indication. So, a three-day immediate release pack size would be safer and applicable to indications where there is severe short-lived pain such as following surgery.

Option 2: Consider a review of the indications for strong opioids

For consideration

- **The option:** The TGA will review indications for the S8 opioids and align them to current clinical guidelines for appropriate prescription of these products.
- **Potential implementation:** This could be done following review of Cochrane and other reviews and meta-analyses of clinical data on opioid efficacy, assessment of therapeutic guidelines for pain treatment and through a standard consultative TGA process. It would require changes to the PI for the products where required (see sections 9D and 25AA of the *Therapeutic Goods Act 1989*). The TGA does have the necessary legal powers to enforce safety-related PI changes.

[17] Makary MA, Overton HN and Wang P BMJ 359 (2017) 98-99

The approved indications from the Australian Register of Therapeutic Goods (ARTG) entries for different strong opioids are both inconsistent between products and inconsistent between members of the class. For example the indication for Oxycontin (oxycodone) is 'The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia', while low-dose (10-15 mg) oral morphine seems to have slight variants between the ARTG entries for different brands, for example 'The treatment of chronic severe pain of cancer' … 'The relief of chronic pain unresponsive to non-narcotic analgesia' … 'Treatment of opioid responsive, chronic severe pain'.

While differences in patient groups which may benefit more from the use of a particular type of opioid may be justified based on their pharmacology (for example oxycodone is a delta, mu and kappa opiate agonist, morphine a mu agonist, fentanyl is more suitable for patients with renal failure, buprenorphine is a partial agonist), the current indications do not seem to be based on differences in pharmacology. Moreover, in many cases there is no mention of cancer pain in the indication; rather it is a broad indication of chronic pain unresponsive to non-opioid analgesia or opioid responsive pain. This can potentially lead to prescribing for non-cancer chronic pain (such as arthritic or neuropathic pain).

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Current guidelines on the management of chronic non-cancer pain focus on non-pharmacological management of pain and there has been a shift towards functional improvement rather than simply focusing on the pain level. Additionally there is little evidence to demonstrate the efficacy of opioids for chronic non-cancer pain, particularly in the long term[18] and because of their low efficacy and high risk of harm current guidelines recommend that health professionals should consider de-prescribing.[19]

Under this option, a review would be carried out of the current indications for strong opioid products and align them to current clinical guidelines for the appropriate use of these products. This review could also consider paediatric indications. This could be done through a standard consultative TGA process and require changes to the PI for the products where required (see sections 9D and 25AA of the *Therapeutic Goods Act 1989*). While the latter can be challenging, the TGA does have the necessary legal powers to enforce PI changes. Most usually this has been for safety reasons, but section 9D of the *Therapeutic Goods Act 1989* provides for a variation in the entry of the Register if the entry contains information that is incomplete or incorrect. In this case, the indication is inconsistent with current clinical practice guidelines and is inconsistent in ensuring the safe use of the medicine due to the risk of misuse or abuse. The Secretary's notice to the sponsor to vary the PI as the Secretary considers appropriate is conditional on the Secretary's satisfaction that a variation to the PI is required. It would also be important to work with the authors and publishers of therapeutic guidelines if indications are to be reviewed, and for non-opioid therapies for pain to receive greater emphasis in these guidelines.

It may also be appropriate to review the indications for codeine, given that it is metabolised in the body to morphine, to ensure they are consistent with current guidelines for chronic and acute pain management.

We agree with this proposal: however, we suggest the addition of the indications of palliative care for dyspnoea and of opioid substitution therapy for dependency care.

[18] https://www.nps.org.au/medical-info/clinical-topics/chronic-pain
[19] https://www.nps.org.au/medical-info/clinical-topics/news/chronic-pain

Option 3: Consider whether the highest dose products should remain on the market, or be restricted to specialist / authority prescribing

For consideration

The option: Review the place of the higher dose S8 opioid products in the management of chronic cancer and non-cancer pain and whether certain high dose products should continue to be registered. We would consider if specific controls, such as approval to prescribe through states and territories or the PBS should be introduced.

Potential implementation: The TGA could undertake a safety review of the benefit/ risk ratio for higher dose S8 opioid products but data is likely to be confounded due to different chronic pain populations (cancer versus non-cancer pain) and opioid tolerance.

Alternatively specialist-only / authority prescribing could be specified for PBS reimbursement, noting that this would not impact on private prescriptions (these could be potentially managed through state and territory regulations).

While many opioid dependent/chronic users of opioids (for example cancer patients) require escalating doses to achieve effective analgesia, these higher doses are associated with greater morbidity and mortality and risk of diversion and abuse. The high dose extended / sustained release versions of oxycodone – even if in notionally abuse-deterrent form – are also most subject to diversion because of their high opioid content.

In August 2017, the US FDA was petitioned by a group of public health officials and physicians to remove opioids that that contained more than 90 Milligrams Morphine Equivalents (MME) in potency, due to the higher risks of addiction or overdose of these products.[20] The US Center for Disease Control and Prevention (CDC) 2016 guidelines on opioid prescribing state that clinicians should avoid prescribing at levels above 90 MME per day or carefully justify why the dose is needed. [21] The CDC also advised that doses at or above 50 MME a day doubles a person's risk of overdose compared with a dose of less than 20 MME a day. This would impact on extended release oxycodone 80 mg (at two times a day equals 240 MME per day) and immediate release oxycodone 30 mg (at four times a day equals 180 MME per day). However, palliative care providers in the US responded that high dose opioids can be beneficial for managing pain in terminal cancer patients and so removing these products could result in patients who need higher doses to manage their cancer pain would not having access and therefore disadvantaged.[22] Under this option it may also be possible through state and territory regulation for general practitioners (GPs) to be permitted to continue treatment for a limited period with the consent of the original specialist permit holder. The impacts on access and cost under this option would need to be considered.

[20] www.pharmacytimes.com/conferences/painweek-2017/health-groups-petition-fda-to-pull-highpotency-opioids

[21] www.cdc.gov/drugoverdose/prescribing/guideline.html

[22] www.pharmacytimes.com/conferences/painweek-2017/health-groups-petition-fda-to-pull-highpotency-opioids

Fentanyl is of particular concern as its use is increasing and is 80-100 times stronger than morphine milligram for milligram.[23] Because of its strength it has a much shorter time to overdose than other opioids and so an increased risk of overdose and death. In the US the number of deaths associated with fentanyl has increased by 540% over the last three years and drug overdose remains the leading cause of cause of death for Americans under the age of 50.[24] Because of the risk of overdose with these products the wider availability of naloxone has been suggested. Health Canada made changes in March 2016 to allow naloxone to be provided proactively to who might experience or witness an opioid overdose.[25] Similar changes could be considered in Australia, noting that naloxone is already Schedule 3 (Pharmacist Only/ over the counter) in Australia when used for the treatment of opioid overdose.

We agree with this proposal. Higher dose or higher morphine equivalence option should be restricted to end-of-life care only. Hydromorphone hydrochloride 32 mg and 64mg, Oxycodone hydrochloride 40mg and 80mg and fentanyl (theoretically dosing at 50 microgram/hour, 75 microgram/hour and 100 microgram/hour) patches may be restricted. We also recommend that non-PBS or private scripts for higher dose or higher volumes are also given regulatory scrutiny. Specific advice about overdose risk could be mandated as part of approval for provision.

We also need to reduce the range of clinicians who may prescribe opioid analgesics. There has been a great push by the pharmaceutical industry to educate nurses in Residential Aged Care Facilities to regularly score pain out of ten and treat higher scores with opioids. Their nurse practitioners are then authorised to do so.

Option 4: Strengthening Risk Management Plans for opioid products

For consideration

The option: Review current risk management plans for opioids to determine whether they currently reflect best practice in opioid prescribing and management of risks.

Potential implementation: Work with sponsors to update their Risk Management Plans (RMPs) to minimise risks associated with overdose, misuse and abuse.

Most opioid medicines were registered before 2009, when the requirement for an RMP was introduced in Australia for new chemical entities and extensions of indications and so do not have an RMP in place.

[23] www.abc.net.au/news/2017-10-13/could-fentanyl-be-australias-next-deadly-drug-epidemic/9048530
[24] www.nytimes.com/interactive/2017/09/02/upshot/fentanyl-drug-overdose-deaths.html?emc=eta1
[25] www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/narcan-nasal-spray-frequently-asked-questions.html

The US FDA mandated a class Risk Evaluation and Mitigation Strategy (REMS) for opioids in 2012 and it would be possible to consider this option.[26] The major focus of the US REMS for opioids was on health care professional education and training. This approach is one of the risk minimisation activities that an RMP can require and has been required for some novel products, such as new anticoagulants where clinical practice was different. In these cases, the TGA has required the sponsor (see notes) to provide an educational activity and that it meets the requirements for Continuing Professional Development (CPD) points for relevant medical colleges. The approach taken by the US FDA to impose a class REMS means that there are a wide range of educational activities provided and would be product-specific.

In Australia we have access to the NPS MedicinesWise which provides education to health professionals, is seen as an independent and therefore a reputable source of information and which has CPD accredited activities for opioid use in chronic pain management[27] as well as resource material for consumers on the use of opioids in the management of chronic pain.[28]

It is beyond the role of the TGA to specify the detailed requirements for an educational program but if it were to be made mandatory, in conjunction with delivery by relevant colleges, some topics have been suggested. These include: how to provide excellent non-addictive (non-pharmacological) chronic pain care, biopsychosocial determinants of pain; acute versus chronic non-cancer pain; pain types; ineffectiveness of opioids in chronic non-cancer pain and their non-core role in management; risks and harms; risks versus benefit prescribing decision making; new and inherited patient management; goals, trials (see previous note about "trials") tapering and cessation aspects. Colleges could also require continuing medical education for the prescribing of opioids such that a mandatory module has been completed. Recent initiatives on better opioid prescribing from a number of the clinical colleges, such as the Royal Australian College of General Practitioners updated guidelines on the for the prescribing of drugs of dependence in primary care is also noted.

We somewhat disagree with this proposal as it assumes opioid provision can be without risk. We presume the "risk" referred to is that of addiction. We believe clinicians need to re-think pain treatment as routinely including assessments of trustworthiness or opioid-addiction risk. Pain is not just an opioid deficiency. Focusing on addiction risk reinforces the old binary of genuine pain patient vs opioid misuser. This is a moral decision and usually unhelpful in managing pain or opioid-related harms. There is poor evidence supporting tools designed to predict and identify addiction risks (18). The majority of overdose deaths occur in those prescribed lower doses, presumably because this is a far larger population and so despite the lower individual rate of overdoses, this group have higher numbers harmed (19).

We would be concerned about any proposal to require the sponsor/pharmaceutical company to "provide" an educational activity. One could be sure this would become education that would aim to maximise sales while being swathed in a cloak of "judicious" prescribing. In the US the Risk Evaluation and Mitigation Scheme (REMS) educational project has failed to meet the target numbers planned. Furthermore, the

Deleted: The effects of opioids in high doses and overdoses, and their adverse drug reactions at lower doses are well known, so we do not see a specific benefit from increased active (rather than passive) post-market surveillance programs here.

[26] www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm
[27] www.nps.org.au/medical-info/clinical-topics/news/chronic-pain
[28] www.nps.org.au/medical-info/consumer-info/chronic-pain-explained?c=opioid-medicines-for-chronic-pain-804d9703

evaluation of the effectiveness of this educational intervention utilises the relatively weak research methodology of pre-workshop and post-workshop surveys (20).

The discussion paper notes, "The effects of opioids in high doses and overdoses, and their adverse drug reactions at lower doses are well known, so we do not see a specific benefit from increased active (rather than passive) post-market surveillance programs here." We beg to disagree. There is not widespread knowledge of how opioids may cause pain, depression, poor function and poor sleep. We believe that there is a lack of evidence about many aspects of pain management in primary care. We have not got an effective model of primary care for chronic pain, nor a clear framework about what educational or other intervention will achieve this goal.

On the topic of current risk-management, we feel that 12-month PBS review is too late and can reinforce a 'set and forget' approach for subsequent scripts. Furthermore, with pharmacists becoming more active in dispensing & monitoring opiates, we would like to see electronic linking of their dispensing systems so that prescribers become fully aware of poly-doctoring, poly-dispensing, & poly-pharmacy.

As we stated above, real time, on-line pharmaceutical monitoring should be embedded with, not separate to, the "My Health Record".

Option 5: Review of label warnings and revision to the Consumer Medicines Information

For consideration

The option: Under this option, warnings could be placed on the packaging of opioid products identifying the risk of dependence and overdose and lack of efficacy in the long term treatment of chronic non-cancer pain, noting that the complexity of appropriate management of chronic non-cancer pain needs to be recognised. The CMI would also be reviewed to provide greater emphasis on risks of dependence, especially those associated with high doses.

Potential implementation: This may be able to be achieved through modification to the current Therapeutic Goods Order around prescription medicines (TGO 91), although changes to appendices to the Poisons Standard (Scheduling) and to conditions of registration of new strong (S8) opioids could also underpin this requirement. We would need to work with sponsors to obtain CMI changes. It would need to be determined whether S4 opioids such as tramadol would be included in this scheme.

Under this option an additional warning would form part of the manufacturers' packaging, although an alternative may be to require it as a supplementary label added by the pharmacist at

the time of dispensing. There are already requirements for a label to be added at the time of dispensing (labels 1 / 1A of the Australian Pharmaceutical Formulary) if a medicine has sedating properties. It is unusual for a prescription medicine to require a warning on the outer physical pack, as the warnings are included in the PI and CMI. This is unlike over-the-counter registered medicines where there is no PI or CMI, and therefore the packaging includes significant safety issues to alert consumers to risks. With the rescheduling of codeine, all analgesic opioids will be prescription medicines from February 2018 and will have both a PI and CMI. While a boxed warning could also be included on the packaging identifying the risks of long term use this may deter the appropriate use of opioids where they are indicated. To date no product has a boxed warning on the packaging.

The TGA has recently introduced a program to reformat the PI. For prescription medicines all PIs in the new format will include the following information 'In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy' this should encourage people to dispose of rather than keep any unused opioid medication. An existing program called Return Unwanted Medicines (RUM), which involves pharmacies to collect unused medicines was established in 1998 and is funded by the Australian Government.[29] In 2015-16 pharmacists collected more than 700,000 kg of unwanted medicines. This service could be actively promoted to encourage the removal of opioid medication from the community but it would be difficult to mandate or enforce this.

Changes to on-pack labelling could also include a requirement for barcoding or QR coding to assist in supply chain management of these products and to reduce the risk of diversion. This builds upon similar initiatives in the EU, although regulators in the EU and USA have powers (or are in the process of obtaining them) over the entire pharmaceutical supply chain. These are not currently available to the TGA.

The consumer warnings in the CMI could be updated to more clearly advise that opioids are not recommended for long-term use in chronic non-cancer pain, and acute treatment should be limited to a few days and then pain managed by non-opioid medication. The CMI could also include information about the risks of overdose associated with high doses of opioids. While the TGA does not approve the CMI it should mirror the information in the PI, therefore ensuring the PI has the correct information about the risks and appropriate use of opioids would ensure it was mirrored in the CMI. Work is necessary to make sure the CMI remains consistent with the PI, as is currently required, but also to make both the PI and CMI much more readily available. The TGA has recently launched the Medsearch App which allows consumers and HCP to readily access PI and CMI information from their mobile phone to assist in easy access to this information.

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We agree with this proposal. Risks on labels could include a range of harms including increased pain and an inability to cease them.

Concerning Tramadol. This pharmaceutical utilises the same metabolic pathways as codeine and so has an unpredictable pharmacokinetics. It has been written, "Giving a known dose of tramadol is tantamount to giving an unknown dose of opioid" (21). Furthermore, tramadol may cause serotonin syndrome, seizures and hypoglycaemia requiring of hospitalisation (22). The relative clinical complacency with tramadol may be mirrored in the community with it appearing to us to be particularly frequently diverted.

[29] www.returnmed.com.au/pharmacists

Option 6: Consider incentives for expedited TGA review of improved products for pain relief and opioid antidotes

For consideration

The option: Provide priority review to new chemical entities that are viable alternatives to opioids for pain relief and also expedite the review of smaller pack sizes and/or abuse-deterrent formulations and products that can be used to negate the effect of opioids.

Potential implementation: This would be responsive to submissions received from sponsors of products and utilise the current regulatory framework.

This may include new therapeutic alternatives for the treatment of pain, in particular chronic pain. While each dossier would be considered on a case-by-case basis by the relevant TGA delegate, it is quite likely that a submission of this type would meet the requirement for priority review. However, while there are some potential novel compounds under development[30] there are few contenders for regulatory approval in the immediate future. So while this option should remain 'on the table' there are few therapeutic alternatives on the immediate horizon. Given the TGA's industry cost-recovered model there is not the option to provide taxpayer-funded financial incentives for the development of alternatives to opioids.

However, this option may also include smaller pack sizes and/or abuse-deterrent formulations for opioids or new formulations or presentations of antidotes. Such commitment to would potentially be 'informal', as it may not meet the current formal criteria for TGA priority review, as set out in regulation. Regulatory fast-tracking of abuse-deterrent formulations of opioids should be considered, especially where there is international evidence that the product is genuinely abuse deterrent in its properties. Abuse deterrent opioids on the market or under development include:[31]

- combinations of the opioid agonist with an antagonist such as naloxone, in a dose form that only releases the antagonist if injected
- delivering the opioid in a form that is difficult to crush and extract
- combining the opioid with a substance that triggers an adverse response if the medicine is taken at a higher dose than indicated
- developing pro-drugs that require enzymatic activation in the digestive system, so lack abuse potential if injected.

There should not be the need to develop TGA-specific guidance for abuse-deterrent opioids, as there are no local manufacturers for these products, and the Australian market would be small on a global scale, and secondly because there remains some uncertainty on which technologies may be the most effective for deterring abuse while avoiding transfer of the abuse to an

[30] Yekkirala AS, David P. Roberson DP, Bean BP and Woolf CJ, Nature Reviews Drug Discovery 16 (2017) 810.
[31] Volkow ND and McLellan AT NEJM 374 (2016) 1253-1263.

alternative and more dangerous opioids. New formulations of antidotes that allow carers to administer antidotes more simply could also be reviewed in an expedited manner.

More rapid review for alternative non-opioid medicines (but still based on assessment of a full safety, efficacy and quality data set) could be a possible inducement (although there are few alternatives among new chemical entities (NCEs); there are some generics to gabapentin and pregabalin coming onto the market although the gabapentoids are not without abuse problems, particularly in individuals with a history of opioid abuse.[32] It is also proposed to provide rapid review of antidotes as these can be used to mitigate the risks associated with overdose and misuse.

We agree with this proposal. This may also include "orphan drugs" such as low dose naltrexone for use in chronic pain and opioid tapering (23). We need to roll out naloxone kits and overdose education for families and friends of those using or misusing opioids. About a fifth of fatal overdoses in a Victorian series involved a witness who usually did not realise the significance of what they were witnessing (24). At this time, we are informed that naloxone autoinjectors are unavailable in Australia. The US has increasing access to nasal naloxone insufflators and these should be made available here as a matter of urgency.

Option 7: Potential changes to use of appendices in the Poisons Standard to provide additional regulatory controls for strong opioids

For consideration

The option: Powers under medicines scheduling could potentially include controls of prescribing for particular populations or classes of medical practitioners, additional safety directions or label warning statements, specific dispensing labels.

Potential implementation: Delegate decision, following public consultation and advice from the Advisory Committee on Medicines Scheduling on additional controls.

These could potentially include controls of prescribing for particular populations or classes of medical practitioners, additional safety directions or label warning statements or specific dispensing labels (see Appendix 2). For example, oral isotretinion (used to treat severe cystic acne) and known to be associated with severe foetal abnormalities has additional controls listed in Appendix D of the Poisons Standard. It can only be prescribed by a dermatologist or specialist physician. Where the patient is of child-bearing age the prescriber must ensure the possibility of pregnancy has been excluded prior to commencing treatment and advise the patient to avoid becoming pregnant during treatment and for one month after completing it. In some

[32] Evoy KE, Morrison MD, Saklad SR. Drugs. 2017 Mar;77(4):403-426 doi: 10.1007/s40265-017-0700-x.

jurisdictions, GPs may seek approval for ongoing prescribing if the patient has been seen by a dermatologist or specialist physician and lives remotely where ongoing specialist services are not accessible.[33]

While the TGA would need to seek legal advice on the potential ability of amendments to the Poisons Standard to limit prescribing of S8 opioids to certain medical practitioners (such as palliative care physicians for high-dose opioids in patients with cancer pain and specialist pain medicine physicians for high-dose opioids in patients with chronic non-cancer pain), allowing access for ongoing prescribing for GPs in remote areas would seem possible. However, this would need to be further examined to determine if product dose rather than a specific product could be limited. The extent of regulatory powers under appendices to the Poisons Standard is generally untested in law, in many cases changes would need to be adopted by the states and territories to have effect.

The US FDA is considering extension of mandatory education for health professionals, to ensure that they are aware of current best practice in prescribing of opioids.[34] In Australia, education is typically viewed as related to clinical practice rather than product regulation, although it is possible that education requirements could be specified in an annex to the Poisons Standard in Australia.

We agree with this proposal. It has been mandated in some US states that those clinicians who wish to prescribe opioids in CP need to complete training in pain and /or addictions. We believe that this TGA paper needs to reframe this proposal away from "misuse" to "use" in CP per se. This is because the misuse binary is subjective and pejorative. Additionally, the binary does not divide those who are harmed from those for whom long-term opioids are without harm.

We need to make fentanyl patch exchanging normalised for community consumers.

Option 8: Increase health care professional awareness of alternatives to opioids (both Schedule 4 and Schedule 8) in the management of chronic pain

For consideration

The option: Existing clinical guidelines for the management of acute and chronic pain provide advice on the use of non-pharmacological and alternate pharmacological therapies for the management of pain. While these are available there may be limited health practitioner awareness and uptake.

Potential implementation: The TGA will work with the NPS MedicinesWise and clinical colleges to increase awareness of health practitioners and the uptake of appropriate pain management guidelines in their practices. This could include developing a comprehensive repository of information about the appropriate use of both S4 and S8 opioids. This could use the active networks

[33] www.health.qld.gov.au/__data/assets/pdf_file/0022/444154/fs-isotretinoin-prescribing.pdf
[34] www.medpagetoday.com/publichealthpolicy/publichealth/65220

established under the Nationally Coordinated Codeine Implementation Working Group.

There are significant resources available from the NPS MedicinesWise (for example www.nps.org.au/medical-info/clinical-topics/chronic-pain), clinical colleges and societies on the management of chronic pain, both cancer pain and non-cancer chronic pain. The current guidelines identify either the limited role of opioids in the management of chronic non-cancer pain (or that evidence is insufficient to recommend them) and focus on the importance of non-pharmacological interventions and de-prescribing or reducing dosage for people who have been on long term opioid therapy.

While these resources are available they may not be readily visible to practitioners. Promoting these activities would ensure that practitioners have access to information to assist them in managing patients with acute and chronic pain according to current guidelines. The information is also difficult to access and the TGA could develop a resource similar to the 'Codeine information hub'[35] for S8 opioids so all relevant guidelines are easily accessible to health professionals.

The New York Department of Health has instituted mandatory prescriber education for all health practitioners able to prescribe controlled substances.[36] They must complete at least three hours of course work on pain management, palliative care and addiction every three years.

It may be possible to work with colleges and the Medical Board to require medical practitioners to undertake mandatory education for prescribing of controlled substances (such as S8 opioids), but this outside the powers of the TGA.

NPS MedicinesWise has developed a National Prescribing Curriculum aimed at undergraduate and postgraduate medical students which includes the use of opioid analgesics in chronic non-cancer pain, opioid dependence, use of analgesics in persistent pain. It may also be possible to work with universities to ensure these modules are undertaken and completed during medical practitioner training.

Better defining the 'clinical pathways' for patients on long-term opioid analgesics, particularly for acute pain after surgery or an accident will be important in reducing the risk of dependence and unnecessary longer-term opioid use. This could involve discussion with the patient of types of pain, de-escalation to over-the-counter non-opioid analgesics after a couple of days of opioid use, and advice on alternative (non-pharmacological) pain management therapies.

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This approach has been utilised successfully to encourage the de-prescribing and de-escalation of oral and steroids in asthmatics after their short-term use. While it is not a strictly regulatory approach (although regulatory education is integral) it could build on the strong planning and communication network NCCIWG that was built around the codeine up-scheduling to prescription-only from 1 February 2018.

Schedule 4 opioids

Following the rescheduling of codeine, the main S4 opioid used for analgesia in Australia is tramadol (noting that neither dihydrocodeine nor dextropropoxyphene are commonly used in Australia). Codeine is present in a significant number of products, and after the rescheduling is

[35] www.tga.gov.au/codeine-information-hub-codeine-use-can-be-harmful
[36] www.health.ny.gov/professionals/narcotic/docs/mandatory_education_guidance.pdf

expected to be available at both low and high doses, typically combined with paracetamol. However, given that it obtains its analgesic effect through metabolism to morphine, and its rate of metabolism varies significantly between individuals, it has some shortcomings as an analgesic. It also is commonly associated with constipation.

Dextropropoxyphene has been associated with a number of significant adverse events (in particular cardiac arrhythmias) yet is relatively weak and variable analgesic. There are some restrictions to its use in Australia.[37] Dextropropoxphene has also been associated with some overdose fatalities, as has codeine.

This leaves tramadol. Its role in therapy and the most appropriate indications may need to be clarified, noting that it is both a mu-opioid agonist and a serotonin and noradrenaline uptake inhibitor (talpentadol, an S8 medicine has a similar mechanism of action). Open for debate is whether the regulation (including the scheduling status) of tramadol would warrant review. While tramadol is one of the six opioids associated with accidental overdose fatalities in Australia, it is in S4 not S8. In the US, tramadol is a Schedule IV drug (along with certain benzodiazepines). This is lower in the risk hierarchy than opioids such as oxycodone (schedule II). It is seen as moderate strength opioid, and has an additional mechanism of action (serotonin and noradrenaline uptake inhibition) to most other opioids. See notes for a discussion about tramadol.

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We agree with this proposal. Over the last few years we have noticed tramadol increasingly present amongst the drugs consumed by poly-drug abusers. Further comments about tramadol were made in response to option 5. We support any increase in funding for medical education research, a field which is perennially under-funded.

Relevant to this option, we believe there needs to be both greater awareness and greater access to alternatives to opioids across the spectrum of pain from acute to recurrent pain to chronic.

Possible role of Pharmaceutical Benefits Scheme prescribing controls

There may also be additional options to better manage opioid prescribing through the PBS. For example, in response to concerns about the significant growth of prescriptions for testosterone in men, PBS restrictions on prescribing were introduced during 2015. A requirement for a specialist review prior to prescription and lowering of the threshold serum levels for testosterone deficiency resulted in the proportion of men getting a prescription in the absence of pathological hypogonadism decreased significantly.[38]

Controls such as narrowing the group of approved prescribers (for example certain specialists) and requiring a telephone authority can also impact on the number of prescriptions for a

[37] www.tga.gov.au/alert/dextropropoxyphene-questions-and-answers[38] www.6minutes.com.au/News/Latest-news/GP-testosterone-scripts-plunge

[38] www.6minutes.com.au/News/Latest-news/GP-testosterone-scripts-plunge

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particular medicine as they require consideration by the prescriber as to whether the prescription meets the requirements for reimbursement.

It is possible that similar PBS prescribing restrictions could have an impact on unsanctioned strong opioid use, although many S8 opioids now fall below the co-payment level for non-concessional patients – for example oxycodone 5-20 mg immediate release products are between $20-28 on private prescription. However, even if private prescription prices are comparatively low, PBS restrictions can cause a prescribing physician to reflect on choice of medicine. It should also be noted that concessional patients are prescribed a disproportionate amount of S8 opioids, especially for the more expensive extended release products. This will also require consultation with the PBAC.

Advisory Committee for Medicines recommendations

The Advisory Committee for Medicines considered an earlier version of this paper at its 5 October 2017 meeting and recommended that in particular further consideration be given to the following:

- The introduction of smaller pack sizes for strong opioids that may be prescribed when short-term use is required, such as for pain relief after surgery.
- A review of the approved indications for S8 opioid medicines and align them to current clinical guidelines.
- Work with the Health Technology Assessment and Access Division of the Department of Health to consider PBS prescribing restrictions, such as smaller quantities and the requirement for specialist medical review of non-cancer pain patients prescribed opioids for extended periods.
- Work with clinical colleges to educate prescribers on judicious use of opioids, treatment de-escalation and the use of non-opioid pain relievers.

Appendix 1: What are the TGA's powers under the Therapeutic Goods Act and Regulations?

One of the key issues is whether the regulatory framework under the *Therapeutic Goods Act 1989* ('the TG Act') and Regulations provides the TGA with similar ability to take public health issues into account as the US FDA can under their Code of Federal Regulations. This includes whether addressing risks of diversion, abuse and off label use of products (for example for use in chronic non-cancer pain) is in the TGA's authorised functions and powers.

Section 25 (1d) of the TG Act states:

> *s25 Evaluation of therapeutic goods*
>
> *(1) If an application is made for the registration of therapeutic goods in relation to a person in accordance with section 23, the Secretary must evaluate the goods for registration having regard to:*
>
> *(d) whether the quality, safety and efficacy of the goods* ***for the purposes for which they are to be used have been satisfactorily established****; so chronic pain would be deleted as this is not "satisfactorily established".*

Prima facie, this suggests that it may be difficult to bring other factors such as abuse, inappropriate use and diversion into account when the TGA is conducting an evaluation of an application to register an opioid. But it would risk individual and public health not to consider the euphogenic potential of each opioid. In the same way as for firearms, one has to consider that they may not just be used by sporting shooters at rifle clubs.

However, there are two other relevant paragraphs of s25(1), namely (f) and (k):

> *(f) whether the goods conform to any standard applicable to the goods;*
>
> *(k) such other matters (if any) as the Secretary considers relevant.*

Paragraph 25(1)(f) might suggest that if we were minded to do so, a specific standard (Therapeutic Goods Order) for opioids could be legally made by the TGA, under section 10 of the TG Act, with specific requirements for that class. When carrying out an evaluation of goods, the TGA would be obliged to consider the conformance of the goods with that standard. However we would need to be assured from a legal standpoint that a court would not find that it is not consistent with the scheme of the Act for the TGA to, in an evaluation decision, use consideration of misuse or diversion by an order under section 10.

Paragraph 25(1)(k) provides for the delegate to take other matters into consideration acknowledging not only that these matters would need to be consistent with the objects of the TG Act but also that section 25(1)(d) might imply a limit to the matters to which the delegate may have regard under section 25(1)(k); that the only use that may be considered is the use for which the goods are intended. Misuse or diversion of a therapeutic good is excluded from being considered. A court may also draw a similar negative inference from the absence of a similar specific reference to the relevance of the potential for abuse of a substance in a scheduling decision (see section 52E(1)(e)).

The TGA published guidelines for addressing potential resistance to antibiotics, specifying data requirements for their pre-market evaluation and also issues relevant to post-market vigilance in 2007 (and updated in March 2017).[39] Antibiotic resistance can be triggered in both 'on label' or appropriate use, aligned with the approved indications, as well as inappropriate (for example

[39] www.tga.gov.au/antibiotic-resistance-guidance

'off-label' use). This guidance document may at least in part be used to explain a consideration that the delegate will take into account under section 25 (1k) when evaluating an application for registration.

Other mechanisms that could be explored are through placing requirements in the RMP for new opioids coming into the system or placing specific conditions of registration on either new or existing products, or both.

Under the US Code of Federal Regulations:

TITLE 21--FOOD AND DRUGS, CHAPTER I--FOOD AND DRUG ADMINISTRATION, SUBCHAPTER D--DRUGS FOR HUMAN USE (PART 314 APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG)[40]

FDA can integrate broader public health considerations into its benefit-risk determinations for new and existing drugs. For example, New Drug Applications must include information related to the (potential for) abuse of the drug. Trials can be required to address risks of abuse, misuse and overdose, and submissions must also consider the broad context within which the drug will be used, including aspects of burden on the public health systems – broader than the confines of use of the drug as directed and the intended patient population. This is critical.

The US National Academies report recommended the development of an 'integrated decision making framework for opioid regulation' that would address public health issues in regulatory decision making in a very broad context – for example looking at community welfare issues such as crime, family well-being, impacts on illicit drug markets and potential unsafe routes of administration. It is likely that such matters are well beyond the scope of consideration of s 25 of the TG Act. However other recommendations, such as conduct of a full review of all currently approved opioids may be appropriate for Australia, too.

[40] www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=314

Appendix 2: What powers may exist under the Scheduling Policy Framework that are relevant to access controls over Schedule 8 opioids?

Unlike the TGA's consideration of safety, quality and efficacy in section 25 of the TG Act, section 52E(1)(e) and (f) make the 'potential for abuse of a substance' and 'any other matters that the Secretary considers necessary to protect public health' obligatory considerations when amending the Poisons Standard. The (medicines) Scheduling Policy Framework expressly refers to the potential for dependence, misuse and diversion/illicit use. Note that additional appendices to the schedule can be added by the delegate, but usually this would be post consultation with the jurisdictions/ Advisory Committee on Medicines Scheduling members. There is also the potential for stronger action under the current appendices – for example Label requirements in Appendix L. Here any action would be implemented under state and territory law.

There are already a number of (differing) jurisdiction-specific requirements for S8 medicines, summarised in the 2015 article: 'State-based legal requirements for Schedule 8 prescriptions: why so complicated?'[41] There may be scope to use state powers more widely – for example limitation of the number of repeats for private prescriptions of strong opioids. See mu notes on uniform regulations

While requirements vary by jurisdiction, they variously have controls on who is permitted to prescribe, length of prescribing permitted, requirements for information on the patient on the prescription, numbers and interval of repeats. Several, but not all jurisdictions require prescriptions for S8 medicines to be written in the doctor's own handwriting, rather than be computer-generated.

Factors for controlled drugs (Schedule 8)

1. The substance is included in Schedule I or II of the UN Single Convention on Narcotic Drugs 1961 or in Schedule II or III of the UN 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.

Appendix D of the Poisons Standard

Appendix D of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) provides for **additional controls on possession or supply of poisons included in S4 or S8**. Inclusion of a substance in Appendix D may be considered by the Secretary appropriate for any human medicine where the assessment of the proposal identifies:

- a specific health risk that may be mitigated by **restricting availability through specialist medical practitioners**; or

[41] Hua AC, Shen F and Ge X, Med J Aust (2015); 203 (2): 64-66

- significant potential for illicit diversion and/or abuse which does not warrant inclusion in S8 but warrants particular control of possession; or
- a specific high potential for abuse, particular international treaty restrictions on availability or other matters of national public health policy which when weighed against the need for access the substance, warrants **in addition to inclusion of the substance in S8, further restrictions on access** such as authorisation by the Secretary of the Department of Health or some other appropriate authority;
- taking into account the implications for professional practice by affected health practitioners and regulatory control by the states and territories.

Inclusion of a substance in Appendix D should be made following consultation with the Advisory Committee for Medicines Scheduling. There are already a number of substances in Appendix D which can only be prescribed by a specialist physician, or not able to be prescribed to particular populations (such as women who are pregnant or of childbearing age). However, the **Appendix is concerned with controls on possession or supply of the specified substances**, and does not presently provide for the exclusion of specific indications. However, it is possible that Appendix D could be used to require medical practitioners to have assessed patients for signs of addiction to opioids before prescribing certain opioids above certain morphine equivalent doses. This is impossible and anyway incorrect. If an archetypal heroin addict breaks a leg or gets cancer they may need high doses opioids. However, similar controls are already in place for strong opioids under some of the state and territory S8 drug prescribing regulations.

Appendix F of the Poisons Standard

Appendix F relates to 'warning statements and general safety directions'. Under poisons legislation, scheduled substances, which may be harmful to the user, must be labelled with appropriate warning statements and/or safety directions. The wording of warning statements and safety directions specified in this Appendix may be varied provided that the intent is not changed. Examples, some of which are used on S8 medicines include:

- Do not take for periods longer than four weeks except on medical advice.
- WARNING – This medication may be dangerous when used in large amounts or for a long time (period).
- This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.
- Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.

Appendix L of the Poisons Standard

This appendix relates to requirements for dispensing labels for human and veterinary medicines. The Secretary may make a new Appendix L entry or vary an existing entry following consultation with the Advisory Committee for Medicines Scheduling. An amendment to Appendix L (to add an additional substance) may be considered following a proposal for a new or existing medicine where:

- specific labelling needs to be applied for safe use of a medicine when dispensed
- professional practice standards require specific labelling of the medicine when dispensed.

Part 2 of Appendix L specifies additional labelling requirements for certain human medicines. Currently no opioids are listed here (instead it lists substances such as fingolimod, isotretinoin, misoprotol and thalidomide). However, utilising this appendix could potentially be considered for strong opioids.

Appendix 3: International Regulatory Responses

US Food and Drug Administration

This includes actions under the FDA Opioids Action Plan as well as more recently-announced initiatives:

- Convening an expert advisory committee before approving any New Drug Application for an opioid that does not have abuse-deterrent properties.
- Development of warnings and safety information for immediate-release opioid labelling (PI).
- Strengthening post-market requirements for drug companies to generate post-market data on the long-term impact of using extended release opioids.
- Updating the Risk Evaluation and Mitigation Strategy (REMS) Program including a requirement for sponsors to fund continuing medical education.
- Manufacturers of immediate release opioids intended for use in the outpatient setting that their drugs will now be subject to a more stringent set of requirements under REMS, including that training be made available to health care providers and with additional pre cautions being added to the boxed warnings with the product.
- Expanding access to abuse-deterrent formulations (including generics) to discourage abuse.
- Supporting better treatment, including over-the-counter availability, to make naloxone more accessible to treat opioid overdose.
- Reassessing the risk-benefit approval framework for opioid use, including formal incorporation of the broader public health impact of opioid abuse in approval decisions.
- Production of regulatory guidance for development of new Medication Assisted Treatment options for opioid dependence.

In addition to FDA, several US states have passed laws that would cap first-time opioid prescriptions at seven days. Some states also encourage tapering.

Health Canada

The Canadian Regulatory Response is part of 'Enabling a coordinated pan-Canadian response to the opioid crisis. The commitments fall within the pillars of prevention, treatment, harm reduction and enforcement, supported by strong evidence'.[42]

Specific regulatory initiatives completed or planned in Canada include:

[42] www.canada.ca/en/health-canada/services/publications/healthy-living/taking-action-canada-opioids-crisis.html

- Amending regulations to allow for mandatory warning stickers on all opioids outlining their risks and information handouts for patients receiving prescribed opioids.
- Proposal to amend regulations to enable the Minister of Health to impose terms and conditions on opioid authorisations in order to require pharmaceutical companies to develop and implement risk management plans to identify, monitor, and or mitigate risks associated with opioid use.
- Update guidance to pharmacies on the destruction of consumer-returned prescription drugs, to encourage them to accept returns while minimising the risks of diversion to illegal markets and problematic use.
- Health Canada to review submissions for non-opioid analgesics more quickly. Amend regulations to allow the importation of drugs that have been authorised for sale in the United States, European Union or Switzerland, but that are not yet authorised in Canada.
- Amend regulations to enable access to diacetylmorphine (pharmaceutical grade heroin) through Health Canada's Special Access Programme. Also to support access to medication-assisted treatments that are not available on the Canadian market for opioid use disorder through this program.
- Health Canada amended the Prescription Drug List to make naloxone available without a prescription, including Narcan nasal spray.
- Make regulatory changes to control fentanyl precursors under the Controlled Drugs and Substances Act and its Precursor Control Regulations.

European Medicines Agency

The European Medicines Agency (EMA) has not coordinated as much work as the US FDA or Health Canada, given that many opioid medicines are generic medicines and managed through individual country programs.

One of the main piece of work was an examination of interactions of certain modified-release products with alcohol in 2009-10. See: 'European Medicines Agency concludes review of modified-release oral opioids of the World Health Organization level III scale for the management of pain.[43,44]

Medicines and Healthcare products Regulatory Agency

The UK's Medicines and Healthcare products Regulatory Agency has developed a learning module for physicians that qualifies them for CPD points.[45] This module identifies the most important hazards of opioids and informs on actions that health professionals can take in order to anticipate, minimise and manage the risks.

[43] www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001063.jsp&mid=WC0b01ac058004d5c1
[44] www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Modified-released_oral_opioids_31/WC500107313.pdf
[45] http://www.mhra.gov.uk/opioids-learning-module/index.htm

Signed

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[redacted]

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