Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

1 March 2018

Therapeutic Goods Administration
Submitted via online portal

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

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) thank you for the opportunity to provide comment on the draft permitted indications of Listed Medicines.

ASCEPT is the leading professional body in Australasia for clinical pharmacology policy and practice and its members' expertise encompasses experimental and clinical pharmacology and toxicology (including: clinical trial and regulatory issues, pharmacovigilance and quality use of medicines). ASCEPT members serve on most Commonwealth and State committees concerned with medicines regulation or quality use of medicines.

Executive summary

ASCEPT supports this proactive approach by the TGA which aims to curtail the rising problem of opioid use and misuse.

We submit that Options 1, 3 and 4 are the priority interventions. We do not support Option 7 as it is currently described.

Although the Electronic Recording and Reporting of Controlled Drugs (ERRCD) was not listed as an option in the consultation, we believe that it must be a priority. ASCEPT believes the Australian Government should lead this process to achieve harmonisation of legislation and processes across states and territories.

These implementations should occur in consultation with specialists in the field and professional groups such as ASCEPT.

Background

ASCEPT is concerned at increasing prescribing and inappropriate use of strong (Schedule 8) opioids. Both of these issues are associated with harm, including death. Statistics note death may be directly due to an opioid (eg. heroin overdoses) or associated with an opioid (overdoses with a combination of medicines which includes opioids).

The National Drug Strategy 2010-2015 included the National Pharmaceutical Drug Misuse Framework for Action which has the following goals:

- 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.[1]

A range of interventions and processes may contribute to the above[2], but the current consultation relates to the regulatory response.

It is acknowledged that the TGA will need to partner with states and territories who are responsible for enforcing many of the proposed regulatory changes.

General comments on the scheduling of strong (Schedule 8) opioids

Some opioids listed in the consultation document were misspelled, and statements regarding the existing scheduling were either incorrect or incomplete. Some are non-prescription, and codeine is only S4 when combined with another therapeutically active agent (otherwise it is S8).

Pholcodine and dextromethorphan are not universally classified as opioids.

There are neither existing formulations nor evidence of efficacy from clinical studies for many opioids listed, for example acetyldihydrocodeine, acetylmorphines (unless this includes diacetylmorphine which is also known as heroin which is currently S9 and there are randomised controlled trials supporting its efficacy), benzylmorphine, dihydromorphine, hydromorphinol, hydromorphine, levophanol, methyldihydromorphine, morphine methobromide, morphine-N-oxide, norcodeine and normethadone. ASCEPT acknowledges the importance of including these drugs as S8 in the SUSMP for the purposes of controlling supply and use, but it would be useful for the TGA to highlight that they have no current role in clinical practice in Australia.

General comments on prescription strong (Schedule 8) opioid use and misuse in Australia

The rising problems of opioid misuse and abuse have been well documented, and a proactive approach to curtailing this problem is lauded. Indeed, better statistics are also needed – the 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[3]. Supplies via private (non-PBS/RPBS)

prescriptions and the increasing availability of generic formulations will further compound the underestimation.

ASCEPT agrees that there are risks to the community from the uncontrolled and inappropriate prescribing and supply of opioids. Action is required in Australia if we are to avoid an escalation to the 'epidemic' of opioid dependence and harm that is currently being experienced in the US. Increased education of the community and training of health professionals regarding pain management is vital.

It should also be acknowledged that there is a degree of confusion amongst prescribers regarding optimal pain management and how the WHO analgesic ladder applies to certain chronic pain syndromes. Palliative care practice is often erroneously adopted in chronic non-malignant pain management with subsequent rapid opioid dose escalation. Recent evidence challenges the role of paracetamol in the management of some chronic pain conditions, and nonsteroidal anti-inflammatory drugs (NSAIDs) have potential adverse effects with regards to cardiovascular, renal and gastrointestinal toxicity. This may give the impression to prescribers that there are few alternatives to S8 opioids. Instead, there should be more focus on non-drug treatments.

Lack of resources, financial incentives and timely access to specialist chronic pain services maybe serving to increase opioid prescribing in community.

High and increasing use of opioids for chronic non-malignant pain in older adults increases the risk of falls and confusion without clear therapeutic benefit. Errors in prescribing potent opioids like fentanyl to older people who are not opioid tolerant can result in harm including deaths. Opioids are also reported as a cause of abuse of the elderly and socially isolated.

In the case of perioperative pain management, if patients are discharged home on opioid medicines then they should be informed about a clear plan for deescalating doses and this should be communicated to the GP.

Therefore, more training and support of prescribers and students regarding appropriate S8 prescribing and deprescribing, is essential. Further, the assessment of pain (in particular chronic non-malignant pain) requires a detailed history and clinical review of a range of contributors, including psychosocial factors, so sufficient time (and, therefore, remuneration) should be provided to GPs and other specialists for such consults.

It is necessary that such changes are implemented with sufficient time to ensure adequate treatment and care of individuals who may already have a substance use disorder. For example, in many parts/practices of the US where there has been a banning or refusal to prescribe opioids, or a practice that encourages abstinence-based approaches to treatment of opioid use disorder, the use of illicit opioids (notably heroin) is increasing and this is associated with increased harms and risk of death. If such changes are introduced without care and consultation, there is a risk of increasing stigma which will be counterproductive. Therefore, planning for change requires engagement with all stakeholders (stakeholder pushback is likely to be a significant barrier to these options), planning for increased demand

on addiction services, increased access to appropriate opioid substitution programs and anticipation of unintended consequences such as conversion to injecting, illicit opioid use and misuse of other illicit substances or prescription medications to manage opioid withdrawal phenomena.

ASCEPT does not wish to discourage the prescribing of opioids in the correct circumstance, so there needs to be a clear distinction between opioids for acute pain and chronic pain. Indeed, the International Association for the Study of Pain position statement is apt: "Opioids are indispensable for the treatment of severe short-lived pain during acute painful events and at the end of life (e.g., pain associated with cancer). Currently, no other oral medication offers immediate and effective relief of severe pain."

Electronic Recording and Reporting of Controlled Drugs (ERRCD) system

ASCEPT strongly supports the implementation of a national real-time prescription monitoring solution using an Electronic Recording and Reporting of Controlled Drugs (ERRCD) system for reportable S8 (and selected S4) medicines. This will allow for real-time monitoring of both PBS and non-PBS (private) supplies.

Adequate surveillance of S8 and selected S4 medicine supply is essential to monitor outcomes of the various options proposed, enforce regulatory change and support decision-making for prescribing opioids and other medicines in clinical practice and we believe that this is best achieved through the ERRCD. Without real-time tracking, the current state- and territory-based authorisation system for opioids and other medicines with abuse potential relies on prescribers proactively engaging with their pharmaceutical services units. This does not always occur and hence the current system for monitoring drugs of addiction is of limited effectiveness prior to the introduction of these new regulations.

The ERRCD should include other drugs at risk of addiction or misuse, notably benzodiazepines. Indeed, if the aim is to reduce accidental overdose and death a real time federal monitoring program covering all prescription drugs (including private scripts) would be superior in all respects. For example, the combined use of opioids with benzodiazepines, gabapentinoids, quetiapine and other sedatives is a significant concern because a very high proportion of fatal opioid overdoses have other substances involved.

The ERRCD will be useful for identifying patients who are taking drug doses and combinations that are potentially hazardous, as well as identifying prescribers with practices that prompt review. Key regulatory and other players could link to the system, for example PBS, MBS, TGA, scheduling committees and Australian Health Practitioner Regulation Agency (AHPRA).

It is not acceptable to simply delegate responsibility to the states and territories because this will allow cross-border prescription/doctor shopping. Ideally, harmonisation of legislation and processes across states and territories is optimal.

Although the ERRCD was not listed as an option in the consultation, we believe that it must be a priority, so it should be an option. ASCEPT believes the Australian Government should lead this process and coordinate necessary intergovernmental communications.

Comments on the specific regulatory proposals

Overall, ASCEPT believe that a multi-pronged approach is likely to be most effective, so a number of the possible options are supported. Regulatory change alone is unlikely to be sufficient. In trying to change innate behaviours, change is best achieved with appropriate education, resources and stakeholder engagement, in addition to regulation.

Option 1: Consider the pack sizes for Schedule 8 opioids

ASCEPT strongly supports this option. ***We believe that it is the top priority and that it is introduced as soon as practicable***. This is consistent with CDC recommendations for the treatment of acute pain[4]. The default option for prescribing software should be the smaller pack size, for example 3 days duration for acute pain, and this should be amenable to prompt introduction.

Further discussion regarding the preferred pack size, relative to the indication, should be determined by Option 2 and in consultation with specialists in the field (see discussion in Option 3 regarding the definition of a specialist for these purposes) and professional groups such as ASCEPT.

Guidance and monitoring by TGA and probably PBAC is necessary to ensure that the pricing of new smaller pack sizes is appropriate because this will maximise uptake.

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

ASCEPT supports this option because it will focus treatment towards evidence-based approaches. Although a lack of data does not mean a lack of effect, the general principles behind this option are valid. This option requires an approach to dealing with conflicting data (especially in cases when there is little evidence to guide regulators). Decision-making around this option should occur in consultation with specialists in the field (discussed in Option 3) and professional groups such as ASCEPT.

However, this option will have a necessary slower implementation time than others (notably option 1) and requires ongoing resources to incorporate new evidence (for and against opioids) into the accepted indications.

ASCEPT also believe that “non-specialist” prescribers would welcome this option because it may facilitate the management of patients who are otherwise resistant to pain management approaches other than simply initiating opioids and progressively escalating the dose.

This option may also encourage initiation and recruitment to research on the management of chronic pain in Australia.

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

ASCEPT strongly supports this option and that it ***be a priority intervention***. These high-dose formulations are largely used for the treatment of chronic pain but should be restricted to pain due to cancer and palliative care in most cases. There are increasing data to suggest that higher opioid doses do not necessarily increase analgesia but have the opposite effect via opioid-induced hyperalgesia and deciding which patients will benefit from escalating doses is a specialised decision.

ASCEPT believe that "non-specialist" prescribers would welcome this option because it may facilitate the management of patients who are otherwise resistant to pain management approaches other than simply initiating opioids and progressively escalating the dose. Here, an 'administrative barrier' can be useful for focusing or redirecting discussion to a more useful direction.

However, ASCEPT believes that further definition of "specialist" is necessary for the purposes of this consultation. According to AHPRA, all doctors who have completed post-graduate fellowship training through a recognised medical College are classified as specialists, which includes general practitioners. Not all specialists are expert in the management of chronic or recurrent pain and the prescribing of opioids for this purpose.

Instead, certain specialists may be eligible for a 'blanket approval' (for example, doctors with fellowships in pain medicine, addiction medicine, addiction psychiatry, medical or radiation oncology or palliative care) while others may be entitled to apply for approval to prescribe S8 opioids following completion of an approved training course. For example, similar processes currently exist in NSW for the prescribing of methadone and buprenorphine for the purposes of opioid substitution therapy. Similar courses on the prescribing of S8 opioids should also be implemented into registrar training programs, and other courses for more junior doctors and medical students. We recommend consultation with appropriate specialists and professional groups such as ASCEPT in the development of such courses or training pathways.

Further definition of "specialist" also applies to non-medical prescribers. A non-medical prescriber could potentially attain "specialist" status for the purposes of S8 opioid prescribing if working within a suitable clinical practice (for example, a multidisciplinary clinic in the above-mentioned specialties) and following completion of appropriate training courses.

It is important to acknowledge the limitations of successful implementation of this option at this current time. There is a misunderstanding (or simply lack of knowledge) by many prescribers who appear to believe that the indications for an Authority prescription also satisfy state-based restrictions on prescribing. This identifies a need for education of prescribers around the requirements of state and territory health departments, see Jammal and Gown (2015)[5].

Restrictions to the reimbursement of higher dose formulations will not prevent private prescriptions being written or increased supplies of lower dose formulations, so engagement

with state health departments is essential. Unfortunately, State and territory health departments are under resourced and unable to perform adequate surveillance and enforcement of opioid prescribing and supply within their jurisdiction. ***Therefore, nationwide introduction of the ERCCD is essential to support regulatory changes and clinical decision making, so this must be a priority.***

Other factors complicating the implementation of this option in Australia at present reflect equitable access. Geographically, there is a maldistribution of specialists (as defined above) and the workforce is relatively small. Telemedicine and related programs and an increase in training positions and posts for specialists (as defined above) are likely to be beneficial, but both require more government investment and lead time.

Prescribers in remote areas may be eligible to prescribe these medicines if the patient is engaged with a care plan that involves an appropriate specialist and regular review by that specialist (eg. every 6 months) and the generalist more frequently with active review of non-drug treatments and opportunities to deescalate the opioid dose. Use of telemedicine needs to be instituted to make sure all citizens and prescribers of opioids have access to expert input into pain management and prescribing.

Patients being prescribed or dispensed these medicines could potentially be educated about the availability of naloxone for the treatment of overdose, for education and to draw attention to their individual risk including death.

Option 4: Strengthening Risk Management Plans for opioid products

ASCEPT strongly supports this option, which links in with Option 3. Government agencies (notably health departments in states and territories) should be involved with (if not responsible for, in conjunction with the colleges) the approval of training courses given that they are responsible for enacting much of this legislation. Independence of information, rather than collaboration with those groups with a potential conflict of interest (to avoid unintended advertising or selection of certain products, which is a key discussion point in the US), should be ensured.

A model that could potentially be followed is the training course that is required for the prescribing of methadone and buprenorphine in NSW for opioid substitution therapy. Similar courses on the prescribing of S8 opioids should also be implemented into registrar training programs, and other courses for more junior doctors and medical students. We recommend consultation with appropriate specialists and professional groups such as ASCEPT in the development of such continuing professional development courses.

The existing PBS requirement for review by another, independent specialist, for opioid treatment exceeding 12 months should be reduced to 3 months.

These strategies should also draw attention to factors that increase the risk of overdose and death by misadventure to patients using opioids, for example 'universal precautions'(assessing the risk of misuse, setting treatment goals, fixing time periods over which to attain these goals and

having de-prescribing strategies.) and co-prescription of benzodiazepines. Patients being prescribed or dispensed opioid medicines (particularly high dose formulations, and those co-prescribed benzodiazepines) could be educated about the availability of peer-administered naloxone for the treatment of overdose, for education and to draw attention to their individual risk including death.

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

ASCEPT supports this option, in particular since many of the existing product information documents are not up-to-date. All information about risks from the use of a medicine is useful and encourage patient-centred care. Patients who have developed opioid dependence have reported being unaware of the risk of this at the time of opioid initiation.

The compulsory inclusion of these statements on boxes prompt discussions by the pharmacist at the time of dispensing in a non-judgemental manner – that is, it is prompted by the box/requirement, rather than by judgements on the patient.

ASCEPT does not agree with the statement "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."

Further research is required to ensure that additional labels on the box do not dilute the impact of each one. For example, it may be reasonable to include three warning stickers for S8 opioids: sedation, risk of dependence and death and "Return Unwanted Medicines" to the pharmacy. It is also necessary to advise patients that S8 opioids should be kept out of view and in a safe place.

These strategies should also draw attention to factors that increase risk to patients using opioids, for example co-prescription of benzodiazepines. Patients being prescribed or dispensed opioid medicines (particularly high dose formulations, and those co-prescribed benzodiazepines) could be educated about the availability of naloxone for the treatment of overdose, for the purpose of education and to draw attention to their individual risk, including death.

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

Regarding products for pain relief, ASCEPT has significant concerns with this option and do not support it as currently described. Although it may appear useful in principle, there are significant safety concerns and various practical limitations e.g. if a major safety signal is subsequently noted then the introduction of new measures to protect the public are required and this is complicated. Such complexities are demonstrated in the present Consultation, experience with dextropropoxyphene in Australia[6] and many other cases.

It is necessary to ensure that new products maximise the effect of the constituents, for example combination drugs may lead to the prescribing of subtherapeutic doses of

paracetamol with opioids, potentially resulting in more opioid use, e.g. a recently registered product with tramadol 37.5 mg + paracetamol 325 mg.

The risk of misuse and dependence of new medicines should also be carefully considered and subject to detailed monitoring and regular review from the regulatory perspective. For example, the recognition of the misuse of gabapentinoids was noted many years after they were introduced to clinical practice in Australia. Safety concerns with tramadol and the 'coxibs' also emerged only after being marketed.

Abuse-deterrent is not abuse-proof, and the pharmacoeconomic implications of new formulations and medicines, particularly for chronic non-malignant pain, should be considered carefully within existing structures. Further, these changes may not have a net-usefulness in isolation if they encourage switching to a more dangerous form/route or drug, for example increased use of intravenous heroin as noted in the US. ***Therefore, nationwide introduction of the ERCCD is essential to support and monitor regulatory changes and clinical decision making, so this must be a priority.***

In terms of antidotes, the supply of naloxone to consumers warrants attention. Appropriate formulations of naloxone would need to be made available via TGA and PBS. Current approaches are not easily used by consumers in an emergency, for example separate ampoule, syringe and needles, or Minijets without attached needles.

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

This option discusses more practical aspects of options 2, 3 and 5. Overall ASCEPT supports the concept of this option. However, as currently described it is inadequate. Consideration should be taken of the comments that have already been made above, particularly regarding equity of access. It is essential that such changes do not add unnecessary bureaucratic complexity.

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

This option discusses more practical aspects of the above discussion about options 3 and 4. Overall, ASCEPT supports this option, with consideration of comments already made above.

It is necessary to also consider the potential for misuse and diversion with some non-opioid, as discussed in option 6.

Increased awareness is important but increased access to non-pharmacological alternatives to opioids (such as multidisciplinary pain clinics, pain psychologists, occupational therapists, physiotherapists, etc.) is equally important. Providing pay-for-performance for incentives such as a chronic pain equivalent of a 'mental health plan' may improve community access to opioid alternatives.

Discussion about the rescheduling of tramadol and other S4 opioids to S8 is proposed, depending on the duration of the proposed prescription, dose and drug. The prescription of 'longer and stronger' opioids should push towards S8 equivalent provisions. In the case of tramadol, it is prone to addiction and misuse (although this appears to be less so compared to other S8 opioids) and while categorised as S4 there is the perception that it is safer than other opioids. The trials looking at tramadol and its potential for misuse were based on intramuscular use, as opposed to oral which is how it is predominantly marketed.

Submission prepared in consultation with ASCEPT expert members. Please do not hesitate to contact the ASCEPT Secretariat Katie Roberson at secretariat@ascept.org for any further information.

Yours sincerely,

[redacted]

[redacted]
ASCEPT President

References:
[1] National Strategy for Quality Use of Medicines
http://www.health.gov.au/internet/main/publishing.nsf/content/nmp-quality.htm
[2] NSW Therapeutic Advisory Group Inc. Preventing and managing problems with opioid prescribing for chronic non-cancer pain. NSW TAG: Sydney, 2015. http://nswtag.gradestage.com/wp-content/uploads/2017/07/pain-guidance-july-2015.pdf
[3] Gisev N et al;. Pharmacoepidemiol. Drug Saf doi: 10.1002/pds 4329 (2017).
[4] Shah, Anuj, Corey J. Hayes, and Bradley C. Martin. "Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use-United States, 2006-2015." *MMWR. Morbidity and mortality weekly report* 66.10 (2017): 265-269.
[5] Jammal W, Gown G. Opioid prescribing pitfalls: medicolegal and regulatory issues Aust Prescr 2015;38:198-2031.
[6] Buckley NA, Faunce TA. Trials and tribulations in the removal of dextropropoxyphene from the Australian Register of Therapeutic Goods. Med J Aust. 2013 Aug 19;199(4):257-60.