ANZCA
AUSTRALIAN AND NEW ZEALAND
COLLEGE OF ANAESTHETISTS

ANZCA House
630 St Kilda Road
Melbourne VIC 3004
Australia
T: +61 3 9510 6299
F: +61 3 9510 6786
www.anzca.edu.au
ABN 82 055 042 852

March 1, 2018

Adjunct Professor John Skerritt
Deputy Secretary for Health Products Regulation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Dear Professor Skerritt

Thank you for the opportunity to provide comment on options for a regulatory response to the potential misuse of prescribed Schedule 8 (S8) opioids in Australia.

The Australian and New Zealand College of Anaesthetists (ANZCA), including the Faculty of Pain Medicine (FPM), is committed to high standards of clinical practice in the fields of anaesthesia, perioperative medicine and pain medicine. As the education and training body responsible for the postgraduate training programs of anaesthesia and pain medicine for Australia, New Zealand and parts of Asia, ANZCA is committed to ongoing continuous improvement, promoting best practice, and contributing to a high quality health system.

The medical specialty of anaesthesia is critical to the provision of safe, effective anaesthesia and perioperative care for patients. Fostering safe and high quality patient care in anaesthesia, perioperative medicine and pain medicine is ANZCA's mission. Furthermore, FPM promotes appropriate prescribing for pain relief through its professional documents.

The attached submission contains a consolidated response to each of the eight options presented with input from FPM members and from members of ANZCA's Safety and Quality Committee. The concerns of the Faculty regarding inappropriate opioid prescribing are strongly voiced in its first two 'Choosing Wisely' recommendations (http://www.choosingwisely.org.au/recommendations/fpm).

We would also like to comment on the potential for educative and regulatory processes at the point of opioid prescription. This would invoke the concept of opioid dose prescription thresholds, expressed in oral morphine equivalent (OME) daily doses.

An educative response might be triggered at a lower OME, for example >40mg per day. A national real time opioid prescription monitoring system would facilitate this process. An alert could be issued to a practitioner seeking to prescribe >40mg OME per day and educational material offered. The PBS regulatory response might be triggered at a higher threshold, for example >100mg OME per day. A practitioner seeking to prescribe above this threshold would be required to seek appropriate (and time-limited) specialist endorsement before access to the PBS Authority program.

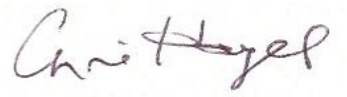
These issues were canvassed in the Outcome Statement of the Opioid Roundtable in May 2015, and remain just as pertinent now as then.

The varying opioid prescription permit systems that operate in each jurisdiction need harmonisation not only with each other but also with the PBS Authority regulatory system. The jurisdictional permit system has the capacity to identify and educate a smaller group of 'higher risk' prescribers and patients particularly in the context of Substance Use Disorder. In this setting more appropriate individualised management recommendations can be proposed.

Should you require any further information in relation to this submission, please contact Jo-anne Chapman, General Manager Policy, Safety and Quality via email policy@anzca.edu.au or telephone (03) 8517 5341.

Yours sincerely

Professor David A Scott
President



Dr Chris Hayes
Dean, Faculty of Pain Medicine

ANZCA
AUSTRALIAN AND NEW ZEALAND COLLEGE OF ANAESTHETISTS

FPM
FACULTY OF PAIN MEDICINE ANZCA

Therapeutic Goods Administration

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

March, 2018

To serve the community by fostering safety and high quality patient care in anaesthesia, perioperative medicine and pain medicine.

About ANZCA

The Australian and New Zealand College of Anaesthetists (ANZCA) is the professional organisation for specialist anaesthetists (Fellows) and specialist anaesthetists in training (trainees) in Australia and New Zealand.

ANZCA is now a world-renowned institution in anaesthesia and pain medicine that has taken a leading role in many areas of anaesthesia, pain medicine and intensive care medicine. These include:

- Being recognised as a world leader in the treatment of pain by establishing the specialty of pain medicine through its Faculty of Pain Medicine.
- Setting high professional standards for patient safety through professional documents and other advocacy activities.
- Answering key questions in medical research by recruiting more than 30,000 patients to help with $A25 million worth of studies for the ANZCA Clinical Trials Network and other research through the ANZCA Research Foundation, which in 2017 alone is funding research worth $1.7 million.
- Training highly skilled future Fellows in anaesthesia and pain medicine.
- Hosting more than 30 medical education events annually including the College's flagship event, the ANZCA Annual Scientific Meeting.
- Supporting anaesthesia in developing nations such as Papua New Guinea with clinical and educational visits, and the seeding of the Essential Pain Management program now being taught in 47 countries.
- Establishing intensive care medicine as a specialty by instituting training and accreditation programs through a joint Faculty of Intensive Care, and then by helping found the College of Intensive Care Medicine of Australia and New Zealand.

ANZCA, including FPM, is committed to high standards of clinical practice in the fields of anaesthesia, perioperative medicine and pain medicine. As the education and training body responsible for the postgraduate training programs of anaesthesia and pain medicine for Australia, New Zealand and parts of Asia, the College believes in ongoing continuous improvement and strives to ensure that its programs represent best practice and contribute to a high quality health system.

ANZCA's mission is to serve the community by fostering safety and high quality patient care in anaesthesia, perioperative medicine and pain medicine. From this mission flows three major objectives:

- To promote professional standards and patient safety in anaesthesia, perioperative medicine and pain medicine.
- To promote training and education in anaesthesia, perioperative medicine and pain management.
- To advance the science and practice of anaesthesia, perioperative medicine and pain management.

ANZCA Fellows and trainees

There are 4635 active and 667 retired ANZCA fellows and 1267 trainees in Australia, whilst there are 721 active and 86 retired ANZCA fellows and 244 trainees in New Zealand (figures as at December 31, 2017).

About FPM

The Faculty of Pain Medicine (FPM) is the professional organisation for specialist pain medicine physicians (Fellows) and specialist pain medicine physicians in training (trainees).

The Faculty is responsible for the training, examination and specialist accreditation of specialist pain medicine physicians and for the standards of clinical practice for pain medicine in Australia and New Zealand. Formed in 1998, the Faculty is the first multidisciplinary medical academy in the world to be devoted to education and training in pain medicine. Although part of ANZCA, the Faculty's fellowship and representation remains multidisciplinary at all levels. It arose out of collaboration between five participating bodies – ANZCA, the Royal Australasian College of Physicians (RACP), the Royal Australasian College of Surgeons (RACS), the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and the Australasian Faculty of Rehabilitation Medicine (AFRM) of the RACP.

In 2005, the discipline was recognised in Australia as a medical specialty in its own right and was accredited as a scope of practice in New Zealand in 2012. This recognises the importance of the problem of unrelieved pain in the community and the need for a comprehensive medical response through education, training and practice.

The field of pain medicine recognises that the management of severe pain problems requires the skills of more than one medical craft group. Such problems include:

- Acute pain (post-operative, post-trauma, acute episodes of pain in "medical conditions").
- Cancer pain (pain directly due to tumour invasion or compression, pain related to diagnostic or therapeutic procedures, pain due to cancer treatment).
- Persistent (chronic) pain (including over 200 conditions described in the International Association for the Study of Pain (IASP) *Taxonomy of Chronic Pain 2nd Edition*, such as phantom limb pain, post-herpetic neuralgia, mechanical low back pain). Chronic pain affects one in five Australians.

In Australia and New Zealand, a career in pain medicine is generally obtained by qualifying as a Fellow of the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (FFPMANZCA). Pain specialist training is also open to vocationally registered general practitioners and other specialists.

Fellows of FPM have a wide knowledge of the clinical, sociopsychobiomedical and humanitarian aspects of pain and are well placed to follow a developing and challenging career path.

Last year, world recognition for the Faculty was achieved through the awarding of the 2017 American Academy of Pain Medicine’s (AAPM) Robert G. Addison, MD Award given in recognition of outstanding efforts to foster international co-operation and collaboration on behalf of the specialty of pain medicine. The European Pain Federation is now also using FPM’s revised curriculum as the basis for its diploma.

FPM Fellows and trainees

There are 316 active and 24 retired FPM fellows and 64 trainees in Australia, whilst there are 34 active and 7 retired FPM fellows and 9 trainees in New Zealand (figures as at December 31, 2017).

Response to consultation options

Option 1: Consider the pack sizes for Schedule 8 opioids

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.

Response

1. Acute pain

For situations of acute pain (meaning here the pain associated with recent active tissue damage such as after trauma or surgery or vascular events), the utility of smaller pack sizes of immediate-release (IR) opioids may be helpful. However this would need to be tempered by consideration of the dose size of each opioid:

- oxycodone (IR) 5mg: Endone ®, OxyNorm® [OME[1] 7.5mg]
- oxycodone (IR) 10mg: OxyNorm® [OME 15mg]
- oxycodone (IR) 20mg: OxyNorm® [OME 30mg]
- morphine (IR) 10mg: Sevredol®
- morphine (IR) 20mg: Sevredol®
- morphine (IR) 30mg: Anamorph®
- hydromorphone (IR) 2mg: Dilaudid® [OME 10mg]
- hydromorphone (IR) 4mg: Dilaudid® [OME 20mg]
- hydromorphone (IR) 8mg: Dilaudid® [OME 40mg]

Clearly the intention is to limit the total quantity of opioid to which a patient may be potentially exposed once they have been discharged from the health care facility in which the opioid was commenced. However the instructions for dosing - tablet size, frequency of ingestion per day and number of days - would need to be explicitly tailored to the individual situation. This is a strong argument against "standard discharge medication" and speaks to the responsibility of the prescriber to make an informed estimate of the total quantity of opioid required over a specified period. This would need to be translated by the dispenser into pack sizes that are considered safe. The same argument would apply to prescriptions in the community for an event of acute nociception that did not require presentation to a hospital.

There is evidence that any opioid taken for acute new pain increases the likelihood of staying on opioids long term if taken beyond 3 days.

It could be argued that there is little if any need for IR-opioids that deliver more than 20mg OME per tablet. It follows that regulation of tablet size is as important as that of pack size. However, limiting pack size will influence the pool of residual unused tablet ‘units’ in the community.

2. Chronic pain due to malignancy

This situation tends to be characterised by (a) the use of modified-release opioid and (b) often very high doses (>100mg OME - per day). Without pre-empting a response to Option 3, this situation is again the responsibility of the prescriber, ideally acting in accordance with guidance to determine the total quantity of opioid required - dose size x daily frequency x number of days - which is then dispensed responsibly.

[1] OME: oral morphine equivalent

3. Chronic non-cancer pain

Patients with chronic non-cancer pain (CNCP) are not explicitly mentioned in Option 1. Although it is considered that opioids have little or no place in their management, it must be recognised (a) that CNCP is not a homogeneous condition, so that instances will arise where a trial of opioid therapy is considered reasonable according to current guidance[2] and (b) that there are patients with CNCP who are established successfully on long-term opioid therapy and who require ongoing care (including rationalisation of their overall pain management plan). Again, the same principle would apply: the prescriber determines the total quantity of opioid for a given period; the dispenser delivers that in a safe form.

4. Is there a role for sponsors to develop smaller dose sizes?

In all three scenarios above, an argument can be made for smaller pack sizes that might help dispensing - but not prescription. Another argument could be made for sponsors to develop smaller dose sizes for IR-opioids, given that the lowest IR dose available is 7.5mg OME and all IR preparations have half-lives of 2-4 hours only. It follows that educational material, including CMI, should incorporate OME information and advice on risks of daily doses exceeding an amount to be specified. CMI should include information about de-escalation and moving to non-opioid pain relief medication as well as to return unused medication to a pharmacy and not to share opioids with others.

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

The option:

The TGA will review indications for the S8 opioids and align them to current clinical guidelines for appropriate prescription of these products.

Response

Such a review, which would collate and update current guidance, would be a resource predominantly for prescribers. Given the effective minimisation of prescription of dextropropoxyphene and the likelihood of significant changes in prescription of codeine following its up-scheduling, it could be argued that "weak" opioids are in abeyance and that the only opioids worth discussion in this context are the "strong" agonists - oral morphine, oxycodone and hydromorphone - and the transdermal preparations of buprenorphine and fentanyl.[3]

Any such review would need to generate a philosophy of prescription in each of the three situations discussed under Option 1 above. In particular, the complexity of CNCP will need to be explicitly addressed. In addition, the concept of "inappropriate prescribing" (aka "poor patient selection") would need to be developed.

However, it is not clear that changes to the PI of themselves would achieve this educational end – an example of this would be the current trends in the use of controlled-release oxycodone in acute pain management against PI recommended indications. Education of the medical and lay community is a key element here.

2

- Royal Australasian College of Physicians. Prescription opioid policy: improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: RACP; 2009. http://fpm.anzca.edu.au/documents/prescription-opioid- policy.pdf
- Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. Professional document PM-01 2010, revised 2015. https://www.fpm.anzca.edu.au/resources/ professional-documents
- NPS MedicineWise. Chronic pain. 2015. https://www. nps.org.au/medical-info/clinical-topics/chronic-pain
- Royal Australian College of General Practitioners. TRACoG. Prescribing drugs of dependence in general practice, Part C2: The role of opioids in pain management. East Melbourne: RACGP; 2017 https://www.racgp.org.au/your-practice/guidelines/drugs-of- dependence-c/.

[3] Whether there is any role at all for codeine would need to be canvassed.

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

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.

Response

There is no need for individual tablet dose sizes >30mg OME outside of palliative care. It follows that dose sizes above that threshold should be subject to prescriber restrictions such as the requirement for appropriate specialist endorsement. This would effectively consign the use of transdermal fentanyl to palliative care only.[4]

Titration up to a suggested daily ceiling dose of 100mg OME for PBS-subsidised prescription without jurisdictional Authority would not require tablet or patch dose sizes >30mg OME. Even specialist-only prescription (with jurisdictional Authority for PBS-subsidisation) outside of palliative care would not require higher dose sizes for maintenance treatment (with the possible exception of transdermal buprenorphine 40mcg/hr).

Private (that is, non-PBS) opioid prescriptions remain a problem, one that could be controlled only at the level of dispensing.

Wider availability of naloxone provides a valuable community safety resource but is no panacea for injudicious opioid prescription and the consequential potential for misuse and diversion.

Option 4: Strengthening Risk Management Plans for opioid products

The option:

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

Response

The key to risk management is education of prescribers. The philosophical framework for such education would include, in particular, the complexity of CNCP and the distinction between inappropriate prescribing and unsanctioned use, to emphasise the responsibility of the prescriber for selection of patient and of product. Experts in pain medicine can exert their influence within the prescribing networks to help achieve this.

In this context the Risk Evaluation and Mitigation Strategy (REMS) program in the USA may provide a useful model. It could be argued that competence in opioid prescribing, as assessed by completion of a formal educational module, should be mandatory for all prescribers. Development of such a module could take a lead from the FPM Better Pain Management program and incorporate guidance from the FPM and RACGP (see footnote 2). Indeed the Better Pain Management program could be used as a component part of the educational approach.

An effective national real time prescription monitoring program for opioids, benzodiazepines and perhaps other psychoactive medications would reduce risk of inappropriate prescribing and provide a means of monitoring potential clinical variation.

[4] It should be noted that the lowest dose of transdermal fentanyl, 12.5 mcg/hr, delivers an OME of 45mg per day which is not appropriate for titration.

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

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. [*Emphasis added here as this is the only mention of this issue in the document]

Response

Who is/are the prime target(s) for "warnings"? If prescribers, then there are better methods of education. If consumers, then there would be concerns not only about adherence to judicious prescription but also - and probably more importantly - about amplifying the stigma already experienced by patients with CNCP in particular and that surrounding "narcotics" (despite the obsolescence of that term).

Warning labels do not usually address lack of efficacy. Effective therapeutics requires utilisation of the context of prescribing as well as its content. A consumer would be entitled to ask, why is my doctor prescribing a medicine that "does not work", in a situation in which it is being prescribed because it might be effective for that patient's individual predicament. Given that current guidance emphasises that opioid pharmacotherapy in CNCP is always an ongoing trial of therapy, the responsibility again devolves to the prescriber. That responsibility entails negotiation with the patient about expected benefits and possible adverse effects. Opioids are not placebos: in fact their NNT of 2-4 suggests better efficacy than many other drugs being advocated for use before them. An informed prescriber, one who ideally has been credentialed in opioid prescription, is in fact in the best position to counsel the patient about the role of any drug in this context. The therapeutic relationship is an integral part of the outcome of any intervention, drug or non-drug. Alarming warnings on packets do not contribute positively to this.

Changes to the CMI should cover safe storage and keeping away from children in a more specific format, as well as risks for driving, in particular subsequent to dose changes, and then a complete outline of the risk/benefit ratio for chronic pain management including highlights on complications seen commonly with long-term use of opioids.

Unfortunately many chronic pain patients are not deterred by explanation of risk if opioids are already a problem. Furthermore, many acute pain patients may not see that in many circumstances opioid therapy for over a week is likely to be counterproductive.

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

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.

Response

Abuse-deterrent opioid preparations are already on the market and indeed do deter parenteral use and therefore diversion. The problem is that generic non-abuse-deterrent preparations remain subsided on the PBS, which it must be stated, is the height of irrationality.

Tamper-resistant and abuse-deterrent opioids have only a limited effect on the overall usage of opioids, are quickly circumvented and may only serve as a selling point of difference to prolong patents.

Not only are there are few if any "new" analgesics in development but also Australian prescribers and therefore consumers have access to a broad array of analgesic drugs. This is a very privileged position in global terms. The challenge is to use this array well, which is a function of prescriber education. Continued availability of non-abuse deterrent formulations means patients seek these, compromising their intended impact.

There are no grounds to expect that generic gabapentin or pregabalin or similar molecules offer a viable alternative to analgesic drugs in any of the contexts under discussion. In fact current issues surrounding PBS-subsidised pregabalin, including lack of efficacy and significant adverse effects, rival those in the opioid arena.

This consultation may be the opportunity to review the places of tramadol (S4) and tapentadol (S8) in the array of analgesic drugs. These drugs have been promoted as having "dual action" - being opioid agonists and (mainly) serotonin-reuptake or (mainly) noradrenaline-reuptake inhibitors respectively. In fact they are very weak opioid agonists, the affinities of tramadol and tapentadol for the mu-opioid receptor being one-270th and one-18th respectively of that of morphine[5]. It does not seem appropriate that they be classed effectively as "opioids" at all but rather as phenylpropylamines and in a category of their own. There may be an argument that tapentadol should be rescheduled as S4.

With respect to "products that can be used to negate the effect of opioids", the best "antidote" is judicious prescribing in the first place. This situation is analogous to prescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs without assessing whether the latter are indicated in the first place. Caution is required when assessing the claims of sponsors in this space. Products to reverse opioid-induced ventilatory failure are readily available.

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

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.

Response

As canvassed under Option 4 above, there is a strong argument that competence in opioid prescribing should be mandatory for all prescribers. The REMS program in the USA may be a useful model.

Further to the points made under Option 3 above, it follows that daily opioid doses in excess of 100mg OME may be appropriate only in palliative medicine (under the advice, direction or supervision of a specialist palliative care physician) and in some cases of CNCP (under the advice, direction or supervision of a specialist pain medicine physician).

However there is the question of whether this desired restriction is better achieved through appendices in the Poisons Standard or through review and counselling when Authority access to PBS-subsided opioids is requested, whether by telephone or post. The latter, which would necessarily entail an educational component for the prescriber, is likely to be more effective. Such a role for the PBS Authority system has been advocated by the Faculty for some time.

The issue of addressing the private (non-PBS) prescription of opioids is again raised (see also under Option 3 above), as is the role of regulation at the stage of dispensing in such circumstances.

State and Territory requirements for opioid prescription authority vary. Harmonisation of State permit and PBS Authority requirements would be helpful, as would the automatic flagging of repeated scripts and multiple opioids.

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

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.

Response

An important factor is the role of prescriber education, particularly with respect to:

- the complexity of CNCP
- the role of non-drug treatment modalities in the management of patients with CNCP
- existing guidance in the Australian context (see footnote 2).

[5] Raffa RB, Buschmann H, Christoph T, et al. Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opin Pharmacother*. 2012;13(10):1437-1449.

Education regarding the sociopsychobiomedical framework for assessing and treating all patients with pain, but those with CNCP in particular, is inextricably linked to competence in prescription of all drugs used in this arena, not only opioids.

Demonstrated (theoretical) competence in opioid pharmacotherapy should be a *sine qua non* for prescribers.

A comprehensive treatise on the array of analgesic drugs available in Australia would be a useful resource, confined to[6]:

- paracetamol
- phenylpropylamines
- opioids.

[6] gabapentin and pregabalin are not analgesic drugs

Contact details

Australian and New Zealand College of Anaesthetists

ANZCA House

630 St Kilda Road,

Melbourne Victoria 3004

President:

Professor David A Scott

president@anzca.edu.au

+61 3 9093 4913

Dean, Faculty of Pain Medicine

Dr Chris Hayes

painmed@anzca.edu.au

+61 3 8517 5337

General Manager, Policy Safety and Quality:

Ms Jo-anne Chapman

policy@anzca.edu.au

+61 3 9510 6299