Therapeutic Goods Administration consultation paper

Prescription strong (S8) opioid use and misuse in Australia – Options for a regulatory response

---

Mundipharma response

February 2018

mundipharma

Contents

Mundipharma Pty Limited ABN 87 081 322 509, 88 Phillip Street, Sydney NSW 2000

Executive Summary

Pain is the most common reason why people seek medical attention,[1] and access to pain management is a basic human right.

The International Association for the Study of Pain (IASP) states that opioids have a role to play across the pain spectrum including acute, cancer, non-cancer, palliative and chronic pain. This is reflected in the TGA consultation paper: ***'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.'***

One in five Australians has chronic pain, and one in three Australians aged over 65 suffers from chronic pain.[1]

The IASP Declaration of Montréal on people's rights goes on to say: ***'Appropriate treatment includes access to pain medications, including opioids and other essential medications for pain...'***[2] It is vitally important that these patients have access to appropriate therapy, and we agree with the TGA that ***'any regulatory response must not unduly restrict informed, rational prescribing of opioids.'***

Since Mundipharma commenced operations in Australia in 1998, patient welfare has been at the centre of our approach to pain management. We have particular expertise in chronic pain. One in five Australians has chronic pain, and one in three Australians aged over 65 suffers from chronic pain.[1] To this end, we advocate a multimodal approach to treating patients with chronic pain that is based on the socio-psycho-biomedical model of pain. Facilitating the multimodal management of chronic non-cancer pain (CNCP) is a core learning objective of the accredited education activity sponsored by Mundipharma, the Pain Management Master Class. Our focus has been, and is always, on the quality use of medicines, which includes the selective use of opioid analgesics. We therefore believe we can make a positive contribution to this consultation process.

Mundipharma believes that opioid analgesics play an important role in the management of CNCP. However, they are associated with potential harms, including unsanctioned use, addiction and overdose. Mundipharma supports the judicious use of opioid medicines in accordance with the principles of quality use of medicines. These principles are recommended as general strategies to help assess, manage and reduce potential risks and to improve patient care. Opioid analgesics are appropriate for carefully selected patients, such as patients with moderate to severe CNCP with impaired physical functioning and quality of life who have not responded to non-pharmacotherapies and non-opioid analgesics. A stepped approach for CNCP management that incorporates considerations of both pain severity and the underlying mechanism of pain is recommended.[3,4]

To this end, we do support:

- The need for more extensive education on pain management for prescribers, potentially in line with the Royal Australian College of General Practitioners (RACGP)-accredited Pain Management Master Class
- The possibility of limiting high-dose opioid prescribing in primary care to 'accredited' GPs and nurse practitioners who have undergone mandatory accredited training

- Incentives to properly adopt a truly multimodal approach to the management of chronic pain, for example the introduction of more comprehensive pain care plans (in line with the existing care plans for diabetes and mental illness)

We also acknowledge the genuine concerns regarding the misuse and abuse of opioids. Although this pertains to the minority of cases, it should be addressed, and to this end we do support:

- The fast tracking of mandatory 'Real Time Monitoring' for S4 and S8 opioids
- The removal of all non-abuse deterrent versions of the high dose formulations from the Australian Register of Therapeutic Goods (ARTG), where there is an alternative abuse deterrent formulation available
- Incentives for expedited TGA review of opioid antidotes – including a federally funded, free Take Home Naloxone program
- Incentives for expedited review of improved products for pain relief (including the consideration to down-schedule low-dose buprenorphine patches)
- The rapid registration and availability of smaller pack sizes for S8 opioids
- Restricting the prescribing of high-dose opioids to specialists, accredited GPs and nurse practitioners.

We do however not support:

- Restricting access to opioids for patients suffering from CNCP
- Restricting GP prescribing of standard doses of opioids (≤ 100 mg oral Morphine Equivalent Daily Dose [oMEDD])
- Restricting the prescribing of opioids in the palliative care setting to patients with cancer
- Any changes to existing indications or Consumer Medicines Information of currently approved opioid products

Opioid use has increased in Australia, but the rate of increase is comparable, or lower than, other medications, including medications used to manage CNCP such as pregabalin and modified release paracetamol.[5] We acknowledge that there is an issue associated with opioid misuse, however to describe the Australian situation as a 'crisis' is alarmist and risks stigmatising patients who have a legitimate need for opioid analgesics to manage their pain.

The assertion that there '*...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*' is from an editorial focused on opioid use in the USA and not Australia.[6] The TGA-approved indication for many opioids in Australia encompasses their use for CNCP. This use is not indication creep.

Mundipharma's input on the eight options under consideration is summarised below (see **Table 1**).

We thank you for the opportunity to provide input into this consultation document. We look forward to continuing to work with the TGA and other stakeholders to support the quality use of medicines whilst protecting the rights of patients with pain to have appropriate access to opioid analgesics.

Table 1: Summary of Mundipharma's submission

Option	Recommendations
Option 1: Consider the pack sizes for Schedule 8 opioids	We: ■ support the rapid registration and availability (including Pharmaceutical Benefits Scheme [PBS] reimbursement) of additional smaller pack sizes, whilst maintaining existing arrangements (indications and PBS reimbursement) of 14 day pack sizes for use in chronic pain including CNCP.
Option 2: Consider a review of the indications for strong opioids	We: ■ believe approved indications should be established for each individual medication following regulatory (TGA) review of the supporting clinical trial data in registration dossiers. ■ do not support adjusting the approved indications for opioid analgesics on a class basis, based on clinical guidelines. ■ query whether: – clinical guidelines should be considered appropriate to re-assess approved indications which have previously been subject to rigorous assessment by the TGA; and – the quoted sections of the *Therapeutic Goods Act* allows the TGA to vary indications without specific and demonstrable evidence of an error in the relevant dossier.
Option 3: Consider whether the highest dose products should remain on the market, or be restricted to specialist/ authority prescribing	We: ■ support tighter controls being applied to the prescribing of high opioid doses (oMEDD > 100 mg), excluding prescribing for patients in palliative care and for patients with acute or cancer pain. ■ recommend the TGA removes all non-abuse deterrent high-dose opioid formulations from the ARTG where there is an alternative abuse deterrent formulation available.
Option 4: Strengthening Risk Management Plans for opioid products	We: ■ agree with the TGA in that ***'we do not see a specific benefit from increased active (rather than passive) post-market surveillance programs here.'*** ■ do not support any new Risk Management Plans being applied to existing approved opioid analgesics. ■ support fast tracking of national, mandatory real-time monitoring of S4 and S8 opioids. ■ support increased healthcare professional education on pain management.

Option	Recommendations
Option 5: Review of label warnings and revision to the Consumer Medicines Information	We: ■ do not support the addition of warnings or statements to the CMI that are inconsistent with the approved indications. ■ support the Return Unwanted Medicines program.
Option 6: Consider incentives for expedited TGA review of improved products for pain relief and opioid antidotes	We: ■ support free access to take-home naloxone without the need for a prescription. ■ support rescheduling naloxone to Schedule 2 to improve access. ■ support accelerated review of abuse deterrent formulations. ■ recommend the TGA removes all non-abuse deterrent high-dose opioid formulations from the ARTG where there is an alternative abuse deterrent formulation available.
Option 7: Potential changes to use of appendices in the Poisons Standard to provide additional regulatory controls for strong opioids	We: ■ do not support any amendments to the Poisons Standard to limit prescribing of S8 opioids to specific medical practitioners. ■ do not support any initiatives to restrict the prescribing of appropriate doses (oMEDD ≤ 100 mg) of opioids, including for patients with CNCP. ■ recommend the rescheduling of low-dose buprenorphine patches (5, 10 and 15 mcg/h) to Schedule 4.
Option 8: Increase healthcare professional awareness of alternatives to opioids (both Schedule 4 and Schedule 8) in the management of chronic pain	We: ■ support initiatives that would increase patient access to non-pharmacotherapies to manage pain, as long as the new measures do not compromise the use of appropriate medications including opioids. ■ recommend Medicare item number(s) for care plans for patients with chronic pain that have appropriate levels of access to allied healthcare professional services. ■ recommend subsidising evidence-based devices for managing pain.

Overview

Access to pain management is a basic human right

Throughout this consultation process, it is paramount that all parties recognise the fundamental human right to access to pain management[2,7] and ensure that no proposals compromise these rights.

The International Association for the Study of Pain's (IASP) Declaration of Montréal outlined three fundamental rights:[2]

1. **'The right of all people to have access to pain management without discrimination'**
2. **'The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed'**
3. **'The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals'.**

   Noting that *'Appropriate treatment includes access to pain medications, including opioids and other essential medications for pain, and best-practice interdisciplinary and integrative non-pharmacological therapies, with access to professionals skilled in the safe and effective use of these medicines and treatments and supported by health policies, legal frameworks, and procedures to assure such access and prevent inappropriate use.'*

Healthcare professional education has a leading role in achieving appropriate balance between access and risk management. In 2016, Dr Alford stated in the *New England Journal of Medicine*, ***'I believe that the medical profession is compassionate enough and bright enough to learn how to prescribe opioids, when they are indicated, in ways that maximize benefit and minimize harm. Though managing chronic pain is complicated and time consuming and carries risk, we owe it to our patients to ensure access to comprehensive pain management, including the medically appropriate use of opioids.'***[8]

Healthcare professional education has a leading role in achieving appropriate balance between access and risk management.

We need to ensure that any new measures strike a balance between providing patients with appropriate access to effective therapies which do not undermine their care, while applying appropriate controls to minimise overuse, illicit use, and unintended adverse consequences. We also need to preserve the GPs' ability to prescribe opioids for pain management, including for patients with chronic pain. As stated in the purpose of the consultation document, it is imperative that *'any regulatory response must not unduly restrict informed, rational prescribing of opioids'.*

The decision on whether to use opioids or not, like all medical decisions, is based on assessing risk and benefit. As pain, and in particular chronic pain, is a complex medical condition, clinical decisions must be made on an individual basis, with the patient's primary care physician (in most cases their general practitioner) needing to make this risk/benefit assessment.[7,9] Hence, any new measures should not unduly restrict a GP's ability to prescribe opioids at appropriate doses.

More education on pain management is a vital part of the solution

We have often heard from pain physicians and peak bodies that healthcare professionals do not receive sufficient education on pain management during their undergraduate training. Mundipharma supports a multimodal approach to treating patients with chronic pain that is based on the socio-psycho-biomedical model of pain. Similarly, we support the quality use of medicines in managing patients with chronic pain. These are core themes of the independently developed accredited Pain Management Master Class sponsored by Mundipharma. Over 5,000 GPs have been educated on the management of CNCP via the Pain Management Master Class.

Increasing education at the undergraduate level and as part of continuing professional development will upskill the healthcare profession on pain management.

Language such as opioid 'crisis' in the Australian context risks further stigmatising patients with a legitimate need for opioid analgesics

Mundipharma acknowledges that opioids have the potential to be misused and abused, and further steps should be considered to reduce the risk of unintended adverse consequences occurring. However, we believe that describing the Australian situation as a 'crisis' risks stigmatising patients who have a legitimate need for these medications.[10] Our assertion is based on:

- Australia has an ageing population. As our nation ages the burden of chronic diseases such as osteoarthritis increases, as do the demands for the use of medications and other services to appropriately manage these conditions.[11]
- The Royal Australasian College of Physicians' Prescription Opioid Policy states: ***'Increased use of prescription opioids may be due to a number of factors, including: increasing prevalence of chronic pain; developments in pharmaceutical opioid preparations (especially the introduction of sustained release morphine and oxycodone) that have enhanced the safety and effectiveness of opioids in treating chronic pain; and consequently, a greater willingness by the medical profession to prescribe opioids, in part reversing a trend of 'under-treatment' of chronic pain of many decades.'***[12]
- A preliminary analysis shows an increase in the use of a number of medications, including pregabalin and modified release paracetamol, which are also used to manage chronic pain (see **Table 2**).[5] Therefore, the growth in use of opioids may reflect a general trend in the increased use of medications more broadly.

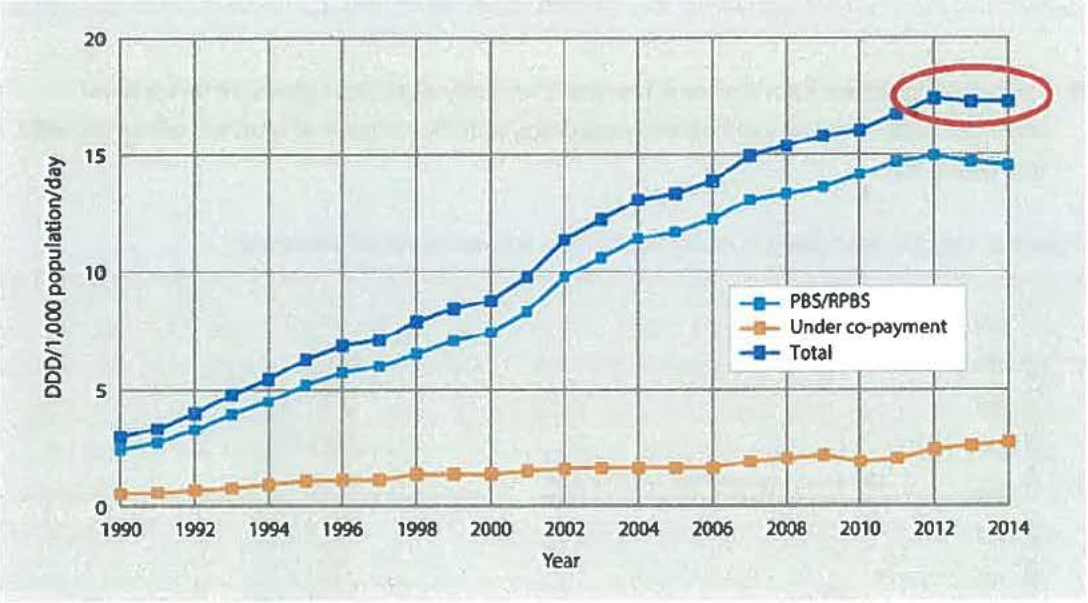
Table 2: Growth in use of opioids is comparable or lower than other medications[5]

Medication	Units 2010	Units 2017	Percentage change	CAGR %
Narcotic analgesics (opioids)	11,756,587	15,693,482	+33%	4.2%
Modified release paracetamol (665 mg)	7,012,137	12,055,126	+72%	8.0%
Pregabalin	2,475,628 (2014)†	4,075,111	+65%	18.1%
Antidepressants	22,707,664	30,265,478	+33%	4.2%
Anti-epileptics	4,167,422	8,793,799	+111%	11.3%

CAGR = Compounded annual growth rate.
† As pregabalin was first listed on the PBS on 1 March 2013, a shorter time period has been applied.

- Opioid use in Australia has plateaued as indicated by the most recent data (2012 to 2014), published by Karanges (2016), (see **Figure 1**).[13] This suggests that existing measures, including healthcare professional education, are moderating opioid prescribing.

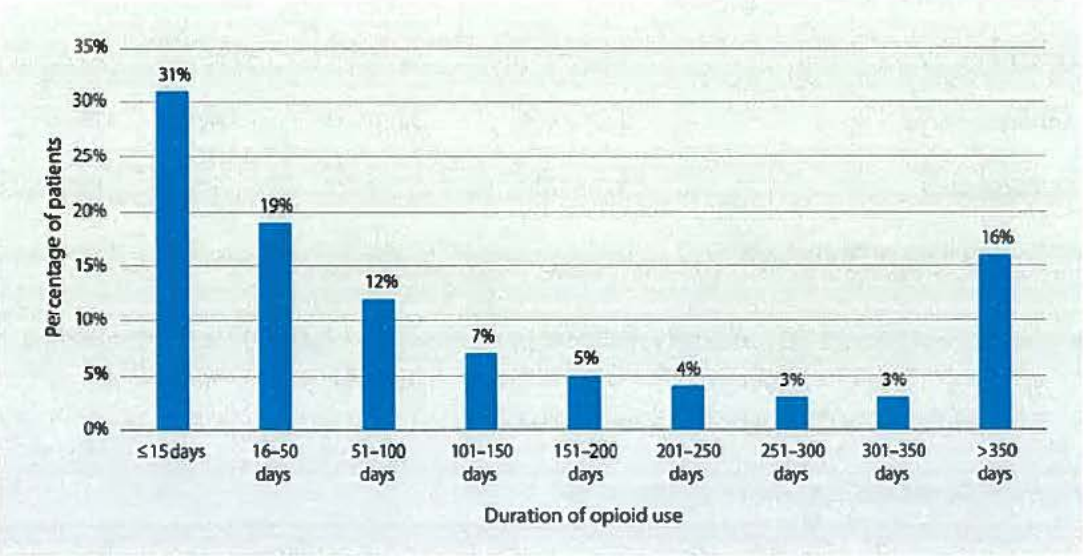
Figure 1: Opioid use in Australia has plateaued[13]



DDD = Defined daily doses

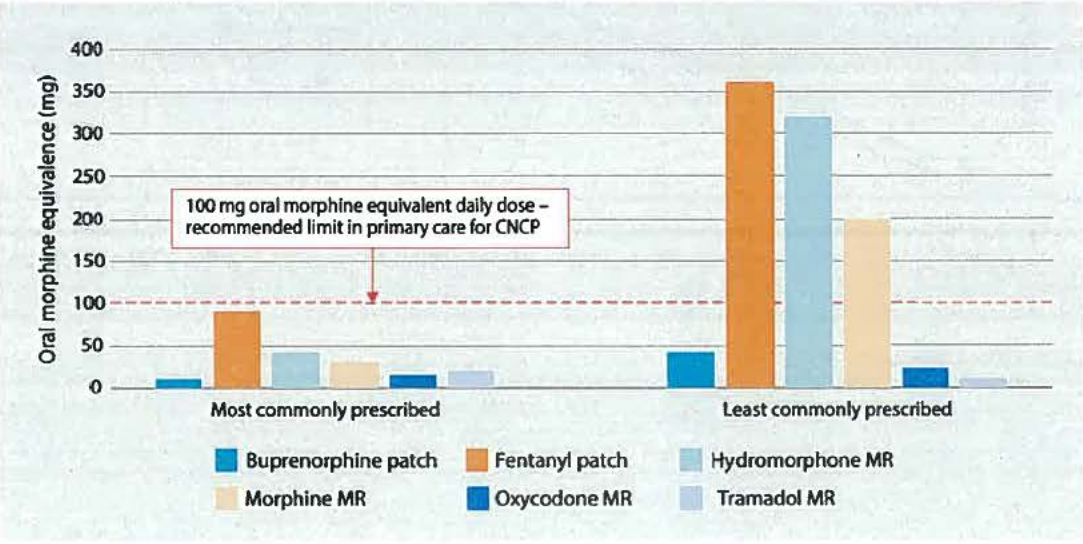
- The use of opioids to manage chronic pain and the chronic or long-term use of opioids are not one and the same. Long-term use of opioids is not the norm. Data on the duration of use of a commonly prescribed modified release opioid in Australia indicates that the majority of people (62%) take it for fewer than 100 days (see **Figure 2**).[14]

Figure 2: Average duration of opioid use for modified release oxycodone/naloxone (May 2016)[14]



- High-dose opioid use is not the norm. The most commonly dispensed opioids are for the lower doses and dispensing was low for the highest doses, with the exception of modified release tramadol (see **Figure 3**).[13]

Figure 3: Opioid prescribing in Australia (2014) is skewed towards low doses[13]



MR = Modified release, CNCP = Chronic non-cancer pain

- Mundipharma has reviewed IMS data on the pharmacy purchasing of opioids in Australia. This data has identified that the average oral morphine equivalent daily doses for modified release opioids in Australia were all below 100 mg (the recommended upper limit to manage CNCP in primary care before seeking specialist advice)[3,4,15] with the only exception being fentanyl patches (see **Table 3**).[5]

Table 3: Average daily opioid doses in Australia are generally below 100 mg oral morphine (October 2017)[5]

Modified release opioid	Average oral morphine equivalent daily dose (mg/day)
Buprenorphine patch	24.6
Fentanyl patch	115.0
MR hydromorphone	83.3
MR morphine	73.2
MR oxycodone	82.8
MR oxycodone/naloxone	38.7
MR tapentadol	85.4

MR = modified release.

TGA approved indications for many modified release opioids include their use in CNCP

One of the underlying themes of the consultation paper is that opioid use should be limited to managing acute pain and cancer pain and that use in CNCP is not evidence based and should be restricted. For example, the consultation paper asserts that one of the contributing factors to increased opioid use in Australia '*...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.*' The TGA-approved indication for many opioids encompasses the use in CNCP (see **Table 4**). In Australia, the use of opioids in CNCP is not indication creep. The above quotation is an opinion from an editorial focused on opioid use in the USA and not Australia.[6]

This quote fails to recognise: (a) substantive differences in prescribing in the US and Australia, and (b) that indications for use of opioids for CNCP has long been approved by the TGA and successfully applied in Australia without significant increase in misuse of those products.

The consultation paper provides no Australian evidence that indication creep has occurred.

Table 4: Approved indications for opioid analgesics in Australia

Opioid	IR or MR	Approved indication
Buprenorphine patch[16]	MR	Management of moderate to severe pain
Codeine/paracetamol[17]	IR	Relief of moderate to severe pain
Codeine (alone)[18]	IR	Relief of mild to moderate pain
Dextropropoxyphene/ paracetamol[19]	IR	Relief of mild to moderate pain in patients who are not able to be adequately treated with other analgesics
Fentanyl patch[20]	MR	Management of chronic pain requiring opioid analgesia
Hydromorphone[21]	MR	Treatment of moderate to severe chronic pain
Hydromorphone[22]	IR	Relief of moderate to severe pain
Morphine[23]	MR	Treatment of opioid-responsive, chronic severe pain
Methadone[24]		Is a suitable analgesic in conditions where morphine would make a reasonable alternative, particularly for the relief of pain of visceral origin
Oxycodone[25]	MR	Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
Oxycodone[26]	IR	Relief of moderate to severe pain
Oxycodone/naloxone[27]	MR	Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/ or prophylaxis of opioid-induced constipation.
Tramadol[28]	MR and IR	Relief of moderate to severe pain
Tapentadol[29]	MR	Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
Tapentadol[30]	IR	Relief of moderate to severe pain

IR = Immediate release, MR = Modified release, CNCP = Chronic non-cancer pain

The IASP this month released a position statement on the use of opioids in the management of pain (IASP Statement on Opioids, February 2018). In this statement, the IASP acknowledges that opioids are indispensable for the treatment of severe short-lived pain during acute painful events and at the end of life. Similarly, they acknowledge that there is a role for low-dose opioids in the management of chronic pain amongst carefully selected patients. This use is consistent with quality use of medicines and Mundipharma's position that there is a clinical need and role of opioid analgesics in the management of CNCP for patients who have an inadequate response to non-opioid therapy.

If opioid use was effectively restricted to use in acute pain and cancer pain, what are the alternative options for patients who are currently using opioids to manage other pain conditions such as CNCP?

- For many patients there will be no effective alternative, as opioid use has been initiated as recommended, after an appropriate trial of non-opioid therapy and when there was an inadequate response to non-opioid therapy.[4] This is particularly the case amongst the elderly and frail, where the use of analgesics such as NSAIDs pose an unacceptable risk[31] and other alternatives such as tramadol are poorly tolerated.[32]
- Limits on prescribing of Schedule 8 opioids will likely result in the increased use of NSAIDs and coxibs, for which there is a lack of 'long-term' evidence for their use.[33,34] However, there is substantial evidence that long-term use of NSAIDs and coxibs increases the risk of adverse renal, gastrointestinal and cardiovascular consequences, which is why guidelines recommend use be intermittent, e.g. for two weeks at a time.[3]

While Mundipharma welcomes appropriate and proportionate regulation of indications for opioid products, it encourages the TGA not to take action which would result in existing patients ceasing to be able to access products demonstrated to be effective and suitable for their condition.

Palliative care is not limited to patients with cancer

Not all patients who need palliative care have cancer.[35] As a person comes closer to death, the prevalence of clinically significant pain increases. For example, a 2010 publication, Smith *et al*, identified that the prevalence of clinically significant pain increases in the last four months of life and was more common amongst patients with arthritic conditions.[36] The *Therapeutic Guidelines: Palliative Care* indicates that any person with a progressive disease leading to death can benefit from palliative care. Half of all expected deaths are due to causes other than cancer.[35] Opioid use in palliative care must not be limited to patients with cancer. All patients in palliative care should be treated equally and have equal access to effective pain management, including access to opioid analgesics.

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.

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.

Fast-track smaller pack sizes

Mundipharma acknowledges that there is a risk of long-term opioid use and misuse following the use of discharge opioids to manage postoperative pain, however this risk is very small. For example, Brat *et al.* (2018)[37] identified that the event rate for opioid misuse within one year after surgery was 0.2% (amongst a cohort of 568,612 opioid-naïve patients who received discharge opioids for postoperative pain). The duration of opioid use was the strongest predictor of opioid misuse and not the dose of opioid prescribed, even for doses greater than 150 mg oMEDD.

Mundipharma supports the recommendation for the registration and introduction of smaller pack sizes of opioid analgesics for the treatment of acute pain. We agree with the TGA that this initiative would support the quality use of medicines in the post-hospital discharge setting as well as the management of other acute pain conditions such as acute dental pain. For this initiative to be effective, some opioids would require a change to their existing approved indications and PBS reimbursement of smaller pack sizes would need to occur.

The introduction of smaller pack sizes should be an additional measure and not alter existing indications or PBS reimbursement of opioid analgesics for the management of chronic pain. This includes patients with cancer pain, patients in palliative care (with cancer or non-cancer pain) and patients with CNCP that is not adequately managed by non-opioid therapies. Suitable pack sizes for the management of chronic pain should retain the availability of 14 days' supply under existing prescribing and PBS reimbursed conditions. Increasing the frequency of doctor consultations to manage patients with chronic pain is impractical for patients and has significant financial and workload implications for the health system.

Mundipharma supports the RACGP's recommendation that any patient discharged from hospital with a prescription for opioid analgesics should have a clear pain management plan (i.e. discharge letter) to facilitate the handover of care.

Patients discharged from hospital with opioids need appropriate assessment and a plan

Other initiatives to enhance the quality use of medicines relate to the discharge of patients with prescriptions for opioid analgesics. This process should be tightened so that:

- Patients discharged from hospital should generally only be discharged with a prescription for opioid analgesics if they required opioid analgesics to manage their pain whilst in hospital.
- Mundipharma supports the RACGP's recommendation that any patient discharged from hospital with a prescription for opioid analgesics should have a clear pain management plan (i.e. discharge letter) to facilitate the handover of care. This letter should include details of opioid dosing, the expected duration of opioid analgesic therapy and the planned opioid taper.[15]

Note: Mundipharma has already recognised this issue and has been sponsoring an independently developed and delivered pain management interactive workshop.

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.

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.

Clinical guidelines have an important role in supporting the quality use of medicines. The purpose of clinical guidelines is to provide healthcare professionals with general guidance on clinical practice. They are not intended to define the approved indications for individual medications.

Mundipharma overall understands the TGA's desire to provide more consistency in the wording of approved indications for the different opioid analgesics. However, we strongly oppose the application of a common indication to all opioids and basing this 'common' indication(s) on clinical guidelines and systematic reviews, because:

- We believe that the same regulatory authority review process that the TGA uses to first approve indications should also be used to adjust the approved indications. This needs to be done for each medication separately.
- Authors of clinical guidelines do not have access to all available data about each medication, including unpublished evidence that forms part of a registration dossier. Hence to base approved indications on clinical guidelines is not sound.
- Regulatory authorities provide sponsors with guidance on the data requirements and design of pivotal clinical trials to enable an indication to be potentially approved. For example, the US Food and Drug Administration recommends that the efficacy of extended-release opioids be established in 'chronic' use trials of 12-week duration with placebo controls.[38] To retrospectively change the required level of evidence without giving sponsors the sufficient opportunity to satisfy these new requirements sets a dangerous precedent. It risks undermining confidence in the regulatory oversight of pharmaceuticals.

We believe that the same regulatory authority review process that the TGA uses to first approve indications should also be used to adjust the approved indications.

Option 2

- As stated, regulatory authorities require studies of 12 weeks' duration to approve analgesics for chronic pain.[38] It is not appropriate to retrospectively alter the approved indications based on clinical guidelines or systematic reviews that apply a different standard to define the existence of appropriate evidence. For example, the Cochrane review by Noble (2010) defined evidence for long-term use as trials of at least 6 months duration.[39] The review by Chou 2015 applied a minimum trial duration of 12 months to define long-term evidence.[40]
- It is clinically inappropriate to align indications across all opioids due to the complex and heterogeneous nature of pain, e.g. acute *vs* chronic, neuropathic *vs* nociceptive *vs* mixed, superficial somatic *vs* deep somatic *vs* visceral, cancer pain *vs* non-cancer pain, paediatric patients *vs* adult patients *vs* elderly patients *vs* frail and debilitated patients, short-acting opioids *vs* long acting opioids, etc.
- There is a plethora of clinical guidelines and systematic reviews that relate to pain management. The consultation document does not indicate which of these are being considered on which to base the review of opioid indications. As the different clinical guidelines are not entirely consistent, the ability of all stakeholders to provide a fully considered response is impaired. The TGA should provide clarity on this issue and further opportunity for stakeholder consultation before any decisions are made.

Clinical guidelines have an important role in supporting the quality use of medicines. However, Mundipharma queries whether clinical guidelines should be considered appropriate to re-assess approved indications which have previously been subject to rigorous assessment and approval by the TGA. The purpose of clinical guidelines is to provide healthcare professionals with general guidance on clinical practice – they are not intended to define the approved indications for individual medications. Guidelines are deliberately general and non-binding to afford medical professionals discretion in treating their patients. Various guidelines are not consistent nor mandatory, demonstrating the concerns related to using guidelines for assessment of indications. If the TGA wishes to reassess existing indications for opioid products, this should be based on strict clinical evidence and assessed against the same factors and risk matrix as applies to the initial approval of all indications.

From a legislative perspective, while section 9D of the *Therapeutic Goods Act* grants the Secretary the right to vary an entry in the ARTG if the entry contains information that is incomplete or incorrect, it is not clear on what basis the Secretary would form the view that an entry would be incomplete or incorrect. Section 25AA(4)(b)(i) will only apply to the extent that section 9D has been satisfied. Accordingly, we query whether the quoted sections of the *Therapeutic Goods Act* allows the TGA to vary indications without specific and demonstrable evidence of an error in the relevant dossier.

It is not appropriate to retrospectively alter the approved indications based on clinical guidelines or systematic reviews that apply a different standard to define the existence of appropriate evidence.

Long-term evidence (> 3 months) is limited for all therapies used to manage chronic pain

Mundipharma acknowledges that there are limited controlled studies that evaluate the efficacy of opioids for durations greater than three months. This reflects the regulatory requirements for obtaining indications for chronic pain[38] and ethical and practical issues (such as patient recruitment and skewed drop-out rates due to lack of efficacy) associated with conducting placebo-controlled studies in people with moderate to severe chronic pain for extended periods of time.[41,42] That is, the lack of 'long-term' evidence is not only for the use of opioids, but also applies to the use non-opioid therapies such as NSAIDs,[33,34] paracetamol[42] and non-pharmacotherapies.[44,45] Therefore, the long-term management of chronic pain for essentially all therapies (medications and non-pharmacotherapies) is based on the extrapolation of short-term clinical trial data. It is inappropriate to apply different evidence requirements for different therapies being used to manage the same clinical condition, as could occur if clinical guidelines are used to set the approved indications for opioid analgesics only.

Opioids may be appropriate for patients with CNCP

The RACGP states that, ***'For well-selected patients with no history of SUDs [Substance Use Disorders], proper management with opioids can contribute to long-term pain relief.[116] However, long-term opioid treatment (≥ 26 weeks) benefits only about 25% of patients.[117] Continuation of opioid therapy is indicated if documentation clearly supports that the opioid results in improvement of existing limitations of pain and functionality,[101] balanced against the adverse effects of the opioid therapy.'***[46]

Opioids may be appropriate for patients with arthritic or neuropathic pain

The consultation paper states, ***'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 inappropriate prescribing for non-cancer chronic pain (such as arthritic [or neuropathic pain).'*** Mundipharma disagrees that the use of all opioids is inappropriate for CNCP such as arthritic or neuropathic pain.

Opioid analgesics are not first-line agents for managing arthritic pain or neuropathic pain outside the palliative care setting, but their use in patients with these conditions, who have not had an adequate response to non-opioid therapy, is appropriate and evidence-based. For example, the Royal Australasian College of Physicians' Prescription Opioid Policy states that:

'The following conclusions may be drawn from these studies [five published clinical reviews]:

- ***Opioids were effective in the treatment of CNMP [chronic non-malignant pain] over short periods, being associated with reduced pain and improved functional outcomes compared with placebo;***
- ***Opioids were more effective than placebo for nociceptive and neuropathic pain;'***[112]

Similarly, a systematic review of the management of neuropathic pain by Finnerup (2015) identified that the efficacy of strong opioids in the management of neuropathic pain was comparable to first-line pharmacotherapies (see **Table 5**).[47] It is also important to recognise that neuropathic pain is difficult to manage and at least 45% of patients require two or more medications to help manage their neuropathic pain,[48] for which one evidence-based option is the addition of an opioid analgesic.[47,48]

Table 5: Summary of efficacy and safety of pharmacotherapies for neuropathic pain[47]

Class of medication	Number of trials	NNT† (95% CI)	NNH (95% CI)
Tricyclic antidepressants	15	3.6 (3.0 – 4.4)	13.4 (9.3 – 24.4)
SNRIs	10	6.4 (5.2 – 8.4)	11.8 (9.5 – 15.2)
Pregabalin	25	7.7 (6.5 – 9.4)	13.9 (11.6 – 17.4)
Gabapentin	9	6.3 (5.0 – 8.3)	25.6 (15.3 – 78.6)
Strong opioids*	7	4.3 (3.4 – 5.8)	11.7 (8.4 – 19.3)
Tramadol	6	4.7 (3.6 – 6.7)	12.6 (8.4 – 25.3)

NNT = Number needed to treat, NNH = Number needed to harm, CI = Confidence interval, SNRIs = Serotonin noradrenaline reuptake inhibitors.
* Strong opioids were predominantly oxycodone or morphine.
† The lower the NNT, the more efficacious the therapy is.

For palliative care patients who are experiencing neuropathic pain, the *Therapeutic Guidelines: Palliative Care* state that, ***'While neuropathic pain commonly responds only partially to opioids, these are still the most effective analgesics for this pain, and opioids should be used in the first instance either by themselves or in conjunction with co-analgesics.'***[35]

Opioids that have positive clinical studies of their use in osteoarthritic pain, which have been reviewed by the TGA, include transdermal buprenorphine[16] and fentanyl,[20] modified release oxycodone/naloxone,[49-51] modified release tapentadol.[29] Therefore, it is incorrect to imply that the use of opioid analgesics in patients with osteoarthritis is inappropriate as it is within the approved indications.

Opioid therapy should be considered an ongoing trial: patients need regular assessment

The consultation paper makes the following statement, on page 19: ***'... and because of their low efficacy and high risk of harm current guidelines recommend that health professionals should consider de-prescribing.'***

From a quality use of medicines perspective, opioid therapy should be considered as an ongoing trial. It is appropriate to continue opioid use if the patient's condition is responding to opioid therapy, in that it is enabling them to function, is well tolerated and is being used responsibly.[12,52,53] The ongoing use is also acknowledged within published guidelines, for example the RACGP guidelines state, ***'If alternatives to opioid treatment fail, have limited benefit or are inappropriate, then supervised opioid treatment may remain an acceptable long-term therapeutic option.'***[15]

Option 2

Mundipharma agrees that as part of the quality use of medicines, prescribers should periodically trial reducing or stopping opioids to determine if the patient's condition can be adequately managed with non-opioid therapy alone. The timing of this should be based on each individual patient's circumstance. It would be a retrograde step if mandatory de-prescribing or the PBS-reimbursed use of opioid analgesics was limited to an arbitrary maximum duration. This would result in increased use of healthcare resources to oversee mandated opioid tapers and increased costs to patients for both additional doctor visits and potentially the full cost of ongoing opioid use, as a private prescription. It is important to recognise that many patients with chronic pain are already under financial stress. Many are from low-socioeconomic circumstances[54] and often chronic pain compromises their ability to maintain employment.[55]

Mundipharma agrees that as part of the quality use of medicines, prescribers should periodically trial reducing or stopping opioids to determine if the patient's condition can be adequately managed with non-opioid therapy alone.

Regarding the issue of de-prescribing, it is important to recognise that many patients want to avoid long-term opioid use and only continue to take opioids if they are needed to help maintain functioning roles within society.[56] This is further supported by prescribing data that indicates the average duration of opioid use for many patients is fewer than 100 days (see **Figure 2**).[14] For the vast majority of patients, the duration of opioid use is driven by clinical necessity and stops when the patient no longer has a clinical need.

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.

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).

Mundipharma acknowledges that it is the high-dose formulations of opioids that are most likely to be misused or abused[57] and we in principle support tighter controls being applied to the prescribing of these high doses. We believe that all approved opioid dosages should remain available in Australia to maintain flexibility in dosing, especially for patients in palliative care or with cancer pain. However, where there is an alternative abuse deterrent formulation (ADF) available (as is the case with modified release oxycodone 40 mg and 80 mg), all non-abuse deterrent high-dose opioid formulations should be removed from the ARTG.

Oral morphine equivalent daily dose > 100 mg is generally considered high-dose

Multiple Australian guidelines recommend that opioid prescribing for patients with CNCP in primary care should remain at or below an oral morphine equivalent daily dose (oMEDD) of 100 mg before specialist review or input should be sought.[3,4,15]

In the event of a patient requiring higher doses, Mundipharma in principle would support tighter controls being applied to any opioid formulation that would result in doses above 100 mg oMEDD, as long as these measures were practical and did not adversely impact the patient's ability to have their pain condition managed in a timely manner.

Mundipharma in principle would support tighter controls being applied to any opioid formulation that would result in doses above 100 mg oMEDD, as long as these measures were practical and did not adversely impact the patient's ability to have their pain condition managed in a timely manner.

Formulations of modified release opioids that would be considered high-dose are summarised in **Table 6.**

Table 6: **High-dose modified release opioids**

Modified release opioid	Formulations considered high-dose (oMEDD > 100 mg)[58,59]
Buprenorphine patch	None
Fentanyl patch	50, 75, 100 mcg/h
MR hydromorphone	32, 64 mg
MR morphine	120 mg (24-hour MR); 60, 100, 200 mg (12-hour MR)
MR oxycodone	40, 80 mg
MR oxycodone/naloxone	40/20, 60/30, 80/40 mg
MR tapentadol	150, 200, 250 mg

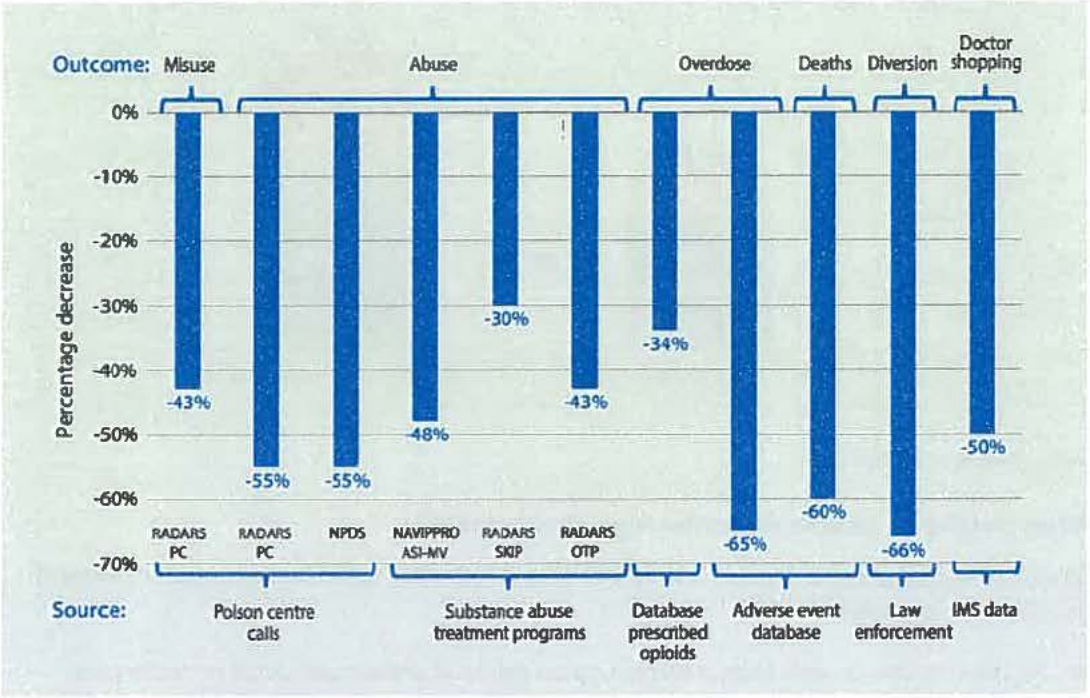
Remove non-abuse deterrent high-dose opioids from the ARTG where there is an alternative abuse deterrent formulation available

Mundipharma considers that where there is an alternative abuse-deterrent formulation (ADF) available (as is the case with modified release oxycodone 40 mg and 80 mg), non-abuse deterrent high-dose opioid formulations could be removed from the ARTG.

Market evaluation of the availability of abuse deterrent formulations of opioids has demonstrated that their prescribing reduces the incidence of illicit use, misuse, abuse and other adverse outcomes associated with the use of opioid analgesics.[57,60-63] However, the public health benefits of ADFs are undermined by the ongoing availability of non-ADFs as is the case with modified release oxycodone in Australia.

There are numerous post-marketing surveillance studies that have demonstrated that the introduction of abuse deterrent formulation of modified release oxycodone has reduced the incidence of problematic opioid use and the associated adverse consequences.[60-63] For example, Coplan (2016) published the results of 10 post-marketing studies that demonstrated that the use of abuse deterrent formulations of modified release oxycodone was associated with a lower risk of misuse, abuse, overdose, deaths, diversion and 'doctor shopping' (see **Figure 4**).[62] Note, in all of these studies the reduction in adverse outcomes was greater for ADF oxycodone than comparator opioids, indicating that other measures introduced to reduce opioid misuse were not responsible for the positive outcomes observed. Also, consistent with the mechanism of abuse deterrence, the greatest decreases in oxycodone abuse were by non-oral routes, e.g. injecting, which is associated with more serious adverse health outcomes.[62]

Figure 4: Reduction in opioid abuse with the introduction of abuse deterrent modified release oxycodone[62]



ASI-MV = Addiction Severity Index-Multimedia Version, NAVIPRO = National Addictions Vigilance Intervention and Prevention Program, NPDS = National Poison Data System, OTP = Outpatient Treatment Program, PC = Poisons Centre, RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance, SKIP = Study of Key Informants' Patients.

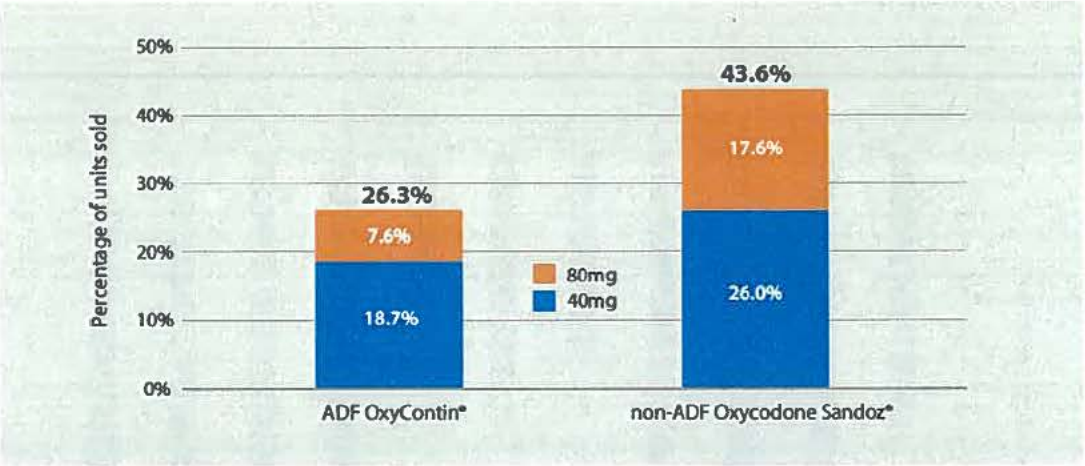
Similar findings were observed with research conducted in Australia following the introduction of the abuse deterrent formulations of modified release oxycodone. At a population level there was a reduction in the use of the two highest doses (40 and 80 mg) which are the doses most commonly used by people tampering with modified release oxycodone. Data from sentinel populations (people who inject drugs, and clients of supervised injecting facilities or needle and syringe programs) found lower rates of misuse of ADF modified release oxycodone (mainly via injection) with no evidence of switching to heroin or other drug use.[57]

The ongoing availability of high-dose non-ADF opioids undermines the public health benefits of ADFs.

The 40 and 80 mg modified release oxycodone tablets are the tablet strengths most commonly misused by people tampering with modified release oxycodone in Australia.[57]

Analysis of the Australian pharmacy dispensing data indicates that the use of the non-abuse deterrent formulations of modified release oxycodone is skewed towards these high-dose tablets relative to the abuse deterrent formulations. Of all units sold of non-ADF Oxycodone Sandoz®, 43.7% was for the 40 mg or 80 mg strengths, compared to 26.2% for ADF OxyContin® (see **Figure 5**). Similarly, the average oMEDD of non-ADF Oxycodone Sandoz® is 98.1 mg, which is higher than the two abuse deterrent formulations, OxyContin® 80.4 mg and Novacodone® 83.8 mg.[5] This data may indicate that the availability of high-dose non-ADFs is supporting ongoing misuse of oxycodone.

Figure 5: Proportion of MR oxycodone units sold as 40 mg and 80 mg tablets by brand in 2017[5]



ADF = Abuse deterrent formulation

Who should be able to prescribe high-dose opioids?

In terms of applying tighter controls to the prescribing of high-dose opioid formulations, the following needs to be considered:

- For palliative care patients (with or without cancer pain) and patients with acute or cancer pain, there should be no new restrictions as to what opioid dose can be prescribed and who can prescribe these doses.
- One in five Australians has chronic pain and the prevalence of chronic pain increases as we age, with one in three Australians aged over 65 years having chronic pain.[1] There are only limited numbers of pain specialists in Australia and the waiting times to access public pain clinics are unacceptably long, often exceeding 12 months.[55] High-dose prescribing should not be restricted to specialists only. For patients with chronic pain, including those with CNCP, Mundipharma believes that 'accredited' GPs and 'accredited' nurse practitioners (those who have completed an accredited Category 1 Active Learning Module on the management of CNCP or equivalent accredited education) should be able to prescribe high-dose opioid formulations.

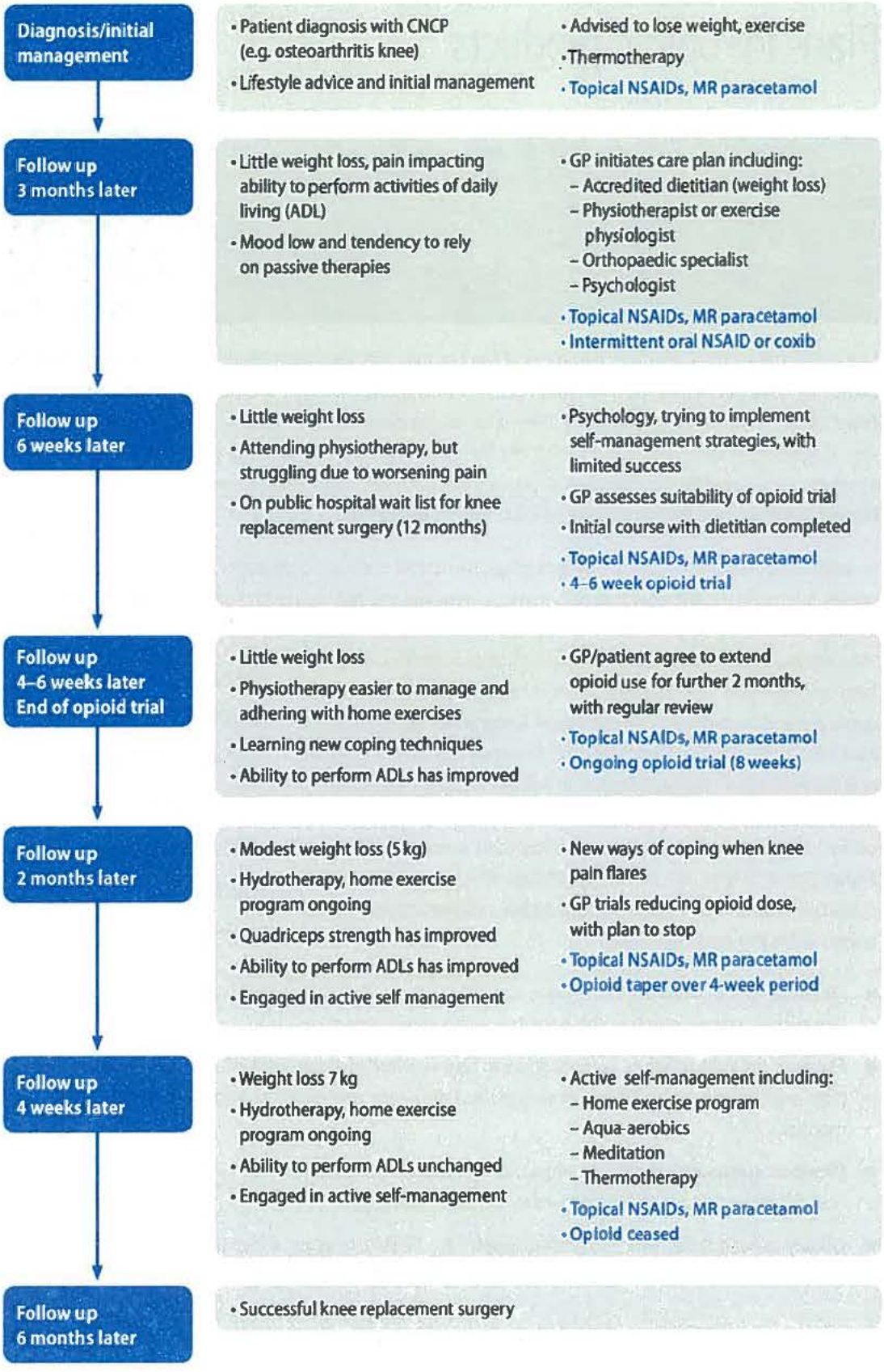
There are only limited numbers of pain specialists in Australia and the waiting times to access public pain clinics are unacceptably long, often exceeding 12 months.[55]

Once the use of a high-dose opioid formulation has been initiated by a specialist or an 'accredited' GP, the ongoing prescribing (repeat prescriptions) of this medication should be able to be done by the patient's GP or nurse practitioner without any additional restrictions. It is not practical for patients to have regular specialist consultations solely for obtaining repeat prescriptions.

Mandating care plans as a condition for high-dose opioid use in chronic pain

Multimodal pain management is considered best clinical practice[34] and care plans facilitate patient access to this. Another measure that the TGA could consider is mandating the use of a care plan, to facilitate the implementation of a multimodal pain management plan. This would need to be balanced with issues of access to allied healthcare professionals, in particular for patients in rural and remote regions.

A patient's treatment under a care plan for chronic pain may look like this



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.

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

Mundipharma supports the final statement of the consultation document relative to this option in that ***'we do not see a specific benefit from increased active (rather than passive) post-market surveillance programs here.'*** Current systems that are in place to monitor and manage product risks are generally functioning well. Furthermore, there are up to 25 years of post-marketing safety surveillance data available for these products. Consequently, the risks associated with them are well defined and there would be little obvious benefit to introducing Risk Management Plans for existing opioids.

In terms of education, Mundipharma recognises the role of continuing education for doctors and other healthcare professionals regarding pain management and the quality use of medicines. We have invested in accredited continuing education on this topic including the independently developed and delivered 'Pain Management Master Class – A practical approach to chronic pain management'. This Category 1 Active Learning Module has been approved and accredited by the two peak General Practice Colleges in Australia, the Royal Australian College of General Practitioners (RACGP) and the Australian College of Rural and Remote Medicine (ACRRM). This educational activity was first run in Australia in 2009. It has been updated several times and continues to be used to enhance GPs' knowledge of chronic pain and the quality use of medicines. Since 2009, 5,254 GPs have completed this accredited educational activity. Topics addressed in this activity include:

Since 2009, 5,254 GPs have completed this accredited educational activity.

- ***Fundamental concepts in chronic pain,*** which focuses on the basic concepts as well as adopting a biopsychosocial approach to the assessment and management of CNCP.
- ***Psychosocial vulnerability – identification, assessment and management,*** which focuses on psychosocial aspects of CNCP (yellow flags) and the use of non-pharmacological therapies to help manage CNCP.
- ***Pharmacotherapies for chronic pain,*** which reviews the evidence for and key issues associated with non-opioid and opioid therapies used to manage chronic pain.
- ***Quality use of opioids,*** which focuses on applying a systematic approach or universal precautions to the use of opioids in CNCP to encourage their selective and appropriate use.

- ***GP pain tool box,*** which uses a case study to demonstrate the use of tools to aid the GP assessment and management of CNCP, including assessing the risk of opioid misuse prior to initiating an opioid trial.
- ***Conversations about pain,*** which uses case studies to aid the GP management of some more complicated clinical scenarios GPs may face, such as managing increasing opioid doses with declining functioning and managing the inherited patient.
- ***Differentiating back and hip pain – how to assess and manage,*** which uses a case study to reinforce overall principles for the management of CNCP.

This education activity is well received by participants, with 91.8% indicating that the education activity is entirely relevant to their clinical practice.

This education activity is well received by participants, with 91.8% indicating that the education activity is entirely relevant to their clinical practice. More details on the aggregated evaluation data for this education delivered in 2017 is summarised below (see **Table 7**).

Table 7: Post-activity evaluation of the Pain Management Master Class in 2017

Learning outcome	Not met	Partially met	Entirely met
Recognise the complexity of chronic pain and the benefits of a multidimensional approach to its assessment and management	0.0%	11.3%	88.7%
Address psychosocial risk factors for developing long-term disability amongst patients with chronic pain	0.0%	16.9%	83.1%
Apply best practice principles when prescribing opioid analgesics in the management of moderate to severe CNCP	0.0%	15.3%	84.7%
Utilise tools to support the assessment and management of chronic pain	0.0%	19.3%	80.7%
Generate new insights into managing the more challenging patient conversations regarding the management of chronic pain	0.3%	24.8%	74.9%
Rate to what degree your learning needs were met?	0.0%	22.8%	77.2%
Relevance	**Not relevant**	**Partially relevant**	**Entirely relevant**
How relevant is the content of this program to your practice?	0.0%	8.2%	91.8%

Option 4

A copy of the ***Quality use of opioids*** module of the Pain Management Master Class is enclosed in **Appendix 1**. Mundipharma extends an invitation for employees of the TGA to attend this accredited education.

Mundipharma extends an invitation for TGA employees to attend this accredited education.

Similar active learning modules have been independently developed and used to educate other healthcare professionals including medical registrars, hospital pharmacists, community pharmacists and nurses. For example, the Aged Care Pain Management Master Class is a Category 1 active learning module accredited by the RACGP, ACRRM and the Australian College of Nursing. It is also has a strong focus on the quality use of medicines to manage chronic pain, as well as addressing issues such as palliative care and assessing and managing pain in people with dementia. Since 2015, 932 GPs and nurses have successfully completed this accredited education. In addition, Mundipharma has been supporting the education in aged care facilities with the Pain Advocacy Nurse in Aged Care for Education & Assessment (PANACEA) program, which aims to raise the standard of the identification, assessment and management of pain by nurses and personal care workers.

Other initiatives that should be considered are detailed below.

Mandating education on pain management for overseas-trained doctors working in rural and remote Australia

We understand a substantial proportion of general practitioners based in rural and remote Australia were trained overseas, often in countries with no or very limited access to opioid analgesics. It is Mundipharma's experience that many of these GPs have limited exposure to pain management and as such have a knowledge gap regarding developing multimodal pain management plans and the quality use of medicines in chronic pain. The public health implications of this knowledge gap are compounded by limited access to other resources such as pain specialists and allied healthcare professionals in these regions. We believe that it should be mandatory for these GPs to complete Category 1 accredited education on pain management as a condition of medical registration.

Increasing undergraduate education on pain management

Education of healthcare professionals could be further enhanced by making pain management, including the management of chronic pain, part of the core curriculum for undergraduate medical, pharmacy, physiotherapy, psychology and nursing degrees.

Change the scheduling of low-dose buprenorphine patches to Schedule 4

Evidence from the USA indicates that buprenorphine patches are associated with the lowest level of risk of misuse and abuse.[64,65] This evidence includes data collected from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS), which indicated that buprenorphine patches are abused or diverted at lower rates than other opioids, including fentanyl patches, modified release opioids and modified release tramadol.[65] Data from the USA National Poison Data System indicates low levels of intentional abuse and suicidal intent with buprenorphine patches compared to other modified release opioids.[64] During this review process, consideration should be given to applying the same scheduling for the lowest doses of buprenorphine patches as is applied to codeine and tramadol, as the lowest doses of buprenorphine patches deliver equivalent opioid doses that is achieved with codeine and tramadol (see **Table 8**).[12,59]

Table 8: Oral morphine equivalent doses of codeine, tramadol and buprenorphine patches[12,59]

	Oral morphine equivalent dose (mg)					
Opioid analgesic	**5**	**10**	**15**	**20**	**25**	**30**
Codeine			30 mg QID			60 mg QID
Modified release tramadol				50 mg BD		50 mg TDS
Buprenorphine patch		5 mcg/h		10 mcg/h		15 mcg/h

BD = twice daily, TDS = three times daily, QID = four times daily

Fast-track mandatory real-time prescription monitoring

Real-time prescription monitoring is potentially an effective way of reducing doctor shopping and opioid misuse.[66] The introduction of real-time prescription monitoring for opioids has been discussed in Australia for more than a decade[12] and is one of the strategies recommended by The National Pharmaceutical Drug Misuse Framework for Action (2012–2015). This initiative should be implemented nationally without further delay. All opioid prescribing should be monitored, avoiding voluntary participation (opt-in models). Monitoring should be applied to the prescribing of both Schedule 4 and Schedule 8 opioids to avoid the inappropriate use of Schedule 4 opioids simply due to lower levels of monitoring.[66]

Fast-track mandatory real-time prescription monitoring … All opioid prescribing should be monitored, avoiding voluntary participation (opt-in models).

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.

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.

Mundipharma supports the 'Return Unwanted Medicines' program to be implemented as approved Product Information and CMIs are being updated.

There are risks associated with warning statements for medications for patients with chronic pain

The consultation document is proposing to add warning statements to the CMI ***'to more clearly advise that opioids are not generally recommended for long-term use in chronic non-cancer pain'*** and that there is a ***'lack of efficacy in the long term treatment of chronic non-cancer pain.'*** Healthcare professionals may be able to understand the nuances of the above statements, but patients with standard health literacy may interpret this as being prescribed a medication that is ineffective or not suitable for their pain.

Chronic Pain Australia's 'Pain is not invisible' project highlights that many patients with chronic pain are frustrated with the medical profession. Patients often feel disrespected, misunderstood and that they are being ***'written off as being "psychologically" defective.'***[67] So the relationship between patient and doctor is often already strained. A strong therapeutic relationship is needed to support the quality use of medicines, such as to trial stopping a therapy, as well as to get patients to use non-pharmacotherapies or see a psychologist. Hence, Mundipharma does not support the addition of extra warnings or statements to the CMI that contradict an approved indication. This may cause unnecessary confusion amongst already vulnerable patients and further undermine the doctor/patient relationship.

> **Patients often feel disrespected, misunderstood and that they are being 'written off as being "psychologically" defective.'**[67]

In addition, qualitative research conducted amongst patients attending Australian pain clinics identified that many patients did not want to take long-term opioid therapy and this resistance led to patients delaying starting opioid therapy, avoiding opioids or self-regulating opioid therapy. Reasons for this resistance included the patient's perception of:[56]

- Poor or inadequate communication with their doctor.
- Resistance of the doctor and the healthcare system regarding prescribing opioids, including a resistance to starting opioids, pressure to reduce opioid doses, and difficulties with supply.
- Concerns about side effects and addiction.
- Concerns about identity and the stigma associated with illicit opioid use.

Therefore, the addition of warning statements to the CMI, as is being considered, risks reinforcing these patient concerns, undermining patient care and the appropriate use of these medications.

We reiterate that the use of opioids in selected patients for CNCP is evidence based and is consistent with the approved indications for many opioid analgesics. To obtain this indication, regulatory authorities have reviewed the clinical evidence and agreed that this evidence demonstrated acceptable efficacy and safety to approve this use.

There are risks associated with warning statements for medications for patients with acute pain

Adding a warning statement into the CMI ***'acute treatment should be limited to a few days and then pain managed by non-opioid medication'*** again has the potential to cause confusion between the prescriber's instructions and the CMI warning. For example, the duration of postoperative opioid use will vary according to the procedure and patient's assessment. If mixed messages are received and opioid use is stopped earlier than instructed, pain control in the first week could be compromised. This not only could cause unnecessary distress, but it also increases the risk of the patient developing chronic postoperative pain, as this is increased if acute postoperative pain is poorly controlled in the first week. We believe that the quality use of medicines in the acute pain setting would be better advanced with improved discharge instructions as discussed in response to Option 1.

Warning statements if applied to Schedule 8 opioids should also apply to other medications

If additional warning statements are mandated for Schedule 8 opioid analgesics then the same warning statements should be added to Schedule 4 opioids as their use is associated with similar risks.

If a statement about ***'lack of efficacy in the long term treatment of chronic non-cancer pain'*** is mandated for Schedule 8 opioids, then this should also be added to other medications (opioid and non-opioid) used to manage chronic pain that don't have supportive 'long-term' (> 6 or 12 month) placebo-controlled clinical trial data, such as gabapentinoids, NSAIDs and paracetamol.

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.

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

Expanding free access to take-home naloxone: implementing a public health program

Take-home naloxone is underutilised in Australia even though it is subsidised on the PBS. The National Drug and Alcohol Research Centre (NDARC) estimates that there are 15,000 opioid-related (all opioids including heroin) fatal and non-fatal overdoses per year,[68] yet in 2017 there were only 744 PBS prescriptions dispensed for take-home naloxone.[5] PBS access to take-home naloxone, although valuable, has limitations. For example, many drug users are unwilling to disclose this to a GP in order to access take-home naloxone.

The National Drug and Alcohol Research Centre (NDARC) estimates that there are 15,000 opioid-related (all opioids including heroin) fatal and non-fatal overdoses per year,[68] yet in 2017 there were only 744 PBS prescriptions dispensed for take-home naloxone.[5]

Naloxone is available without a prescription as a Schedule 3 medicine. Even though this is a positive initiative, it is also failing to deliver real public health outcomes as the cost of non-prescription supply is a barrier to use.[69]

Mundipharma in principle will support initiatives that will enable free access to take-home naloxone without the need for a prescription, such as the initiative implemented in Ontario, Canada, where take-home naloxone kits are available at no cost through pharmacies without a prescription (see **Appendix 2**).[70,71] To enable this type of access scheme to be effectively implemented in Australia, further down-scheduling of naloxone is recommended. This way, supervised injecting rooms and needle exchange services could more readily become access points for take-home naloxone.

Similarly we support the RACGP's recommendations that:

- Patients who present to hospital emergency departments with non-fatal overdose be considered for take-home naloxone therapy on discharge.[15]
- Consideration should be given to the co-prescribing of naloxone to pain patients with elevated risk of opioid overdose, such as patients with complex care and those prescribed high doses of opioids.[28]

We support the accelerated review of abuse deterrent formulations and products that can be used to negate the effect of opioids

Mundipharma supports the accelerated review of new chemical entities, abuse deterrent formulations and products such as naloxone that can be used to negate the effect of opioid overdose. This accelerated review should not be restricted to medications that would be reviewed by the prescription branch to the TGA, but an accelerated review process should also be created for the over-the-counter (OTC) branch as novel formulations of naloxone would be reviewed via the OTC branch.

Remove non-abuse deterrent high-dose opioids from the ARTG where there is an alternative abuse deterrent formulation available

Mundipharma also agrees with the sentiment to improve access to abuse deterrent formulations (ADF), especially those with evidence of positive clinical benefits. The TGA should remove from the ARTG all non-abuse deterrent high-dose opioid formulations where there is an alternative abuse deterrent formulation available, as is the case with modified release oxycodone 40 mg and 80 mg. As outlined in our response to Option 3, there is substantial evidence regarding the public health benefits following the introduction of ADF modified release oxycodone, demonstrated both in Australia[57] and overseas.[60-63] The ongoing availability of high-dose non-ADF modified release oxycodone undermines these public health benefits.

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.

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

Pain is the most common reason why people seek medical attention.[1] Any additional restrictions on the prescribing of opioids for managing pain, including CNCP, need to be carefully considered to ensure that they do not deny vulnerable patients access to evidence-based therapies.

As discussed in the response to Option 3, it is essential that GPs maintain the ability to prescribe opioids for the management of acute pain, cancer pain, palliative care and CNCP. The ability to prescribe opioids is already regulated with State authority schemes. Mundipharma does not support any amendments to the Poisons Standard to further limit prescribing of S8 opioids to specific medical practitioners.

Pain is the most common reason why people seek medical attention.[1]

As stated in Option 3, Mundipharma would consider supporting tighter controls to the initial prescribing of high-dose opioids (oMEDD > 100 mg) being limited to specialists and 'accredited' GPs and nurse practitioners. Once high-opioid dose has been initiated, all GPs should be able to provide ongoing prescribing of high-dose opioids as per the initial prescriber's guidance.

Mundipharma does not support any initiative that would provide new restriction on who can prescribe appropriate opioid doses (oMEDD ≤ 100 mg), including for patients with CNCP.

No additional restrictions are warranted or supported for the prescribing of opioids in palliative care patients or patients with cancer pain, irrespective of the dose.

As previously stated, the potential consequences of limiting GP prescribing of Schedule 8 opioids need to be considered. It is likely that:

- The use of short-acting Schedule 4 opioids such as codeine will increase even though clinical guidelines and the TGA discourages their use for patients with chronic pain.[3,4,15,72]
- The use of NSAIDs and coxibs will increase, placing patients at increased risk of adverse renal, gastrointestinal and cardiovascular consequences.[3]
- Many patients who have not achieved an adequate response to non-opioid therapy will be subjected to extended periods of poorly controlled pain while waiting to see a specialist.

Option 8: Increase healthcare 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.

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 established under the Nationally Coordinated Codeine Implementation Working Group.

Patient welfare is at the centre of Mundipharma's approach to chronic pain management. We endorse a multimodal approach to treating patients with chronic pain that is based on the socio-psycho-biomedical model of pain. Facilitating the multimodal management of CNCP is a core learning objective of the Pain Management Master Class accredited education activity sponsored by Mundipharma.

Mundipharma in general supports initiatives that would increase patient access and use of non-pharmacotherapies to manage acute and chronic pain.

Expand subsidised access to non-pharmacotherapies

A key issue for patients with pain is being able to access these services or therapies at an affordable cost. Care plans exist for patients with chronic health conditions; however, the level of access to allied healthcare professionals is greater for patients with diabetes and mental illness. As such, the TGA should consider methods to increase the level and breadth of services that patients with chronic pain can access via care plans. Similarly, subsidised access to medical devices such as transcutaneous electrical nerve stimulation (TENS) machines should be expanded.

Consider methods to increase the level and breadth of services that patients with chronic pain can access via care plans.

We also recognise that pharmacotherapies, including opioids, have an important role to reduce the severity of pain, creating a window of opportunity for patients to use these non-pharmacotherapies and learn new skills to cope with ongoing pain. Hence, any new measures to encourage the use of non-pharmacotherapies should not be at the expense of the appropriate use of medications.

Down-scheduling of low-dose buprenorphine patches

The consultation document acknowledges that ***'tramadol is one of the six opioids associated with accidental overdose fatalities in Australia'.*** As previously discussed in response to Option 4, there is evidence from the USA indicating that buprenorphine patches are associated with the lowest level of risk of misuse and abuse[64,65] and this includes a comparison to modified release tramadol.[65] If the TGA concludes that tramadol should remain as a Schedule 4 medicine, consideration should be given to applying the same scheduling for the lowest doses of buprenorphine patches.

In considering this recommendation, it important to recognise that the:[12,58,59]

- Lowest buprenorphine patch dose 5 mcg/h delivers the same oral morphine equivalent dose over 24 hours as a single tablet of the lowest dose of modified release tramadol (50 mg)
- 10 mcg/h buprenorphine patch is equivalent to taking two 50 mg modified release tramadol tablets per day, the lowest standard dosing schedule (see **Table 8**).

Glossary

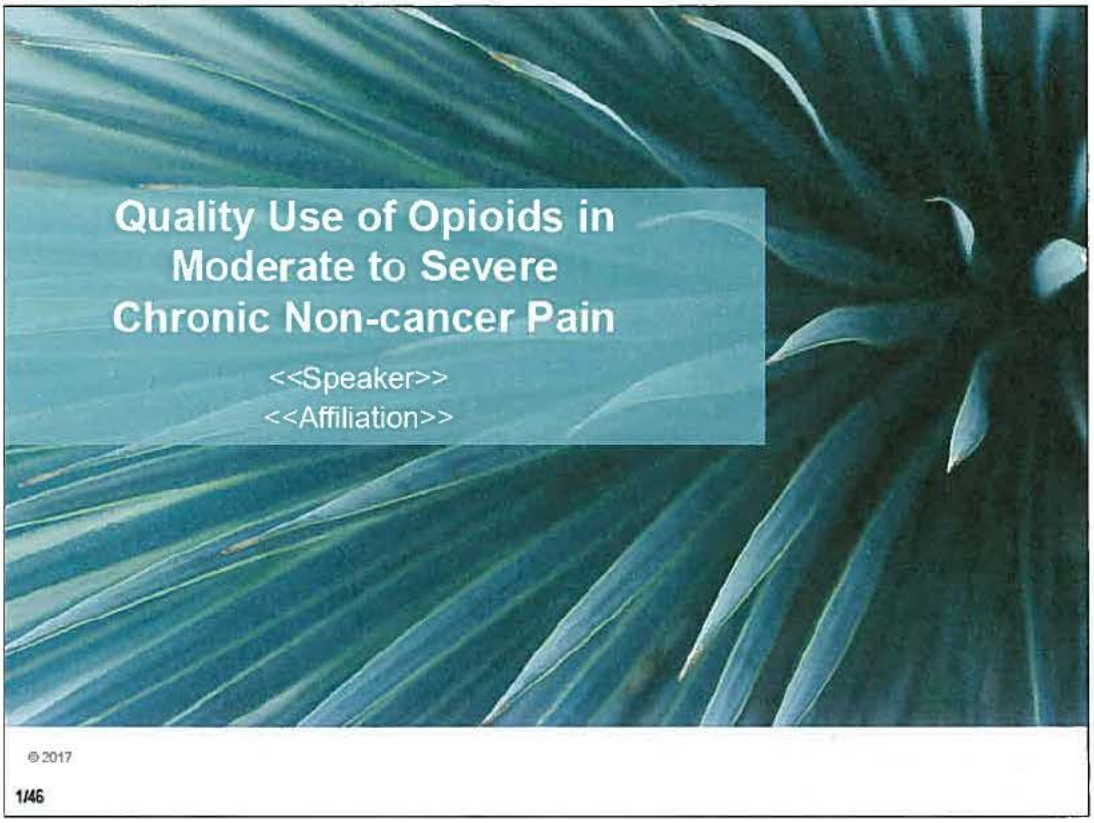
ACCRM	Australian College of Rural and Remote Medicine
ADF	Abuse deterrent formulation
ADL	Activities of Daily Living
ARTG	Australian Register of Therapeutic Goods
ASI-MV	Addiction Severity Index-Multimedia Version
CAGR	Compounded annual growth rate
CI	Confidence interval
CMI	Consumer Medicines Information
CNCP	Chronic non-cancer pain
Coxib	COX-2 selective inhibitors
DDD	Defined daily doses
IASP	International Association for the Study of Pain
IR	Immediate release
MR	Modified release
NAVIPRO	National Addictions Vigilance Intervention and Prevention Program
NPDS	National Poison Data System
NNT	Number needed to treat
NNH	Number needed to harm
NSAID	Non-steroidal anti-inflammatory drug
oMED	oral Morphine Equivalent Dose
oMEDD	oral Morphine Equivalent Daily Dose
OTC	Over-the-counter
OTP	Outpatient Treatment Program
PANACEA	Pain Advocacy Nurse in Aged Care for Education & Assessment
PBS	Pharmaceutical Benefits Scheme
PC	Poisons Centre
PI	Product Inforamtion
RACGP	Royal Australian College of General Practitioners
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
SKIP	Study of Key Informants' Patients
TGA	Therapeutic Goods Administration

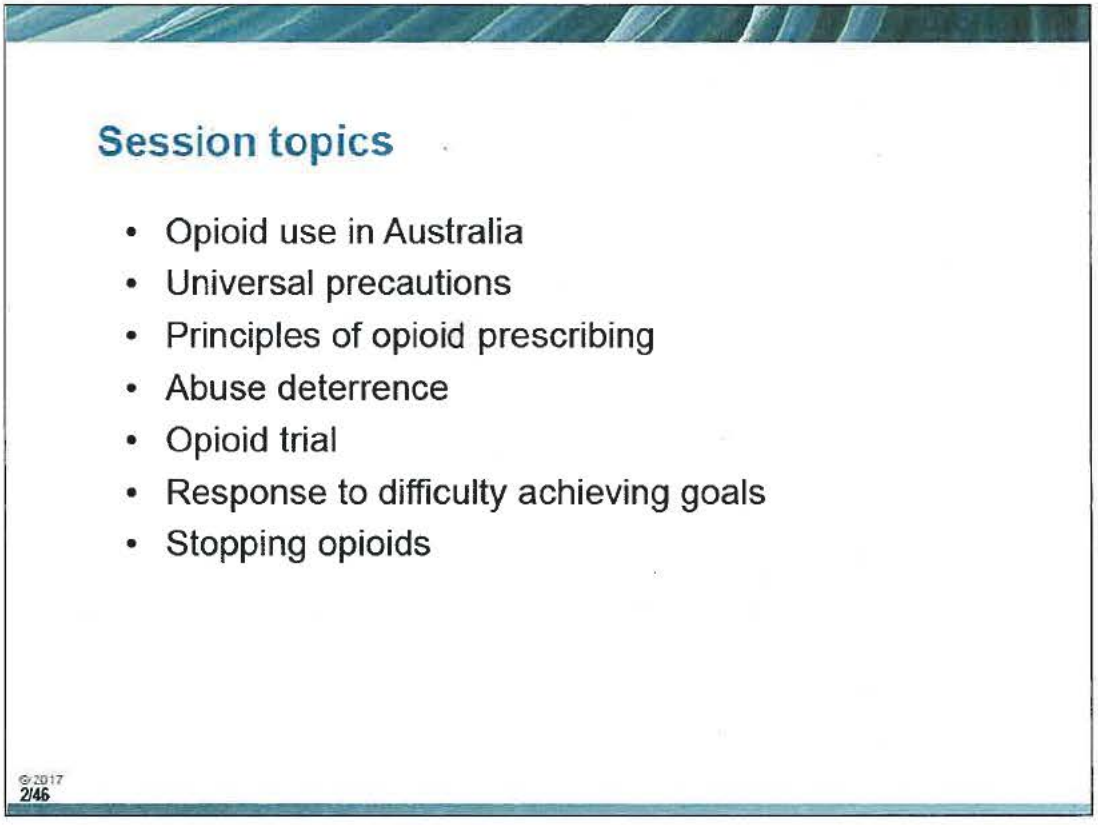
References

1. PainAustralia. Painful facts [accessed 13 December 2017]. Available from http://www.painaustralia.org.au/about-pain/painful-facts
2. International Association for the Study of Pain. Declaration of Montréal – Declaration that access to pain management is a fundamental human right. International Association for the Study of Pain. 2010.
3. Analgesic Expert Group. Therapeutic Guidelines: Analgesic. Version 6. Melbourne: Therapeutic Guidelines Limited; 2012.
4. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. Australian and New Zealand College of Anaesthetists. 2015.
5. IMS. Data on file. 2018.
6. Becker WC, Fiellin DA. Limited evidence, faulty reasoning, and potential for a global opioid crisis. BMJ 2017; 358: j3115.
7. Faculty of Pain Medicine. Statement on patients' rights to pain management and associated responsibilities. Australian and New Zealand College of Anaesthetists. 2010.
8. Alford DP. Opioid Prescribing for chronic pain – achieving the right balance through education. N Engl J Med 2016; 374: 301-303.
9. Ballantyne JC. Opioid analgesia: perspectives on right use and utility. Pain Physician 2007;10:479-491.
10. Opioids Roundtable Outcomes Statement. 2015.
11. Ackerman IN, Zomer E, Gilmartin-Thomas JF, Liew D. Forecasting the future burden of opioids for osteoarthritis. Osteoarthritis Cartilage 2017.
12. The 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 2009.
13. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. Br J Clin Pharmacol 2016;82:255-267.
14. QuintilesIMS. Data on file Mundipharma 88: Pain Patient Journey – Targin. 2017.
15. Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part C1: Opioids. Melbourne. Royal Australian College of General Practitioners. 2017.
16. NORSPAN® patch Product Information. November 2015.
17. Panadeine® Forte Product Information. June 2017.
18. Codeine phosphate hemihydrate tablets. August 2016.
19. Digesic® Product Information. October 2017.
20. Durogesic® Product Information. February 2017.
21. Jurnista® Product Information. April 2017.
22. Dilaudid® Product Information. September 2017.
23. MS Contin® Product Information. June 2017.
24. Physeptone® Product Information. June 2016.
25. OxyContin® tablets Product Information. July 2017.
26. Endone® Product Information. June 2015.
27. TARGIN® Product Information. September 2017.
28. Tramal® Product Information. May 2017.
29. Palexia® SR Tablets Product Information. March 2017.
30. Palexia® IR Product Information. March 2017.
31. McLachlan A, Bath S, Naganathan V, Hilmer S, Le Couteur D, Gibson S, Blyth F. Clinical Pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. Br J Clin Pharmacol 71[3],351-364. 2011.
32. The Australian Pain Society. Pain in residential aged care facilities. Management strategies. 2005.
33. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2016;4:CD007400.
34. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst Rev. 2016;2:CD012087.
35. Palliative Care Expert Group. Therapeutic Guidelines Palliative Care Version 3. Melbourne: Therapeutic Guidelines Limited, 2010.
36. Smith AK, Cenzer IS, Knight SJ, Puntillo KA, Widera E, Williams BA, *et al.* The epidemiology of pain during the last 2 years of life. Ann Intern Med 2010; 153: 563-569.
37. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, *et al.* Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ 2018; 360: j5790.
38. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Guidance for industry: analgesic indications: developing drug and biological products. 2014.
39. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010; CD006605.
40. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, *et al.* The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162:276-286.
41. Gudin J, Nalamachu S, Wallace LE, Matsuno RK, Coplan PM. The long-term analgesic effectiveness of opioid therapy in chronic noncancer pain patients: a literature review of randomized controlled, open-label, and epidemiologic studies. PainWeek. 2016.
42. ICH Expert Working Group. ICH harmonised tripartite guideline: choice of control group and related issues in clinical trials. E10. Step 4 version. 2000. Geneva, Switzerland: International Council for Harmonisation:
43. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel SC, Maher CG. Paracetamol for low back pain. Cochrane Database Syst Rev. 2016;CD012230.
44. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, *et al.* Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166:493-505.
45. Wylde V, Dennis J, Beswick AD, Bruce J, Eccleston C, *et al.* Systematic review of management of chronic pain after surgery. Br J Surg. 2017;104: 293-1306.
46. Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part C2: The role of opioids in pain management. Melbourne. Royal Australian College of General Practitioners. 2017.
47. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, *et al.* Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162-173.
48. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev. 2012;7:CD008943.
49. Lowenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, *et al.* Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opin Pharmacother 2009;10: 531-543.

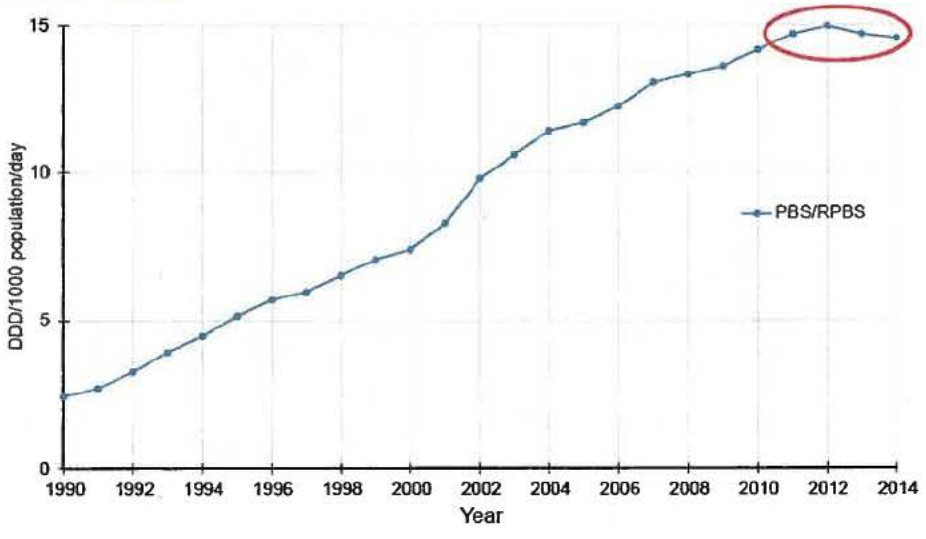
References

50. Lowenstein O, Leyendecker P, Lux EA, Blagden M, Simpson KH, *et al.* Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC Clin Pharmacol 2010;10:12.
51. Simpson K, Leyendecker P, Hopp M, Muller-Lissner S, Lowenstein O, *et al.* Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. Curr Med Res Opin 2008;24:3503-3512.
52. Cohen ML, Wodak AD. Opioid prescribing in general practice: a proposed approach. Medicine Today 2012; 3:24-32.
53. Cohen ML. Principles of prescribing for persistent non-cancer pain. Aust Prescr 2013;36:113-115.
54. Australian Commission on Safety and Quality in Health Care. Australian atlas of healthcare variation opioid medicines. 2015.
55. National Pain Summit Initiative. National Pain Strategy. Pain Management for all Australians. 2010. PainAustralia.
56. Paterson C, Ledgerwood K, Arnold C, Hogg M, Xue C, Zheng Z. Resisting prescribed opioids: a qualitative study of decision making in patients taking opioids for chronic noncancer pain. Pain Med 2016;17:717-727.
57. Larance B, Dobbins T, Peacock A, Ali R, Bruno R, *et al.* The effect of a potentially tamper-resistant oxycodone formulation on opioid use and harm: main findings of the National Opioid Medications Abuse Deterrence (NOMAD) study. Lancet Psychiatry 2018.
58. Australian Medicines Handbook Handbook online. [accessed 1 February 2018]. Available from: https://amhonline.amh.net.au
59. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. Opioid dose equivalence. Australian and New Zealand College of Anaethetists. 2014.
60. Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, *et al.* Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. J Pain 2013;14:351-358.
61. Chilcoat HD, Coplan PM, Harikrishnan V, Alexander L. Decreased diversion by doctor-shopping for a reformulated extended release oxycodone product (OxyContin). Drug Alcohol Depend 2016;165:221-228.
62. Coplan PM, Chilcoat HD, Butler SF, Sellers EM, Kadakia A, *et al.* The effect of an abuse deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. Clin Pharmacol Ther 2016;100:275-286.
63. Severtson SG, Bartelson BB, Davis JM, Munoz A, Schneider MF, *et al.* Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. J Pain 2013;14:1122-1130.
64. Coplan PM, Sessler NE, Harikrishnan V, Singh R, Perkel C. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. Postgrad Med 2017;129:55-61.
65. Wiegand TJ, Le Lait MC, Bartelson BB, Dart RC, Green JL. Analysis of the Abuse and Diversion of the Buprenorphine Transdermal Delivery System. J Pain 2016;17:745-752.
66. Kovitwanichkanont T, Day CA. Prescription opioid misuse and public health approach in Australia. Subst Use Misuse 2018; 53:200-205.
67. Chronic Pain Australia. Pain is not invisible project interim report. 2009. Parramatta, Chronic Pain Australia.
68. Warner-Smith M, Lynskey M, Darke S, Hall W. Heroin overdose: Prevalence, correlates consequences and interventions NDARC Monograph No. 46. 2000. Sydney, National Drug and Alcohol Research Centre.
69. Pricolo A, Nielsen S. Naloxone rescheduling in Australia: Processes, implementation and challenges with supply of naloxone as a 'pharmacist only' over-the-counter medicine. Drug Alcohol Rev 2017.
70. Ontario Government. Recognize and temporarily reverse an opioid overdose. 2017.
71. Kahan M, *et al.* Cost coverage of naloxone and take-home naloxone kits. 2017. The Canadian Centre on Substance Use and Addiction.
72. Therapeutic Goods Administration. Tips for talking about codeine; Guidance for pharmacists. Australian Government. 2017.


Quality Use of Opioids in Moderate to Severe Chronic Non-cancer Pain
<<Speaker>>
<<Affiliation>>
© 2017
1/46


Session topics
• Opioid use in Australia
• Universal precautions
• Principles of opioid prescribing
• Abuse deterrence
• Opioid trial
• Response to difficulty achieving goals
• Stopping opioids
© 2017
2/46

Opioid use in Australia has been increasing since 1990[1]



©2017
4/46

DDD = Defined daily doses

1. Karanges EA, *et al*. Br J Clin Pharmacol. 2016;82:255-267

Opioid use in Australia

- Legitimate reasons:[1,2]
  - Increasing prevalence of chronic non-cancer pain
  - Ageing & obese population
  - Subsidy of modified release formulations in chronic non-cancer pain
  - Greater willingness to address the under-treatment of chronic pain
- Overall use is consistent with appropriate use:[1,3,4]
  - Most prescriptions for morphine, oxycodone and fentanyl were for older patients[3,4]
  - Most commonly prescribed opioid strengths were either of the lowest two doses[1]

Evidence for misuse/abuse including a number of opioid-related deaths with codeine and strong opioid use[3-5]

5/46

1. Karanges EA, *et al.* Br J Clin Pharmacol. 2016;82:255-267. 2. The Royal Australasian College of Physicians. Prescription Opioid Policy, 2009. 3. Roxburgh A, *et al.* Med J Aust 2011;195(5):280-284. 4. Roxburgh A, *et al.* Drug Alcohol Rev. 2013;32:269-275. 5. Roxburgh A, *et al.* Med J Aust 2015;203:299.

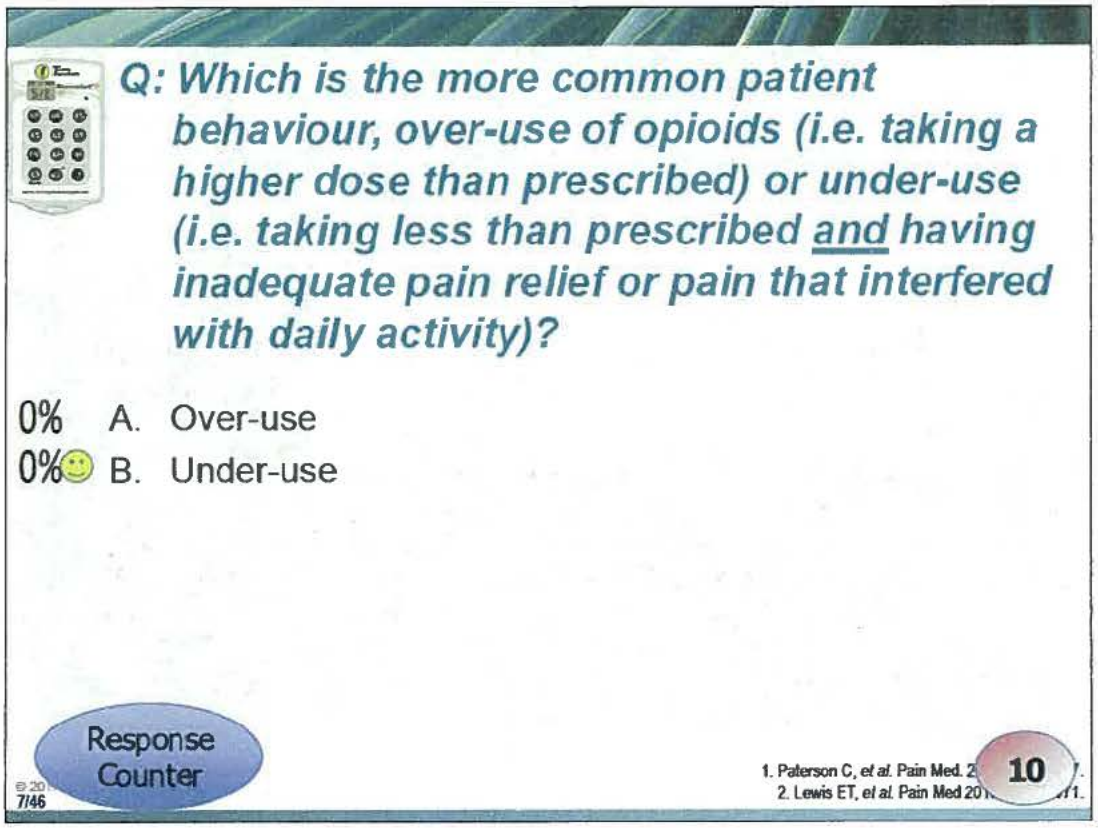
Challenges to appropriate opioid use[1]

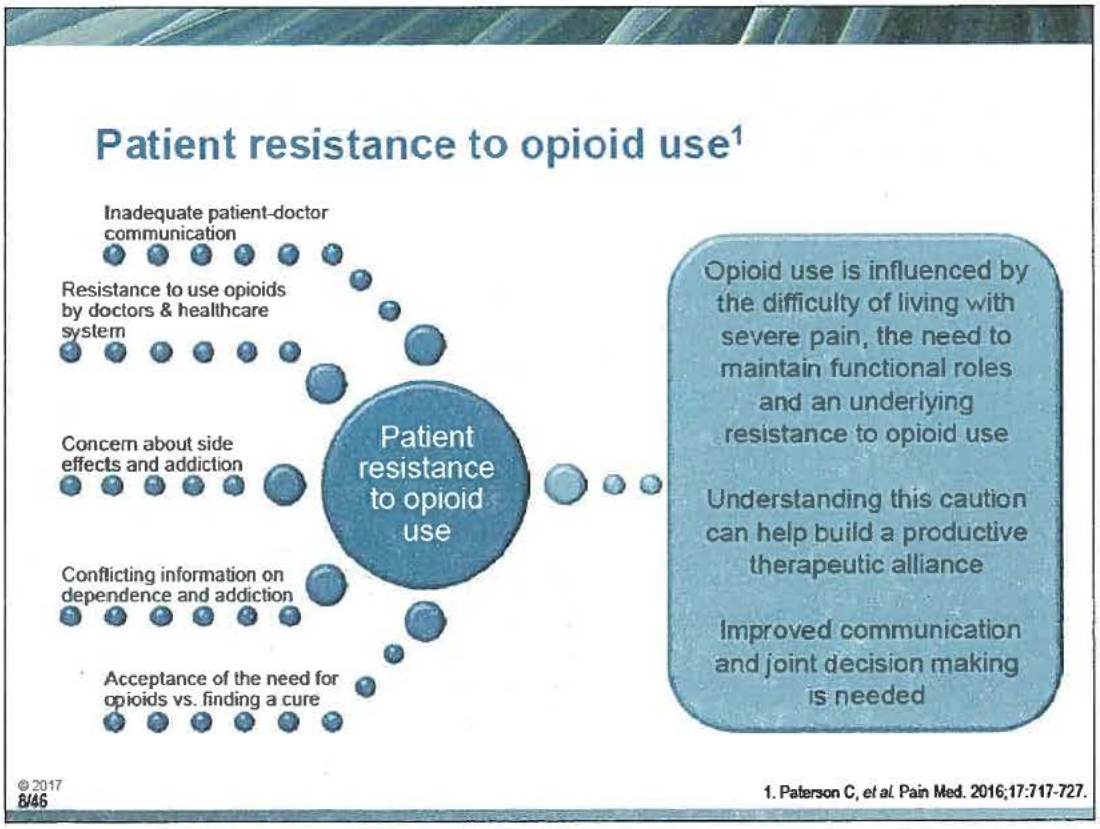
Inappropriate prescribing

Unsanctioned use

6/46

1. Okie S. N Engl J Med 2010;363(21):1981-1985.


Q: Which is the more common patient behaviour, over-use of opioids (i.e. taking a higher dose than prescribed) or under-use (i.e. taking less than prescribed and having inadequate pain relief or pain that interfered with daily activity)?
0% A. Over-use
0% B. Under-use
Response Counter
7/46
1. Paterson C, et al. Pain Med. 2
2. Lewis ET, et al. Pain Med 20
10


Patient resistance to opioid use[1]
Inadequate patient-doctor communication
Resistance to use opioids by doctors & healthcare system
Concern about side effects and addiction
Conflicting information on dependence and addiction
Acceptance of the need for opioids vs. finding a cure
Patient resistance to opioid use
Opioid use is influenced by the difficulty of living with severe pain, the need to maintain functional roles and an underlying resistance to opioid use
Understanding this caution can help build a productive therapeutic alliance
Improved communication and joint decision making is needed
© 2017
8/46
1. Paterson C, et al. Pain Med. 2016;17:717-727.

9/46

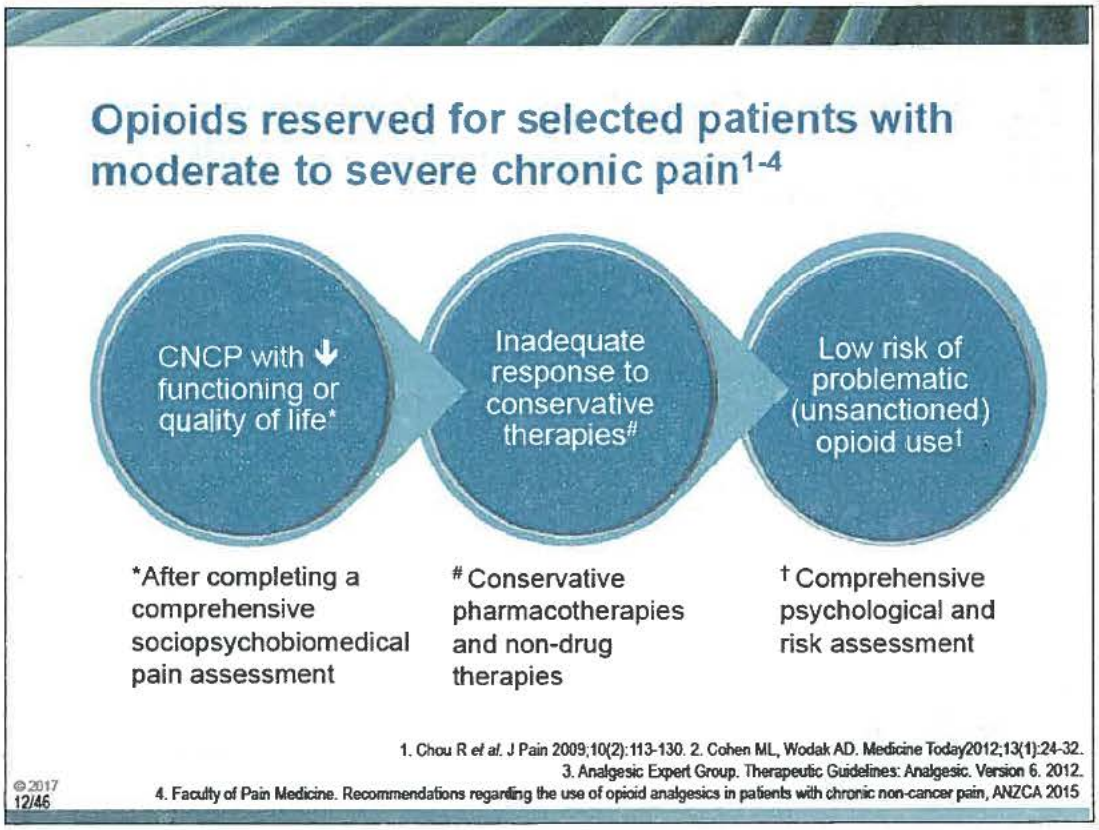
Applying the same precautions to all patients without prejudice[1]

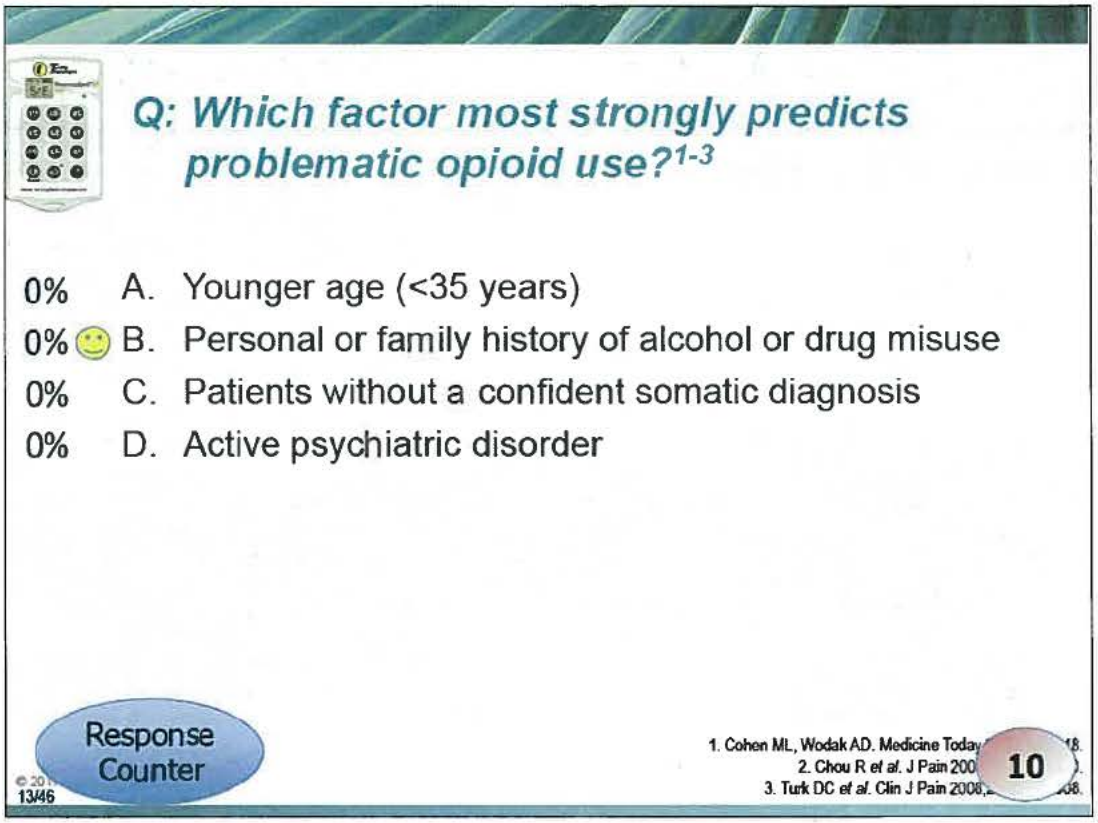
- To reduce the risk of problematic opioid use emerging
- Is essential as no single factor can 100% predict who may develop problems

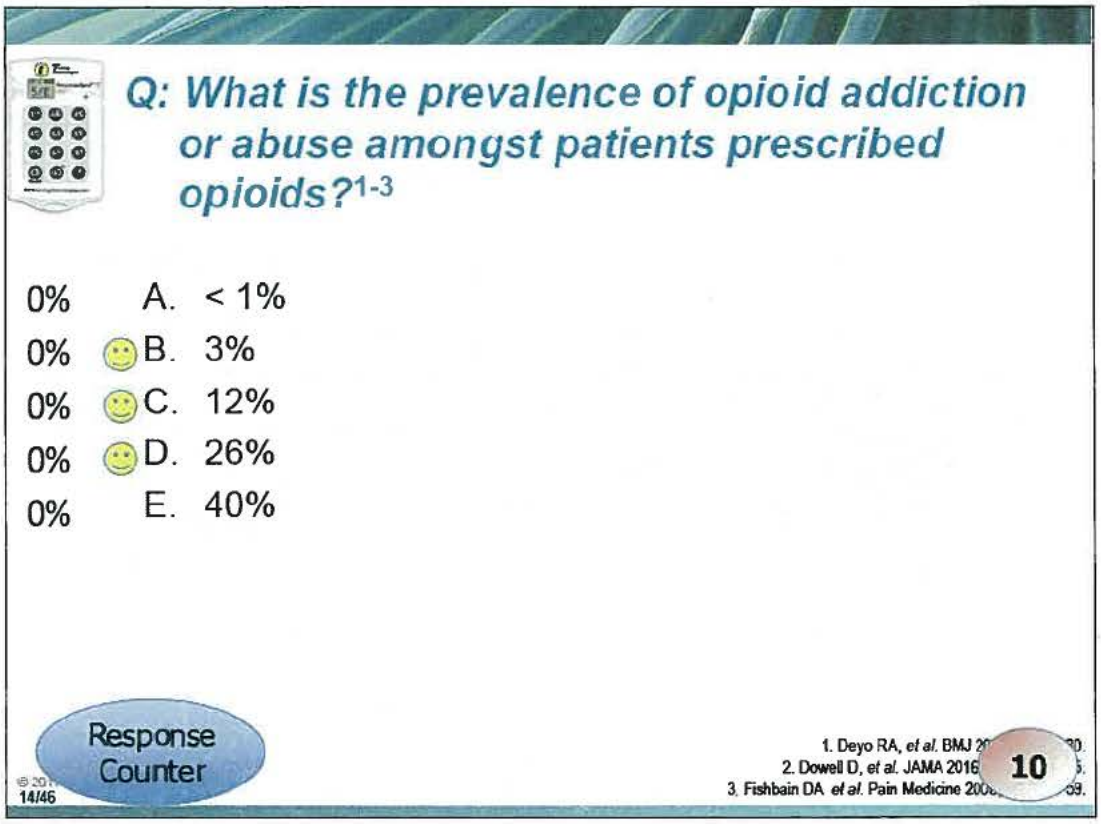
10/46

1. Gourlay DL et al. Pain Med 2005; 6(2): 107-112.


Principles of opioid prescribing
1. Comprehensive assessment
© 2017
11/46
1. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015


Opioids reserved for selected patients with moderate to severe chronic pain[1-4]
CNCP with ↓ functioning or quality of life*
Inadequate response to conservative therapies#
Low risk of problematic (unsanctioned) opioid use†
*After completing a comprehensive sociopsychobiomedical pain assessment
Conservative pharmacotherapies and non-drug therapies
† Comprehensive psychological and risk assessment
1. Chou R et al. J Pain 2009;10(2):113-130. 2. Cohen ML, Wodak AD. Medicine Today2012;13(1):24-32.
3. Analgesic Expert Group. Therapeutic Guidelines: Analgesic. Version 6. 2012.
4. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015
© 2017
12/46


Q: Which factor most strongly predicts problematic opioid use?[1-3]
0% A. Younger age (<35 years)
0% B. Personal or family history of alcohol or drug misuse
0% C. Patients without a confident somatic diagnosis
0% D. Active psychiatric disorder
Response Counter
13/46
1. Cohen ML., Wodak AD. Medicine Today
2. Chou R et al. J Pain 200
3. Turk DC et al. Clin J Pain 2008,
10


Q: What is the prevalence of opioid addiction or abuse amongst patients prescribed opioids?[1-3]
0% A. < 1%
0% B. 3%
0% C. 12%
0% D. 26%
0% E. 40%
Response Counter
14/46
1. Deyo RA, et al. BMJ 20
2. Dowell D, et al. JAMA 2016
3. Fishbain DA et al. Pain Medicine 200
10

Q: What is the prevalence of opioid addiction or abuse amongst patients with no history of drug or alcohol problems?[1]

0% ☺ A. 0.2%
0% B. 1%
0% C. 3%
0% D. 10%
0% E. 25%

Response Counter

15/46

1. Fishbain DA *et al.* Pain Medicine 200[illegible]

10

Opioid Risk Tool[1]

Factor	Males	Females
Family history of substance abuse		
- Alcohol	❑ 3 points	❑ 1 point
- Illicit drugs	❑ 3 points	❑ 2 points
- Prescription drugs	❑ 4 points	❑ 4 points
Personal history of substance abuse		
- Alcohol	❑ 3 points	❑ 3 points
- Illicit drugs	❑ 4 points	❑ 4 points
- Prescription drugs	❑ 5 points	❑ 5 points
Aged between 16 and 45	❑ 1 point	❑ 1 point
History of preadolescent sexual abuse	❑ 0 points	❑ 3 points
Psychiatric disease		
- Attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	❑ 2 points	❑ 2 points
- Depression	❑ 1 point	❑ 1 point

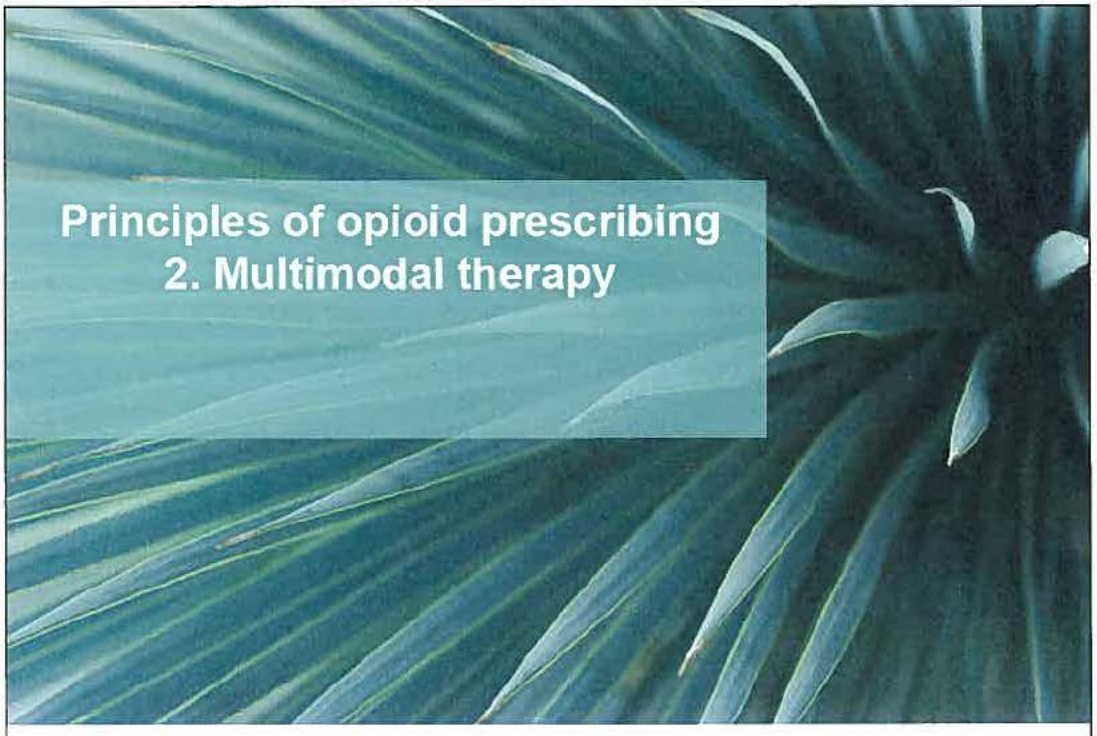
8+ HIGH RISK

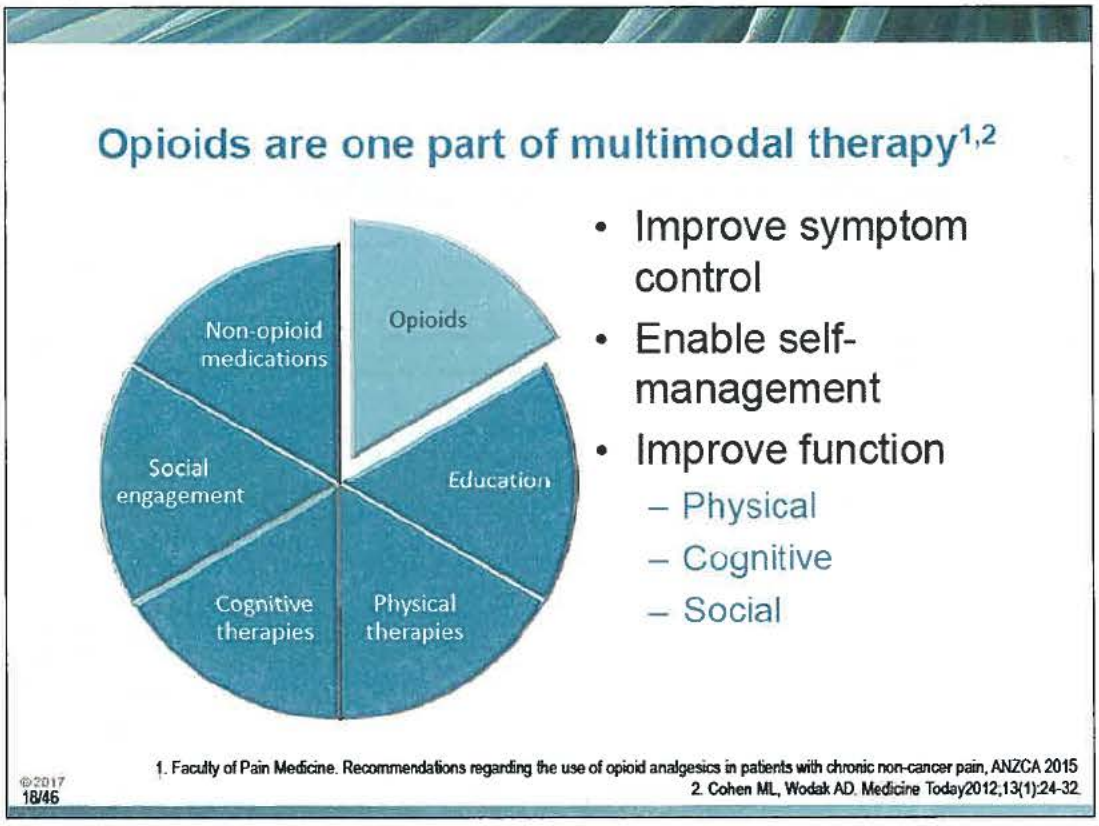
4-7 MODERATE RISK

0-3 LOW RISK

16/46

1. Webster LR, Webster RM. Pain Med 2005;6(6):432-442.


Principles of opioid prescribing
2. Multimodal therapy
© 2017
17/46
1. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015


Opioids are one part of multimodal therapy[1,2]
Non-opioid medications
Opioids
Social engagement
Education
Cognitive therapies
Physical therapies
• Improve symptom control
• Enable self-management
• Improve function
– Physical
– Cognitive
– Social
©2017
18/46
1. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015
2. Cohen ML, Wodak AD. Medicine Today2012;13(1):24-32.

Three types of tamper-resistant technologies[1]

- Abuse-resistant formulations
  - Physical barrier that makes it difficult to tamper with or extract the active medicine or renders it unsuitable for injecting or snorting
- Abuse-deterrent formulations
  - Modify the formulation pharmacologically to decrease pleasurable effects or induce aversive effects
    - E.g. adding an opioid antagonist to the formulation to reduce or deter the euphoria associated with abuse[2]
- A combination of both

©2017
20/46

1. Australian Government. National Pharmaceutical Drug Misuse Framework for Action (2012-2015).
2. US FDA. Guidance for industry abuse-deterrent opioids – evaluation and labelling January 2013.

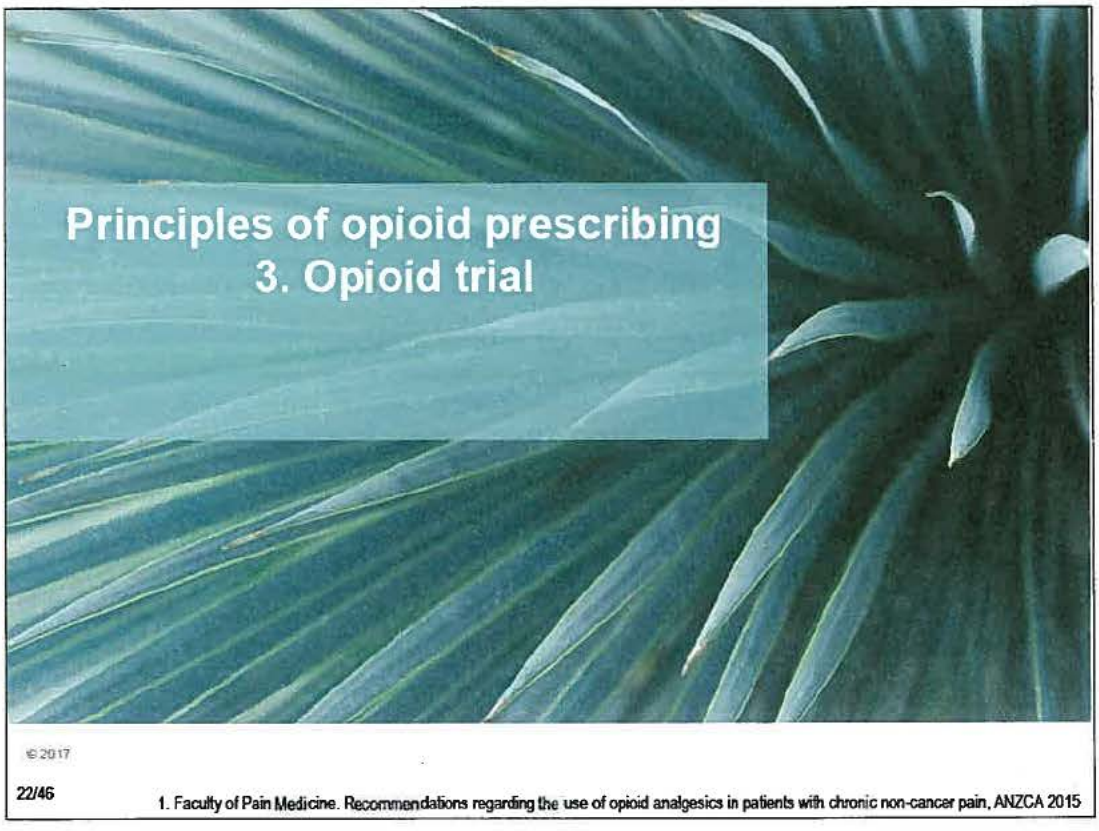
Additional considerations regarding the availability of tamper-resistant technologies

- If the tamper-resistant brand is preferred, prescribers need to remember to check the 'no substitution' box[1]
- Use may result in behaviour changes,[2,3] e.g.:
  - Preference for the generic/standard formulation[3]
  - Requesting switch to a different opioid[3]
- Behaviour changes should trigger a comprehensive pain assessment[4]

These formulations do not overcome all forms of misuse or abuse,[2] applying universal precautions remains essential[5]

1. National Prescribing Service. Unexpected deaths from legitimate opioid prescribing. Health News and Evidence, 2014.
2. Butler SF *et al.* J Pain 2013;14(4):351-58. 3. Cicero TJ *et al.* N Engl J Med. 2012;367:187-189.
4. Cohen ML, Wodak AD. Medicine Today 2010;11(2):10-18. 5. Gourlay DL *et al.* Pain Med 2005;6(2):107-112.

21/46



22/46

1. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015

Informed consent prior to commencing an opioid trial

A. Treatment goals	• Reduction in pain with manageable side effects and improved functioning[1,2]
B. Risks & benefits	• Discuss potential benefits and adverse events[3]
C. Rules (therapeutic structure)	• Outline patient and GP responsibilities[1-3]
D. Cessation plan	• A cessation plan should be in place at the start of the trial[2,4] • Cease opioid therapy if goals are not achieved, side effects are unmanageable or if aberrant behaviours emerge[2,4]

1. Cohen ML, Wodak AD. Med Today 2012; 13(1): 24-32.
2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015.
3. Gourlay DL et al. Pain Med 2005; 6(2):107-112. 4. Freynhagen R *et al.* BMJ 2013; 346: f2937.

23/46

Q: What are your most important rules when prescribing opioids?[1,2]

(You can choose up to three answers)

- 0 A. One prescriber
- 0 B. Back-up provision if the prescriber is unavailable
- 0 C. One dispensing pharmacy
- 0 D. No early prescriptions
- 0 E. No replacement prescriptions for loss
- 0 F. No unsanctioned dose escalations
- 0 G. Regular review
- 0 H. Random urine drug tests and/or pill counts
- 0 I. Upfront explanation of when opioids will be stopped

Response Counter 10

1. Cohen ML, Wodak AD. Med Today 20[illegible]2.
[illegible] of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, A[illegible]015.

24/46

Q: Who has used a written opioid treatment agreement (consent form) when initiating opioid therapy for moderate to severe chronic non-cancer pain?

0% A. Yes, on all or most occasions

0% B. Yes, but only on selected occasions

0% C. No, not previously used

Response Counter

25/46

10

Brief table discussion (Allocated time 5 minutes)

- At your tables, review the opioid treatment agreement in your workbook **(see pages 57 and 58)**

Discuss:

- What are the potential benefits of using this pain management tool?
- For which patients or in which situations would you use this pain management tool?

26/46

Feedback

- What are the potential benefits of using an opioid treatment agreement?

Potential benefits:
- Aids prescriber focus on reasons for the trial
- Functional goals to assess response to therapy
- Set outs rules, therapeutic structure
- Time-limited trial
- Explains indications for stopping opioids
- Informed consent

27/46

Q: Moving forward, when initiating opioid therapy for moderate to severe chronic non-cancer pain, when would you use a written opioid treatment agreement (consent form)?

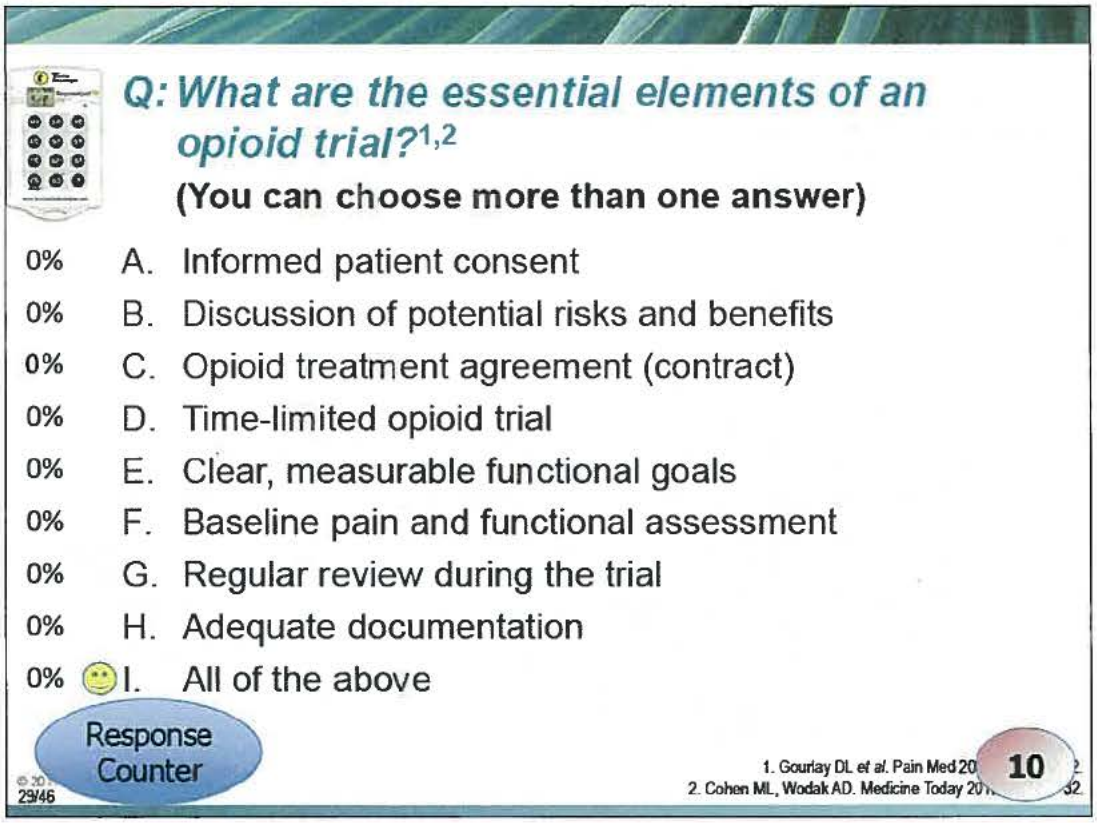
0% A. For all or almost all patients
0% B. Only for younger patients (e.g. age < 45 years)
0% C. Only for higher risk patients (e.g. assessed by ORT)
0% D. Only for patients who I don't know well
0% E. On an exception basis
0% F. Unlikely to use it

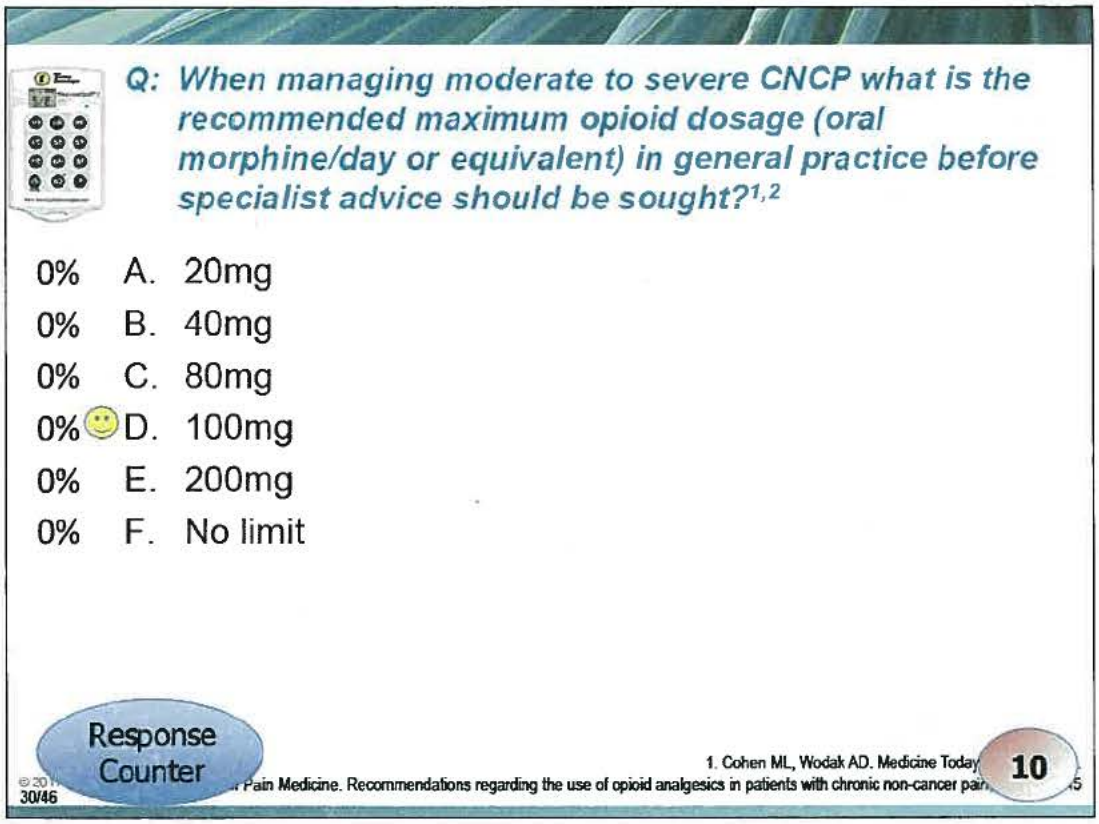
Response Counter

28/46

Opioid Risk Tool

10


Q: What are the essential elements of an opioid trial?[1,2]
(You can choose more than one answer)
0% A. Informed patient consent
0% B. Discussion of potential risks and benefits
0% C. Opioid treatment agreement (contract)
0% D. Time-limited opioid trial
0% E. Clear, measurable functional goals
0% F. Baseline pain and functional assessment
0% G. Regular review during the trial
0% H. Adequate documentation
0% I. All of the above
Response Counter
29/46
1. Gourlay DL et al. Pain Med 20
2. Cohen ML, Wodak AD. Medicine Today 20
10


Q: When managing moderate to severe CNCP what is the recommended maximum opioid dosage (oral morphine/day or equivalent) in general practice before specialist advice should be sought?[1,2]
0% A. 20mg
0% B. 40mg
0% C. 80mg
0% D. 100mg
0% E. 200mg
0% F. No limit
Response Counter
30/46
1. Cohen ML, Wodak AD. Medicine Today
Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain
10

Maximum opioid doses for CNCP in General Practice prior to specialist input[1*]

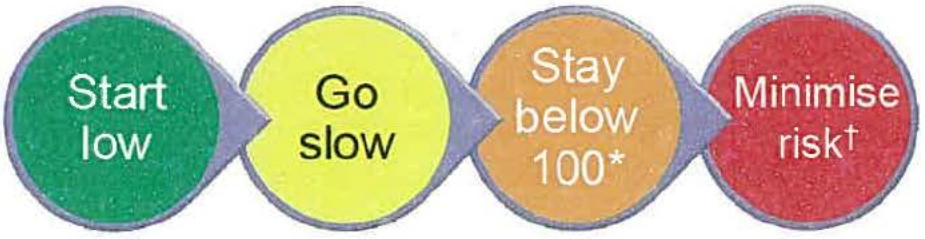
Oral Opioids	
Morphine	100 mg/day
Oxycodone	60 mg/day
Oxycodone/naloxone	60/30 mg/day
Hydromorphone	16 mg/day
Methadone	30 mg/day
Tramadol	400 mg/day
Tapentadol[2]	200 mg/day
Transdermal Opioids	
Buprenorphine	40 mcg/hr every 7 days
Fentanyl	25 mcg/hr every 3 days

* Based on available product strengths. Doses listed above are not equianalgesic doses for switching between opioids

31/46

1. Cohen ML, Wodak AD. Medicine Today 2012;13:24-32. 2. Faculty of Pain Medicine, ANZCA. Opioid dose equivalence 2014.

Appropriate opioid dosing[1,2]

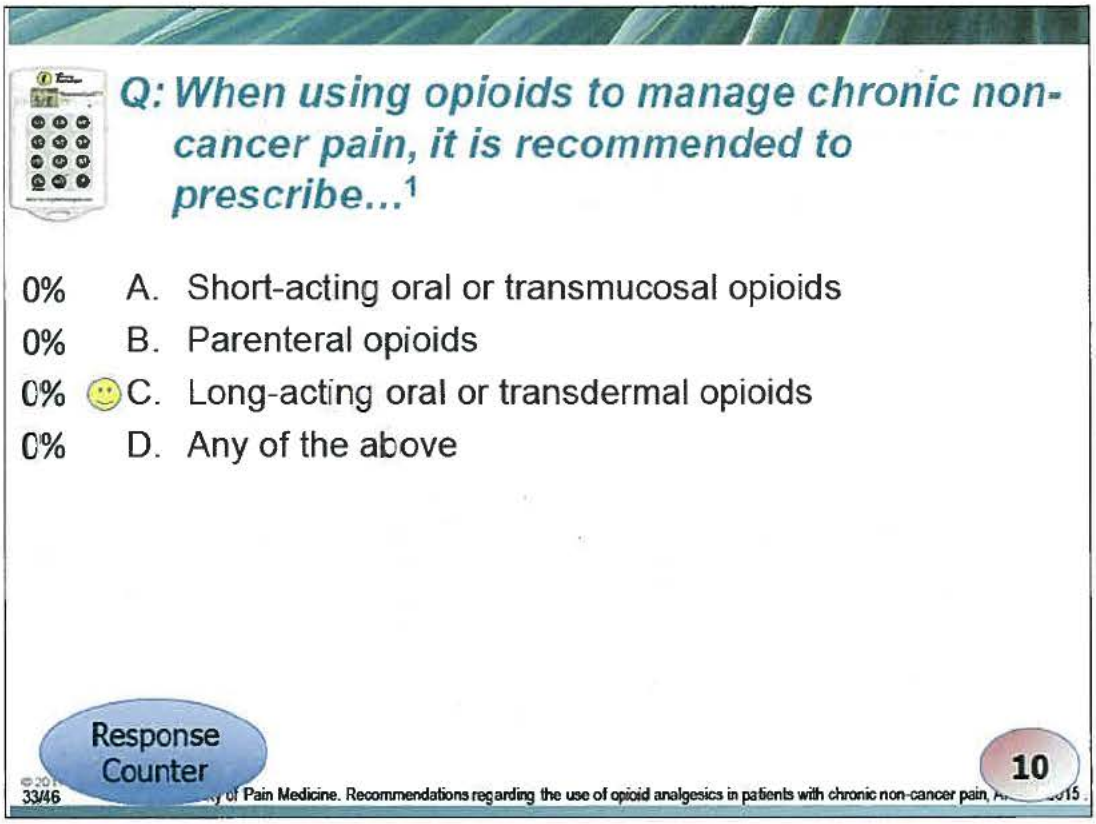


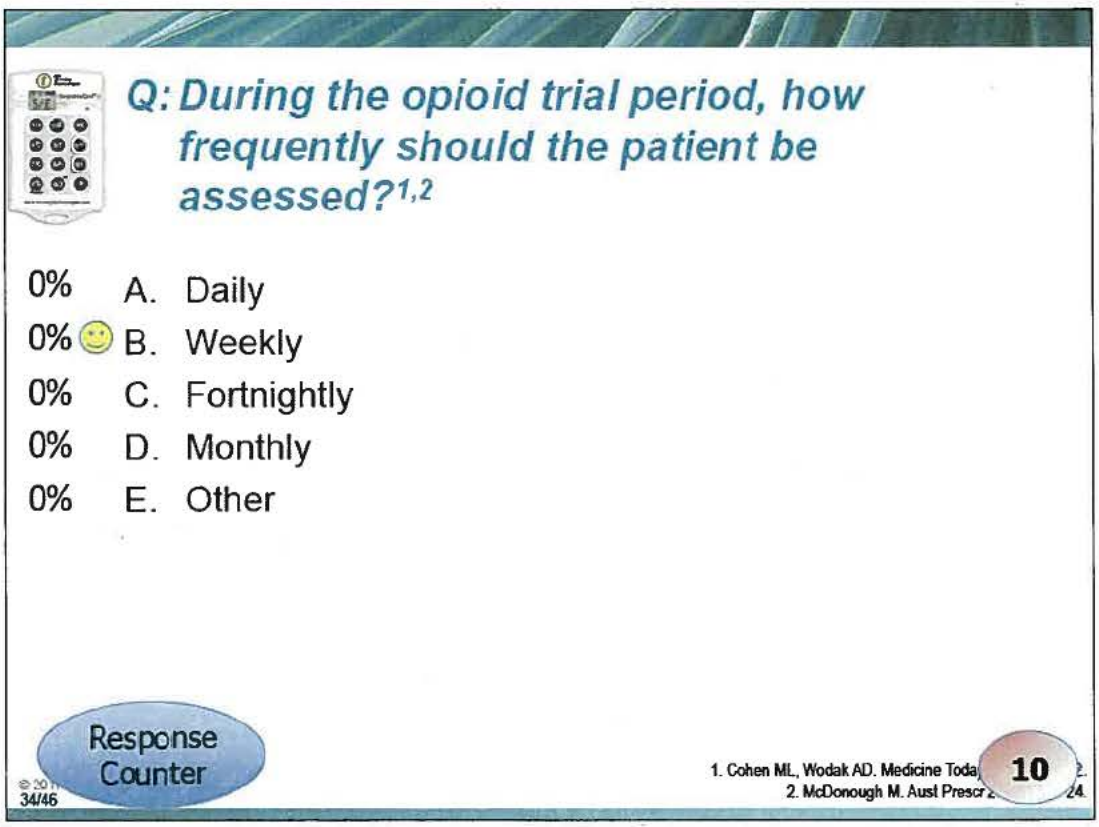
* 100 mg/day oral morphine equivalence

† avoid other CNS depressants (benzodiazepines, alcohol)

32/46

1. Cohen ML, Wodak AD. Med Today 2012;13(1):24-32.
2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015.


Q: When using opioids to manage chronic non-cancer pain, it is recommended to prescribe...[1]
0% A. Short-acting oral or transmucosal opioids
0% B. Parenteral opioids
0% C. Long-acting oral or transdermal opioids
0% D. Any of the above
Response Counter
33/46
of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain,
10


Q: During the opioid trial period, how frequently should the patient be assessed?[1,2]
0% A. Daily
0% B. Weekly
0% C. Fortnightly
0% D. Monthly
0% E. Other
Response Counter
34/46
1. Cohen ML, Wodak AD. Medicine Toda
2. McDonough M. Aust Prescr
10

Patient monitoring – 6 As[1-3]

Analgesia	• Average pain, reduction in pain • Use pain scales or BPI or PEG[4]
Activity	• Physical activity • Ability to function
Adverse effects	• Common, e.g. constipation, nausea, sedation[5]
Aberrant behaviours	• Urine drug testing, pill counts • Family member questioning/corroboration
Affect	• Mood (e.g. depression, anxiety) • Psychological status
Accurate records	• Keep thorough documentation • Record rationale for decisions made

1. Cohen ML, Wodak AD. Med Today 2012;13: 24-32. 2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015. 3. Gourlay DL, *et al.* Pain Med 2005; 6(2):107-112. 4. Krebs EE, *et al.* J Gen Intern Med 2009;24:733-738. 5. Benyamin R, *et al.* Pain Phys 2008; 11: S105-S120.

35/46

Opioid titration

- Opioid initiation and titration should be individualised according to:[1,2]
  - Patient's health status
  - 6 As
- Increased activity may result in "incident" pain[2]
  - Titrate the long-acting opioid
  - Do not add a short acting opioid

1. Chou R *et al.* J Pain 2009;10(2):113-130.
2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015

36/46

Q: What tools/resources do you routinely use to monitor aberrant behaviours?[1-4]

(You can choose more than one answer)

0 A. GP intuition
0 B. Pharmacist collaboration
0 C. Family/significant other collaboration
0 D. Pill counts
0 E. Urine toxicology
0 F. Prescription Shopping Information Service
0 G. Medicare and PBS information*
0 H. Other

Response Counter

* Patient consent is required to access the patient's Medicare/PBS

1. The Royal Australasian College of Physicians. Prescription Opioid Policy 2009. 2. Chou R *et al.* J Pain 200
3. Turk DC *et al.* Clin J Pain 2008;24(6):497-508. 4. James J. Aust Prescr. 2

37/46

10

Discussion point:

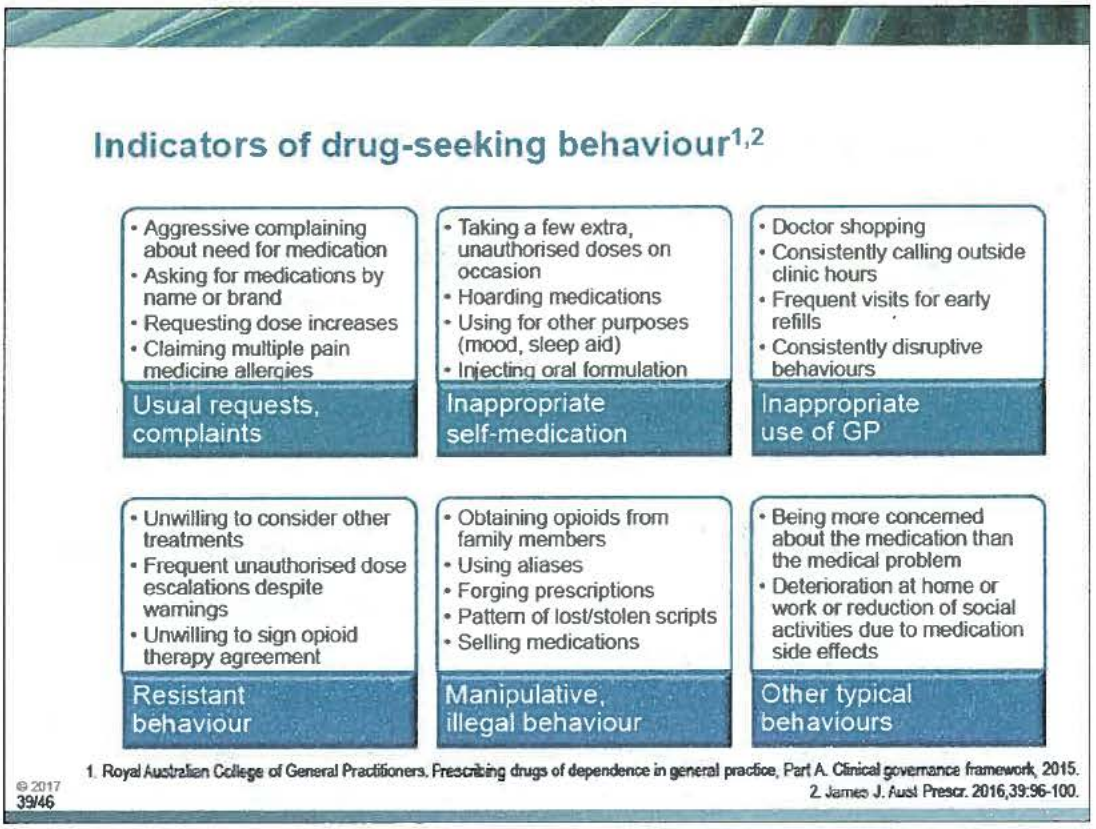
- *How do you manage the situation where after a period of being managed on a stable opioid dose, the patient is now having difficulty maintaining their level of functioning?*

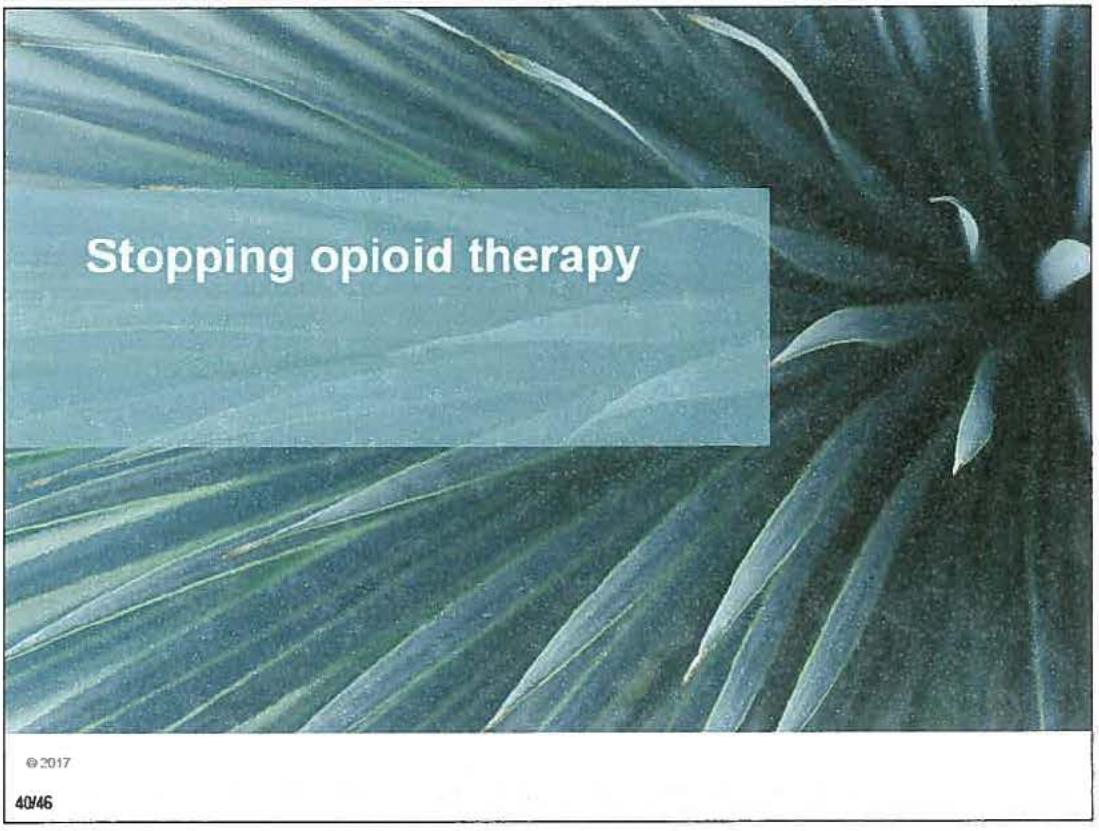
Comprehensive reassessment may result in:[1,2]
- Adjusting the goals of therapy
- Adjusting pain management plan:
  - New therapies
  - Adjusting opioid dose

Consult a colleague or specialist referral

1. Cohen ML, Wodak AD. Medicine Today 2012;13:24-32.
2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015

38/46


Indicators of drug-seeking behaviour[1,2]
• Aggressive complaining about need for medication
• Asking for medications by name or brand
• Requesting dose increases
• Claiming multiple pain medicine allergies
Usual requests, complaints
• Taking a few extra, unauthorised doses on occasion
• Hoarding medications
• Using for other purposes (mood, sleep aid)
• Injecting oral formulation
Inappropriate self-medication
• Doctor shopping
• Consistently calling outside clinic hours
• Frequent visits for early refills
• Consistently disruptive behaviours
Inappropriate use of GP
• Unwilling to consider other treatments
• Frequent unauthorised dose escalations despite warnings
• Unwilling to sign opioid therapy agreement
Resistant behaviour
• Obtaining opioids from family members
• Using aliases
• Forging prescriptions
• Pattern of lost/stolen scripts
• Selling medications
Manipulative, illegal behaviour
• Being more concerned about the medication than the medical problem
• Deterioration at home or work or reduction of social activities due to medication side effects
Other typical behaviours
1. Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part A. Clinical governance framework, 2015.
2. James J. Aust Prescr. 2016;39:96-100.
© 2017
39/46


Stopping opioid therapy
© 2017
40/46

Clear opioid cessation plan

When?

- No longer helping the ability to function[1,2]
- Pain is not opioid responsive, inadequate analgesia[1]
- Evidence of aberrant drug-related behaviour[2]
- Excessive adverse effects[3]

How?

- Discuss stopping opioid therapy upfront, prior to initiating the opioid trial[3-5]
- Be clear on your planned response to unsanctioned use[4]
- Counsel the patient on stopping the opioid gradually to minimise withdrawal symptoms[3,6]

1. Cohen ML, Wodak AD. Med Today 2010;11:10-18 2. Freynhagen R *et al.* BMJ 2013; 346: f2937. 3. Cohen ML, Wodak AD. Medicine Today 2012;13(1):24-32. 4. Gourlay DL *et al.* Pain Med 2005;6(2):107-12. 5. McDonough M. Aust Prescr 2012;35:20-24. 6. Washington State Agency Medical Directors' Group. Interagency guideline on opioid dosing for chronic non-cancer pain: an educational pilot to improve care and safety with opioid treatment. 2010 update.

41/46

Opioid taper[1]

Long-term opioid use (e.g. years)	Short-term use (e.g. months)	Previous difficulties with cessation
• 10-25% reduction per month	• 10-25% reduction per week	• Increase time interval between dose reductions

- If the primary problem is opioid dependency rather than pain, refer to an addiction medicine service

1. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. ANZCA, 2015.

42/46

43/46

Finding balance

"Though managing chronic pain is complicated and time consuming and carries risk, we owe it to our patients to ensure access to comprehensive pain management, including the medically appropriate use of opioids."[1]

44/46

1. Alford DP. N Engl J Med 2016;374:301-303.

Opioid prescribing within the box[1,2]

Opioid prescribing is consistent with best practice principles e.g.:

- Selected patients, following comprehensive assessment
- One component of multimodal management plan
- Ongoing trial
- Low opioid dose

Opioid prescribing is out of the box, e.g.:

- Painful condition is one where opioid use is controversial (e.g. migraine, headache)
- High opioid dose
- Co-prescribed with other CNS sedatives
- Active psychiatric comorbidity or substance abuse disorder
- Patient is in contact with non-medical users

45/46

1. Passik SD, Kirsh KL. Exp Clin Psychopharmacol 2008;16(5):400-404.
2. Faculty of Pain Medicine. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain, ANZCA 2015.

46/46 ORBIS-AU-3547-Dec16

Ontario

Recognize and temporarily reverse an opioid overdose

Naloxone can temporarily reverse an opioid (e.g. fentanyl) overdose.

Be prepared: Learn how to recognize an overdose, where to get a free naloxone kit (https://www.ontario.ca/page/where-get-free-naloxone-kit) and how to use it.

This page is not for emergencies. If you are with someone who has overdosed, call 911 immediately.

(Don't let legal fears stop you – you have some protection (https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/about-good-samaritan-drug-overdose-act.html#a2).)

What naloxone does

Naloxone (pronounced na-LOX-own, also known by the brand name Narcan) is a drug that can temporarily reverse an opioid (https://www.ontario.ca/page/understanding-opioids) overdose. Opioids are drugs that are usually used to treat pain, but some people use opioids to get high. Some commonly used opioids include:

- fentanyl (https://www.ontario.ca/page/understanding-opioids#section-3)
- morphine
- heroin
- methadone
- oxycodone

When someone overdoses on opioids, their breathing either slows or stops completely. If used right away, naloxone can help them breathe normally and regain consciousness. Naloxone can either be injected or given as a nasal spray.

Who can get a free naloxone kit

You are eligible for a free kit if you are:

- a current opioid user or a past user who is at risk of using again
- a family member, friend or other person able to help someone at risk (https://www.ontario.ca/page/understanding-opioids#section-2) of an opioid overdose
- a client of a needle syringe program or hepatitis C program
- newly released from a correctional facility

Where to get a free naloxone kit

Search our map (https://www.ontario.ca/page/where-get-free-naloxone-kit) of pharmacies, community organizations and provincial correctional facilities where you can get kits and training on how to use them.

Find a location (https://www.ontario.ca/page/where-get-free-naloxone-kit)

Pharmacies

Participating* Ontario pharmacies offer free injectable naloxone kits (https://www.ontario.ca/page/get-naloxone-kits-free#injectable-contents). You don't need a prescription to get one but you will need to show your Ontario health card. The pharmacist will train you on how to recognize an opioid overdose and how to use the naloxone kit.

***Not all pharmacies carry naloxone kits.** Call ahead to check if your pharmacy has naloxone kits in stock. You can also ask the pharmacist any questions you might have.

Community-based organizations

Please note: Only clients, their friends and family, as well as newly released inmates can access naloxone from community-based organizations.

You do not need a prescription or an Ontario health card to get free nasal spray naloxone kits (https://www.ontario.ca/page/get-naloxone-kits-free#nasal-contents) from:

- needle syringe programs
- hepatitis C programs

The program staff will train you on how to recognize an opioid overdose and how to use the nasal spray naloxone kit.

Provincial correctional facilities

Inmates from provincial correctional facilities are trained on how to use nasal spray naloxone (https://www.ontario.ca/page/get-naloxone-kits-free#nasal-how) and are given kits when they are released from custody.

What's in a naloxone kit

Injectable kits

Each injectable naloxone kit includes:

- 1 hard case
- 2 (0.4 mg/1 ml) vials or ampoules (a small glass container) of naloxone
- 2 safety-engineered syringes with 25g, 1" needles attached
- 2 devices (known as "breakers," "snappers," or "openers") for opening ampoules safely
- 1 pair of non-latex gloves
- 1 card that identifies the person who is trained to give the naloxone

Nasal spray kits

Each nasal spray naloxone kit includes:

- 1 hard case
- 2 doses of Narcan® Nasal Spray (4 mg/0.1ml)
- 1 pair of non-latex gloves
- 1 card that identifies the person who is trained to give the naloxone
- 1 insert with instructions (English and French)
- 1 insert with additional information on the medication (English and French)

Check the expiry date

Naloxone has an expiry date. The expiry date is written on the ampoules or vials (for injectable naloxone) or on the nasal spray device.

If you have expired naloxone, get a new kit (https://www.ontario.ca/page/where-get-free-naloxone-kit) . You can return any unused or expired naloxone kits to your nearest pharmacy.

How to recognize an opioid overdose

If you are with someone who has overdosed, **call 911 immediately**.

(Don't let legal fears stop you – you have some protection (https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/about-good-samaritan-drug-overdose-act.html#a2) .)

Someone may have overdosed if they:

- can't stay awake, walk or talk
- are breathing slowly or not at all
- have a limp body

Other signs of overdose include:

- not responding to noise or knuckles being rubbed hard on their breastbone
- snoring or gurgling sounds
- pale or blue skin – especially on their nail beds and lips – and they feel cold
- tiny pupils (pinpoint) or their eyes are rolled back
- vomiting

How to use a naloxone kit

When you receive a naloxone kit, you will be trained on how to use it.

Injectable naloxone kit

If you are with someone who is having an opioid overdose:

1. Shake their shoulders and shout their name.
2. Call 911 if they are unresponsive.
3. Give chest compressions
    a. put your hands on top of one another in the middle of the person's chest
    b. keep your arms straight
    c. PUSH FAST, PUSH HARD, with no interruptions, except to give naloxone.
4. Inject 1 vial or ampoule (a small glass container) (0.4 mg/1 ml) of naloxone into their upper arm or upper leg.
5. Resume chest compressions.
6. Continue compressions until the person responds or EMS arrives. If they are not awake after 2-3 minutes, give a second dose of naloxone.

If the person begins breathing on their own, or if you have to leave them on their own, put them in the recovery position.

Stay until the ambulance arrives in case paramedics need help or information, or the overdose symptoms return. With more powerful opioids (fentanyl and carfentanil) there is a possibility that a person will overdose again even after they have been given naloxone.

Nasal spray naloxone kit

If you are with someone who is having an opioid overdose:

1. Shake their shoulders and shout their name.
2. Call 911 if they are unresponsive.
3. Give chest compressions:
    a. put your hands on top of one another in the middle of the person's chest
    b. keep your arms straight
    c. PUSH FAST, PUSH HARD, with no interruptions, except to give naloxone
4. Give naloxone:
    a. make sure the person is lying on their back
    b. insert tip of nozzle into one nostril
    c. press the plunger firmly
5. Resume chest compressions.
6. Continue compressions until the person responds or EMS arrives.
7. If they are not awake after 2-3 minutes, give a second dose of naloxone.

If the person begins breathing on their own, or if you have to leave them on their own, put them in the recovery position (https://www.ontario.ca/page/get-naloxone-kits-free#recovery_position).

Stay until the ambulance arrives in case paramedics need help or information, or the overdose symptoms return. With more powerful opioids (fentanyl and carfentanil) there is a possibility that a person will overdose again even after they have been given naloxone.

Note: This information is intended to reduce the harms related to drug use, including deaths. Not using drugs is your best defense.

Updated: December 19, 2017
Published: March 17, 2017

Related

Where to get a naloxone kit near you (https://www.ontario.ca/page/where-get-free-naloxone-kit)

Learn about opioids (https://www.ontario.ca/page/understanding-opioids)

Ontario naloxone program for pharmacies (http://www.health.gov.on.ca/en/public/programs/drugs/naloxone.aspx)

News: Naloxone now available without a prescription in Ontario pharmacies (https://news.ontario.ca/mohltc/en/2016/06/naloxone-now-available-without-a-prescription-in-ontario-pharmacies.html)

Get help with an addiction (http://www.connexontario.ca/Home/Index)

What youth need to know about addictions (https://kidshelpphone.ca/)

Addiction help for post-secondary students (http://www.good2talk.ca/)

Descriptive transcript: Pharmacies can help communities facing the opioid crisis with naloxone (http://media.ontarionewsroom.com/desctxt/pharmacies-can-help-communities-facing-the-opioid-crisis-with-naloxone.html)

Descriptive transcript: Saving people from opioid overdoses with naloxone (http://media.ontarionewsroom.com/desctxt/health-centre-saving-people-from-opioid-overdoses-with-naloxone.html)