2020

BEST PRACTICE OPIOIDS MANAGEMENT

RAPID REVIEW

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BEST PRACTICE OPIOID MANAGEMENT

Summary

Opioids are now commonly and increasingly used for the treatment of pain (acute, cancer and chronic non-cancer pain), despite limited of high-level evidence for its effectiveness. There is increasing concern about the use of opioids for the management of chronic pain. Furthermore, there is growing concern about people requiring escalating doses when used in the chronic setting and accumulating evidence of harm. This is due to tolerance that can result in dose escalation with major side effects with high dose, long-term use, as well as problems with dependence and misuse.

Although many clinicians would agree that opioids have a place in the management of chronic pain, there is increasing acknowledgement that this place is limited. If used at all, opioids need to be used with appropriate safeguards and cautions to limit potential harm. Patients need to be warned about the risks of dependence, tolerance and driving while using opioids. Common side effects such as nausea and constipation require appropriate treatment.

Opioids should generally not be prescribed in those who have a history of substance misuse. The use of opioids for chronic non cancer pain (CNCP) should be considered only in uncommon circumstances or after failure of other therapeutic modalities when the benefit outweighs the risks.

Effectiveness of therapeutic prescription of opioids for pain is limited. Opioid use is justified in treatment of acute pain where there has been major trauma or after surgery, but evidence to support using opioids to treat long-term chronic pain is weak and insufficient.

Data about the public health impacts clearly indicate that the amounts and patterns of opioid use influence levels of adverse effects in the population. There has been a growing evidence about risks and harms from long-term opioid use. There is good-quality evidence showing the harms/risks can occur in people with chronic non-cancer pain who use opioid medicines for longer than two weeks. The problems of constipation, biliary dyskinesia and cognitive impairment are well known. Additional adverse effects include increased risk of death, sleep apnoea, sexual and other endocrine dysfunction, immunosuppression, opioid induced hyperalgesia, driving impairment, opioid use to manage psychological distress, misuse, addiction and diversion.

Harm reduction measures used today include overdose education, naloxone distribution, availability of fentanyl test strips and safe consumption sites. No single intervention is enough to address the opioid overdose epidemic. Integrating harm reduction measures with easier access to effective treatment can create a better, more humane approach to care.

In Australia, many prescribers are not aware that an authority from the Pharmaceutical Benefits Scheme (PBS) is not the same as seeking an authority, or a permit, from the state-based pharmaceutical services unit or equivalent. Within Australia, different states have different authority requirements and prescription rules. A Canadian study concluded that a high proportion of persistent opioid use was observed in a cohort of workers' compensation claimants.

Indications for compensable populations:

- Don't start opioids in the first place
- Follow recommendations i.e. set goals with reference to disability and functioning and measure progress towards these

- Consider non-pharmacological strategies

Clinical summary

Opioid Indications:

- Acute pain (limited nature of treatment, needs to be clearly stated): ***strong evidence***
- Chronic non-cancer pain: ***limited evidence***
- Cancer pain, palliation toward end of life, opioid dependency: ***strong evidence***

Opioid Prescribing:

- Prescribing recommendations in non-cancer pain
    - Maximum 90 days treatment duration
    - ≤ 40mg daily oral morphine equivalent
- Prescribing recommendations in cancer pain:
    - ≤ 300mg daily oral morphine equivalent
- Choice of opioids:
    - Short acting agents for acute pain or cancer breakthrough pain
    - Long acting agents for chronic non-cancer pain
    - Injectable opioids are not recommended for long-term use and injectable strong opioids should be avoided.
    - Use lower dose with old age and co-morbidities: "start low and go slow".
    - Beware increased opioid sensitivity in hepatic impairment.
    - Beware accumulation of opioid metabolites in renal impairment.
    - Long-acting opioids formulation are often preferable to short-acting formulations.
    - Pethidine should be avoided because of the availability of other effective opioids, the high risk of dependence and the possibility of convulsions from the metabolite norpethidine.
    - Use methadone with caution due to long half-life and frequent drug interactions
- Opioid misuse
    - Do not prescribe opioids to people with a history of substance abuse.
    - Assess risk of opioid misuse: drug and alcohol history or Opioid Risk Tool.
    - Adjust prescribing boundaries for patient "at risk".
- Prescribe opioids in conjunction with other self-management approaches.
- Review of opioid therapy should occur regularly.
- Negotiate an appropriate time frame for weaning maintenance opioids.

Other important consideration:

- Inappropriate opioid prescribing can lead to patient harm as well as a medicolegal risk to prescribers.
- Prescribers need to be familiar with the indications, contraindications and harms associated with opioids.
- When prescribing opioids, doctors must be aware of their clinical, ethical and legal responsibilities, particularly the legislative requirements in their respective state. Failure to comply with these can result in disciplinary action.
- To avoid potential conflict with differing state regulations on opioid prescribing, doctors should advise patients to get their prescription dispensed in the same state in which it was written.

Contents

Rapid reviews methodology

The following steps were used to perform this rapid review:

Table below summarise the objective, PICO and search strategies for this rapid review:

Objectives and research questions	• Are opioids a problem for people injured at work or on the roads in NSW? • What are the risks / harms of opioid use? • What works to reduce these harms? • Are there differences or interventions that work in other compensable jurisdictions?
Study design	Rapid review (narrative review)
Search strategies	We included studies that were published in English language, irrespective of age and were published within last 10 years. We excluded studies with findings about illicit drugs. We planned to search evidence in the below order of preference[#] to identify reports of relevant studies: 1. Overview of reviews (Cochrane and non-Cochrane) 2. Systematic reviews (Cochrane and non-Cochrane) 3. National clinical guidelines *# - a more restricted rapid review process was adopted, i.e. inclusion of only systematic reviews and evidence based clinical practice guidelines due to limited time duration to undertake this review.* The following electronic searches were conducted to identify potential studies.

	1. Cochrane Library (search date: 19 March 2019) *Purpose*: for searching reviews. *Search terms*: • #1 (workers compensation OR compensation scheme):ti,ab,kw OR (injury compensation):ti,ab,kw AND (pain) AND (opioids):ti,ab,kw with Cochrane Library publication date Between Jan 2009 and Mar 2019, in Cochrane Reviews • #2 (adverse events):ti,ab,kw AND (Opioids):ti,ab,kw AND (pain management):ti,ab,kw with Cochrane Library publication date Between Jan 2009 and Mar 2019, in Cochrane Reviews • #3 (risks):ti,ab,kw AND (pain management):ti,ab,kw AND (Opioids):ti,ab,kw AND (workers compensation OR injury compensation):ti,ab,kw • #4 (adverse events):ti,ab,kw AND (workers compensation):ti,ab,kw AND (pain management or injury compensation):ti,ab,kw AND (opioids):ti,ab,kw *Total search results: 31 records* 2. Google Scholar (search date: 19 March 2019) *Purpose*: for searching clinical guidelines. *Search terms*: The **first** Google Scholar search combined the following terms using "in the title of the article": [with all of the words] compensation guidelines; [with at least one of the words] opioids for pain management; [Return articles dated between] 2009 to 2019. The **second** Google Scholar search combined the following terms using "in the title of the article": [with all of the words] compensation clinical guidelines; [with at least one of the words] opioids for pain management; [Return articles dated between] 2009 to 2019. The **third** Google Scholar search combined the following terms using "in the title of the article": [with all of the words] injury OR workers compensation guidelines; [with at least one of the words] opioids for pain management; [Return articles dated between] 2009 to 2019. The **fourth** Google Scholar search combined the following terms using "in the title of the article": [with all of the words] guidelines for compensable population; [with at exact phrase] opioids for pain management; [Return articles dated between] 2009 to 2019.

	The **fifth** Google Scholar search combined the following terms using "anywhere in the article": [with all of the words] workers compensation guidelines; [with at exact phrase] opioids for pain management; [with at least one of the words] compensable population; [Return articles dated between] 2009 to 2019. *Total search results: 2 records* 3. We also identified other potentially eligible studies or publications by searching the reference lists of retrieved studies.
Population	• Adults and children • Compensable population CTP claimants or injured workers in NSW (or like populations)
Inclusions/ exclusions	• English only • Last 10 years • Exclude illicit drug use
Outcomes	Summary of the evidence base to inform this priority project. **The adverse event outcomes of interest for this rapid review**: • Number of participants with any adverse event; • Number of participants with any serious adverse event; • Number of participants who withdrew from the studies due to adverse events; • Number of deaths; • Number of participants who experienced the following specific adverse events (of any severity): o addiction; o cognitive dysfunction; o constipation; o depressive symptoms or other mood disturbances; o hypogonadism or other endocrine dysfunction; o infection; o respiratory depression; o sexual dysfunction; o sleep apnoea or sleep-disordered breathing; o xerostomia.

Rapid review: research questions

SIRA regulates the NSW compulsory personal injury schemes and has a mandate to provide funding for injury prevention, injury minimisation and road safety education.

This review will address the following four questions:

Question 1: Are opioids a problem for people injured at work or on the roads in NSW?

Question 2: What are the risks / harms of opioid use?

Question 3: What works to reduce these harms?

Question 4: Are there differences or interventions that work in other compensable jurisdictions?

Question 1: Are opioids a problem for people injured at work or on the roads in NSW?

Globally, people injured at work or on the roads have a high risk of being associated with significant chronic pain that may last for many years, or for some, a lifetime. Certainly, chronic pain can be a significant co-morbidity, especially in injury sustained in a motor vehicle crash. Opioids are now commonly and increasingly used for the treatment of pain *(Zutler 2011)*, despite safety concerns and a lack of convincing evidence for effectiveness *(Kidner 2009; Chapman 2010; Bohnert 2012*). There is no evidence to support if opioids are a problem for people injured at work or on the roads in NSW, but an inception cohort study (FISH study) is under way for better understanding of problems related to opioid use in people injured at work or on the roads in NSW (*Jagnoor 2014*).

Facts and figures

Globally

- There has been increase in the number of opioid prescriptions, globally since the 2000s, for instance, in Australia *(Leong 2009)*, the UK *(Zin 2014)* and the USA *(Manchikanti 2012a)*.
- The rate of dispensing of high-dose opioids specifically (i.e. doses of 200 morphine milligram equivalents per day or greater) increased in Canada by 23% between 2006 and 2011 *(Gomes 2014)*.
- Data from the United States Food and Drug Administration Adverse Event Reporting System shows that oxycodone contributed to the largest number (5548) of all drug-related deaths in North America during the period 1998 to 2005 (and morphine ranked fourth, contributing to 1616 deaths) *(Moore 2007)*.
- Hegmann and colleagues summarised the substantial increase in the use of opioids and the increase in deaths associated with opioids (*Hegmann 2014b*). Opioid-related deaths are common and can occur even when the prescription is in accordance with guidelines.
- Most opioid-related deaths in the USA (60%) occurred in people given prescriptions based on prescribing guidelines by medical boards (with 20% of deaths at doses of 100 morphine milligram equivalents per day or less, and 40% in people who received doses above that threshold). The remaining 40% of deaths occurred in people abusing the drugs (*Manchikanti 2012a*).

In Australia

- Australia's consumption of opioid analgesics is ranked 10th internationally *(Roxburgh 2011)*.
- Previous research in Australia has documented increases in the number of prescriptions for morphine in the late 1990s *(Berbatis 2000)* and, more recently, increases in consumption of oxycodone *(RACP Prescription Opioid Policy 2009)*.
- According to the 2013 Australian National Drug Strategy Household Survey:
    - ✓ One in three Australians aged 14 or older reported having used an over-the-counter codeine combination product in the past 12 months.
    - ✓ 29% used a prescription-only codeine product.
    - ✓ Two in 500 people (0.4%) reported recent use of some form of pharmaceutical opioids for non-medical purposes.
    - ✓ Males were twice as likely to use pharmaceutical opioids for non-medical purpose as females
    - ✓ Use was highest among people aged 55 and older.

- A recent Australian population study *(Campbell 2015)* examined a cohort of patients on long term opioid therapy and found:
    - ✓ Two-thirds were unemployed or receiving a government benefit
    - ✓ Almost half had low income.
    - ✓ 80% of the cohort reported multiple pain conditions, 50% significant depression, 50% suicidal ideation, over 50% a history of childhood abuse or neglect and over 30% had a lifetime alcohol use disorder.

In compensable populations

- In a Victorian study conducted in 2016, authors stated the significance of post-injury prescription drug use cannot be established without taking pre-injury use into account, because the pre-injury use of prescription opioid and benzodiazepine was substantial (*Berecki-Gisolf 2016*).
- A retrospective cohort study conducted in USA that collected workers' compensation claims data for 8 years (2008 to 2016) concluded that a high proportion of persistent opioid use was observed. Of the workers' compensation claimants in Maryland with an initial opioid prescription, 28.6% filled a subsequent opioid prescription more than 90 days from injury. Persistent opioid use was significantly associated with age 60 years or older (odds ratio (OR 2), crush injuries (OR 2), strain and sprain injuries (OR 2), annual income >$60,000 (OR 1), and concomitant diagnoses for chronic joint pain (OR 2). Workers with medical-only claims were significantly less likely to have persistent opioid use at 90 days post injury compared with workers whose claims were designated as permanent partial disability (OR 0.17) (*O'Hara 2018*).
- Evidence of utilisation of larger doses of opioids for the treatment of pain is emerging. For example, one analysis of Workers' Compensation Board data (where the vast majority of claimants with pain have non-cancer pain) from Manitoba, Canada, demonstrated a dramatic increase in the average opioid dose prescribed over time, i.e. from less than 500 morphine milligram equivalents per person per year in 1998 to over 6000 morphine milligram equivalents per person per year in 2010. Moreover, compared to other Manitobans, the WCB claimant population was about twice as likely to be prescribed doses above 120 morphine milligram equivalents per day *(Kraut 2015)*.
- Opioid use continues post claim, and interestingly, both duration and dose of post-claim opioid use are correlated with the dose during the claim *(Shafer 2015)*.
- In South Australia, 47% of the population (approximately 803,000 individuals) are workers. The most common injuries for which workers seek compensation in SA (and those which incur the highest cost to the compensation system) are traumatic joint/ligament and muscle/tendon injuries, musculoskeletal and connective tissues diseases and fractures.

Effectiveness of opioids

The effectiveness of opioid therapy is supported by strong evidence from randomised controlled trials in acute pain *(MacIntyre 2010*) and from systematic reviews in cancer pain *(Caraceni 2012; Colson 2011)*, palliative care *(NICE 2012)* and opioid dependency/addiction *(Amato 2005)*.

In CNCP systematic reviews report modest short-term analgesic benefit *(Furlan 2006; Manchikanti 2011)*. However, the duration of the RCTs reviewed (up to 4 months) was too short to adequately inform the long-term role of opioid treatment in CNCP.

A recent systematic review that examined the evidence of long-term opioid efficacy and risk *(Chou 2015)* concluded that "evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function". There is also a dose-dependent risk of serious harms especially when opioids are combined with other psycho-active agents including alcohol. Tolerance *(Moulin 1996; Ballantyne 2008)* and other adverse effects are potential limiting factors with long term opioid use.

Although opioids are often recommended for the management of severe pain, there is increasing concern about the use of strong opioids for the management of chronic pain. However. there is growing concern about people requiring escalating doses when used in the chronic setting and accumulating evidence of harm. This is due to tolerance that can result in dose escalation with major side effects with high dose, long-term use, as well as problems with dependence and misuse.

Therefore, while many clinicians would argue that opioids have a place in the management of chronic pain, there is increasing acknowledgement that this place is limited. If used at all, opioids need to be used with appropriate safeguards and cautions to limit potential harm. Patients need to be warned about the risks of dependence, tolerance and driving while using opioids. Side effects such as nausea and constipation require appropriate treatment. Opioids should generally not be prescribed in those who have a history of substance abuse, with addiction risk assessed using a suitable tool, such as Opioid Risk Tool (*Webster 2005)*.

There is increasing consensus that doses above 60 mg/day of oral morphine equivalent should be avoided due to the substantial increase in risk above this level. If pain is poorly controlled at this level, it is recommended that specialist pain medicine advice is obtained rather than increasing the dose further. If used, long-acting formulations of opioids are often preferable to short-acting formulations for chronic pain that is constant in nature. In the chronic pain setting, parenteral administration (i.e. non oral such as injection) of strong opioids should be avoided. Pethidine should be avoided because of the availability of other effective opioids, the high risk of dependence and the possibility of convulsions from the metabolite norpethidine. Even if a decision is made to prescribe opioids, they should be used in conjunction with other self-management approaches.

Opioid adverse events (including opioid abuse and addiction)

In contrast to the early and more permissive approaches to opioid use for CNCP, more recent evidence suggests that opioid abuse and addiction are well documented among people with chronic pain *(Vowles 2015)*. There is a potential for opioid addiction to develop even if these compounds are used for the management of severe pain *(Kosten 2002; Huffman 2015; Vowles 2015)*. The risk for addiction increases with increasing opioid doses.

A 50 mg increase in oral morphine milligram equivalent dose almost doubled the risk of addiction

A 100- mg dose increase was associated with a three-fold increase in that risk

Huffman and colleagues 2015

There is furthermore the potential for serious adverse events. Some outcomes, including sleep-disordered breathing and respiratory depression, may result in opioid-associated deaths and

demonstrate a clear relationship to dose *(Walker 2007; Jungquist 2012)*. Drug interactions are another concern, as is interaction with alcohol, which can result in several types of serious adverse events *(McCance-Katz 2010).*

A strong and reproducible dose-response relationship for efficacy led to the recommendation for a morphine equivalent dose limit of 50 mg per day; higher doses are only recommended with documented functional improvement, risk-benefit consideration, and monitoring of adverse events (*Hegmann 2014b).*

Implications: Use of long-term opioids in people with CNCP

A systematic review was undertaken by Noble and Colleague (*Noble 2010*) assessed the safety and effectiveness of long-term use of opioids in people with CNCP. The findings suggested that a proper management of a type of opioids in well-selected patients (with no history of substance addiction or abuse) can lead to long-term pain relief as well as a very small (though not zero) risk of developing addiction, abuse, or other serious side effects for some patients. However, the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients who are most likely to benefit from treatment.

Implications: Use of high dose opioids

The below implications are based on the findings of an overview of reviews (*Els 2017a*) that aimed to assess available evidence from Cochrane Reviews and Overviews on the use of high-dose opioids in the management of CNCP in adults. No such evidence was found.

For consumers

There is no evidence to support the use of high-dose opioids for CNCP. Opioids are associated with increased risks for adverse events (such as addiction, overdose, and death). Patients should be made aware of the potential risks and the absence of evidence. Physicians should consider explaining this to patients in conjunction with alternative strategies.

For policy makers/ insurance regulators

There is insufficient evidence to either support or refute the effectiveness of high-dose opioids in CNCP. In term of known established risks such as addiction, overdose and death, policy makers should consider not supporting the use of high-dose opioids for treating CNCP.

Question 2: What are the risks / harms of opioid use?

Effectiveness of therapeutic prescription of opioids for pain is limited. Opioid use has some benefits for treatment of acute pain, but evidence to support using opioids to treat long-term chronic pain is weak and insufficient. Data about the public health impacts clearly indicate that the amounts and patterns of opioid use influence levels of adverse effects in the population.

> Increases opioid use = Increase in morbidity and mortality
>
> **A study in USA** (Bohnert 214; Modarai 2013)
> Strong correlations over time between opioid use and opioid-related deaths and between levels of morbidity

There has been a growing evidence about risks and harms from long-term opioid use. There is good-quality evidence showing the harms/risks can occur in people with chronic non-cancer pain who use opioid medicines for longer than two weeks.

The problems of constipation, biliary dyskinesia and cognitive impairment are well known (*ACI Pain Management Network Website 2019; Freynhagen 2013*). Additional adverse effects include increased risk of death *(Dunn 2010)*, sleep apnoea *(Guilleminault 2010; Webster 2008)*, sexual and other endocrine dysfunction *(Vuong 2010; Katz 2009)*, immunosuppression *(Sacerdote 2008)*, opioid induced hyperalgesia *(Lee 2011; Hutchinson 2007)*, driving impairment *(Drug and Alcohol Services SA 2009; Dassanayake 2011)*, opioid use to manage psychological distress *(Kirsh 2007)*, misuse, addiction and diversion *(Sehgal 2012).*

Patients with mental health and substance abuse problems are more likely to receive chronic opioid therapy (adverse selection) and at higher doses than people without those risk factors *(Edlund 2010)*. Opioid dependence makes it hard to wean and cease established opioids despite lack of analgesic benefit (Ballantyne 2007). The use of over-the-counter opioids such as codeine also has questionable benefit and significant risk of harm *(Nielsen 2012)*. A focus on opioid therapy can distract both patient and prescriber from the evidence based active management strategies which demonstrate sustained long-term pain reduction.

A full list of potential effects on each of the systems of the body are summarised below:

Effects	Statements
Respiratory system	Respiratory depression and death (occur in overdose, and particularly opioids interaction with benzodiazepines or other sedatives)
	Worsened sleep apnoea (in a cohort study: 75% of chronic opioid users have an abnormal apnoea-hypopnoea index)
Gastrointestinal system	Up to 80% of patients: Opioid-induced bowel dysfunction (this includes constipation, nausea and biliary dyskinesia).
	Increased prevalence of dental caries (reduced production of saliva and poor nutrition).
Nervous system	Amplify pain (sensitisation of the nervous system, also known as opioid induced hyperalgesia). Over time contribute to declining opioid effectiveness.
	Dose dependent changes (affects structure, function of reward and processing areas of the brain).

	Neurophysiological effects (include the potential for driving impairment and interference with sleep architecture).
	Mood disorders.
	There is an increased risk of falls and consequent fracture particularly in older people.
Endocrine system	Hypopituitarism (opioid therapy can suppress the hypothalamic pituitary axis and cause). This in turn can cause hypogonadism, impotence, infertility and osteoporosis.
	85% prevalence: Hypo-gonadotrophic hypogonadism in men.
	Secondary amenorrhoea common in pre-menopausal women. Hypoadrenalism (ACTH deficiency) and growth hormone deficiency are less common (15% prevalence of both). TSH deficiency and increased prolactin levels are rare.
	Endocrine abnormalities (reported in a few).
Immune system	Immunosuppression (depend on multiple factors including structure of the individual opioid agent and dose range used).
	Inhibition of humoral and cellular immune response (including antibody production, lymphocyte activity, and cytokine expression).

Implications: Adverse events related to opioids use in people with for CNCP

The implications listed below are based on the findings of an overview of reviews (*Els 2017b*), that included 16 Cochrane Reviews, of which 15 reported quantitative data, and 14 of these contained data not already presented in earlier reviews. The 14 Cochrane Reviews reporting unique quantitative data had 18,679 participants and investigated 14 different opioids for a variety of chronic non-cancer painful conditions where opioids were administered for longer than two weeks. There is a 42% higher risk of any adverse events and a 175% increased risk of serious adverse events associated with opioid use when compared to placebo. The risks of specific adverse events were increased for constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting.

For consumers

Number of adverse events can occur, including serious adverse events, when opioids are used for CNCP in adults.

For clinicians

Clinicians should be aware that a significant risk increase exists for a number of adverse events when opioids are used for CNCP in adults. As there is limited evidence to support the effectiveness of long-term use of opioids in CNCP, an absence of evidence of improvement in function and pain scores when high doses of opioids are used, and robust evidence of harm associated with medium to long-term opioid use, prescribers should proceed with caution prior to initiating treatment with opioids and with even greater caution when transitioning from short-term to medium- and long-term use of opioids for people with CNCP.

For policy makers/ insurance regulators

There are known adverse events, including serious adverse events that can occur when opioids are used for CNCP. This should be considered in policy decisions. The use of opioids for CNCP only in exceptional circumstances or after failure of other therapeutic modalities, when the benefit outweighs the risks.

Question 3: What works to reduce these harms in compensable setting?

Opioid use related disorder is a chronic but treatable illness. However, if untreated, this can cause many direct or indirect harms, including death. Effective treatment strategies must incorporate harm reduction measures for broader implementation. Harm reduction measures used today include overdose education, naloxone distribution, availability of fentanyl test strips and safe consumption sites. No single intervention is enough to address the opioid overdose epidemic. Integrating harm reduction measures with easier access to effective treatment can create a better, more humane approach to care.

The harm reduction measures can be a **four-level approach**, as follow:

LEVEL 1: Prevention and education

Prevention and Education refers to measures that seek to prevent or delay substance use, and which address root causes of problems. These measures may involve GP and patient education, mentoring programs, and a few other approaches to enhance the knowledge about harms related to opioid use.

1. *Enhance surveillance activities and use of overdose data across sectors.*
   Collecting and analysing health-related data is essential in planning, implementing, and evaluating public health programs and interventions. There are no data about how many people in compensation schemes have overdosed due to opioids. By enhancing the surveillance activities a comprehensive and timely understanding of the opioid overdose and its associated harms could be achieved, timely local reports could be generated, and an early warning system could be created.

2. *Increase end-user awareness about opioid misuse, diversion, and overdose prevention.*
   Among the best approaches to addressing opioid use is to intervene before it occurs (*Hahn 2011*). Education and prevention activities should be implemented to increase awareness of opioid use and associated dangers. Community campaigns and promotional messaging can be an effective tool when it comes from multiple partners and from multiple sources such as radio, television, billboards, and social media.

3. *Increase healthcare provider and patient education on opioid use and managing chronic pain.*
   Increased education for healthcare providers about safe prescribing practices has been identified as a key strategy to Prevent Opioid Addiction and Overdose (*Ministry of Health and Long-Term Care 2017*). There is an evidence to suggest that recent prescribing patterns may be improving such as dispensing smaller quantities of opioids, there still may be opportunities for education. Patients that need to take opioids for treating pain must also be provided with clear information about risks associated to impaired driving, dependence, addiction, and co-use with depressants (*Centre for Addiction and Mental Health 2016*).

4. *Increase awareness about non-pharmacological interventions for managing pain.*
   Some of the more widely used interventions such as physical and manual therapies for the treatment of musculoskeletal pain problems have strong evidence supporting some of these interventions. For example, physical conditioning programs that include a cognitive behavioural approach plus intensive physical training are effective in reducing disability, and physiotherapist-directed exercise and advice have significant beneficial effects on pain and function in people with sub-acute low back pain at 6 weeks. Some of these interventions should be encouraged as a first line of treatment and may prevent harm of excessive opioids use.

LEVEL 1 potential strategies

- Improve data sharing between law enforcement, public health, and other community stakeholders to improve response plans and early warning to reduce harms.
- Develop "real-time" overdose surveillance/monitoring system in health sectors to provide consistency and clear alerts to end-user.
- Develop and create a shared communication plan across all healthcare providers for a comprehensive management approach (including non-pharmacological intervention).

LEVEL 2: Harm reduction

Harm Reduction refers to measures that seek to reduce the harms associated with opioid use (for more details see Section B).

1. *Increase access to Naloxone through changes in practice and policy.*
   Naloxone is an antidote to opioid overdose. It reverses the effects of opioids by temporarily preventing the opioids from having an effect (*Webber 2016*). Naloxone distribution programs have recently been extended and are successful in a variety of clinical settings (*Orkin 2015*).

2. *Improve overdose prevention education, training, and services.*
   Best practice guidelines for these harm reduction measures include training opioids users, their friends and families on how to avoid overdosing and how to act if they see another person overdosing. Existing evidence shows that overdose education and the distribution of naloxone improves people's willingness to intervene in an overdose, reduces mortality and is cost-effective (*Strike 2013*).

3. *Develop a local evidence-based harm reduction framework*

LEVEL 2 potential strategies

- Provide access to naloxone for medical and non-medical staff working in community settings where overdoses occur.
- Develop "take home naloxone" program sites for at-risk groups and the general public.
- Educate broader community and target staff in community settings on strategies to prevent, recognise, and respond to overdose.
- Recognise and support the role that people who use drugs have in reaching others at risk of overdose and support more peer training opportunities.

Level 3: Treatment and recovery

Treatment and Recovery refers to interventions that seek to improve the physical and emotional well-being of people who use or have used opioid.

1. *Increase treatment options and ensure people can access appropriate services when they need them.*
   Treatment for opioid use disorder should be provided in the community and where primary care is also available. A medical model for opioid treatment must also be combined with a community based social services model to be effective in meeting the needs of those experiencing opioid dependence issues.

LEVEL 3 potential strategies

- Increase awareness of treatment services among community and enforcement agencies and understanding of recovery pathways.

Level 4: Update policies and laws enforcement

This refers to enforcing new policies and laws for use of opioids.

1. *Effective policy to reduce harms from prescription opioids.*

2. *Enforce laws to reduce prescribing and using opioids.*

LEVEL 4 potential strategies

- Increase awareness of treatment services among community and enforcement agencies and understanding of recovery pathways.
- Reconsidering policies and laws related to multiple prescriptions/ 'double-doctoring', requesting early refills, and drug diversion.
- Standardised, real-time, electronic prescription monitoring systems for opioids should be established across the country, and medical professionals should be required to consult them before prescribing or dispensing opioids.
- Enforceable guidelines with the aim to have opioids prescribed only in cases supported by good scientific evidence and to be considered an exceptional treatment.

Adapted from Windsor-Essex Community Opioid Strategies 2017.

Question 4: Are there differences or interventions that work in other compensable jurisdictions?

1. ***Australia***

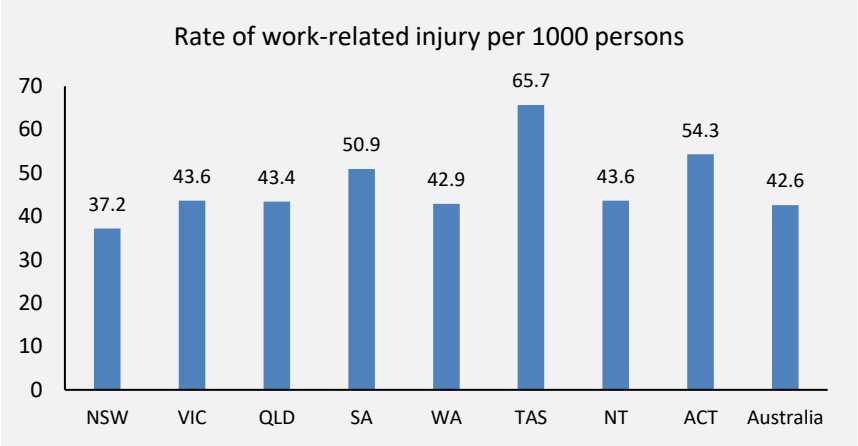


Figure 1: Work injury in Australia – 2013/14
Source: ABS 6324.0 - Work-Related Injuries, Australia, JUL 2013 TO JUN 2014

In early 2018, the Therapeutic Goods Administration (TGA) Australia released a range of regulatory options to seek feedback to address the problems with excessive or inappropriate use of opioids. The focus of the paper is on powers available under the Commonwealth *Therapeutic Goods Act 1989* and regulations, but where these powers and the potential options below interact with other schemes, references to the PBS, states and territories and education of health professionals are made.

- Option 1: Consider the pack sizes for Schedule 8 opioids.
- Option 2: Consider a review of the indications for strong opioids.
- Option 3: Consider whether the highest dose products should remain on the market, or be restricted to specialist / authority prescribing.
- Option 4: Strengthening Risk Management Plans for opioid products.
- Option 5: Review of label warnings and revision to the Consumer Medicines Information.
- Option 6: Consider incentives for expedited TGA review of improved products for pain relief and opioid antidotes.
- Option 7: Potential changes to use of appendices in the Poisons Standard to provide additional regulatory controls for strong opioids.
- Option 8: Increase health care professional awareness of alternatives to opioids (both Schedule 4 and Schedule 8) in the management of chronic pain.

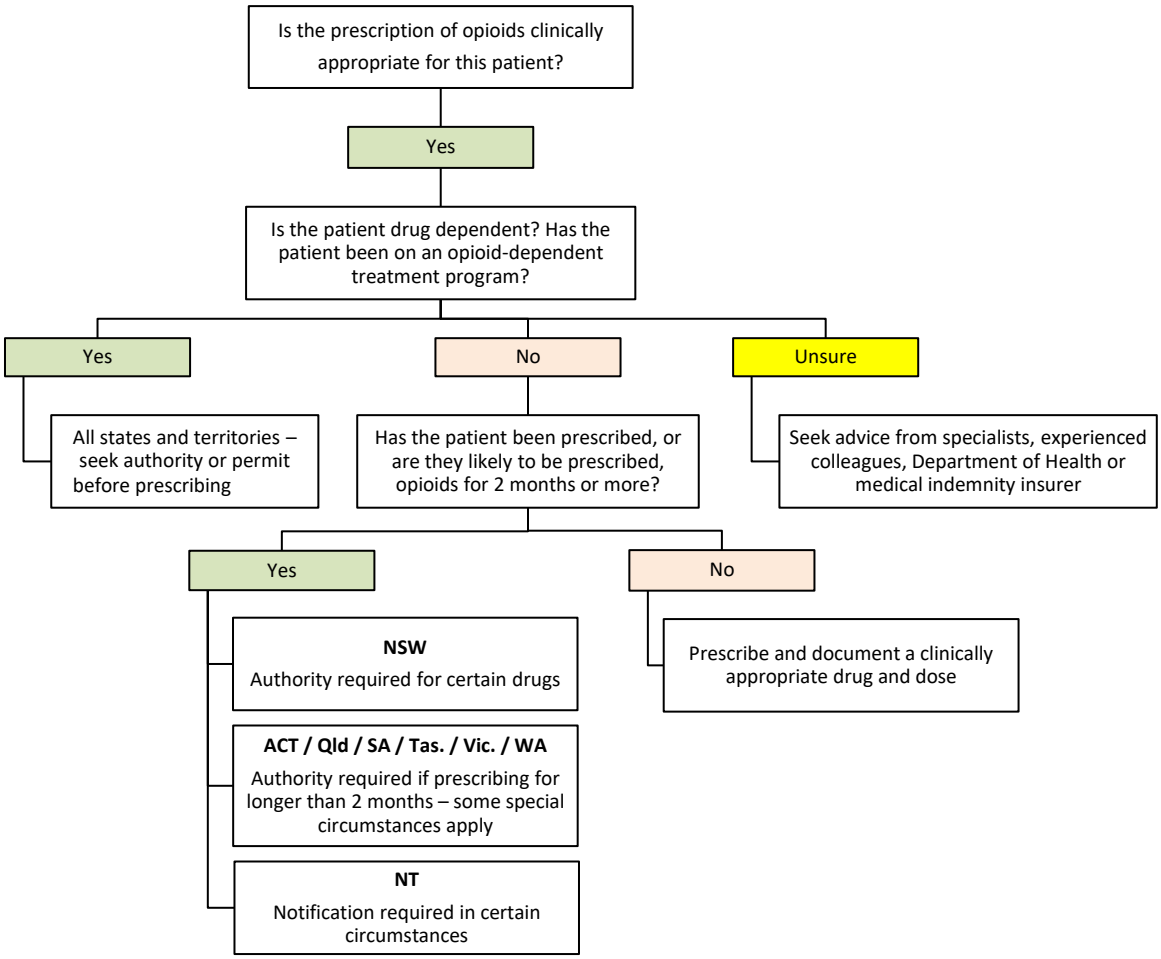
South Australia

The National Centre for Education and Training on Addiction investigated prescribed opioid use resulting from compensable work-related injuries in South Australia. A retrospective 10-year longitudinal study (2003 to 2012) was undertaken including clients who submitted a WorkCover SA workers compensation claim and were dispensed S8 prescribed opioids. Approximately 10,000 persons acquired a work-related injury and received S8 prescribed opioids during the study period. The data was linked and collected from four sources, namely- (1) work-related accidents and injuries (Work-Safe Health and Safety Tabulator); (2) dispensed S8 prescribed opioids (Drugs

of Dependence Unit, SA Health); (3) Emergency Department presentations (SA Emergency Department Data Collection), and (4) public hospital admissions (SA Admitted Patient Activity Data Standards). The findings are not yet published.

In Australia, many prescribers are not aware that an authority from the Pharmaceutical Benefits Scheme (PBS) is not the same as seeking an authority, or a permit, from the state-based pharmaceutical services unit or equivalent. Within Australia, different states have different authority requirements and prescription rules (*Jammal 2015*).

Figure 2: Guide to the steps required to lawfully prescribe opioids in different states of Australia.
Source: Jammal W 2015, p200



2. Canada

Ontario recently announced a set of policy measures aimed at reducing opioid harms that includes standards for opioid prescribing (to be released), the delisting of high-strength opioid formulations from the provincial formulary, and increased access to pharmacotherapy with buprenorphine/naloxone and naloxone availability (Dyer 2016; Toronto MoH 2016). The effects of these measures will need to be evaluated rigorously.

Opioids should be dispensed in the lowest possible dose and for the shortest possible duration. Similar measures have been implemented recently in British Columbia and Nova Scotia, which adopted the CDC guideline as a professional standard (CPS, BC 2016; CPS, NS 2016).

3. **USA**

In a study using a Community-Based Participatory Research approach, formative research was conducted to inform the eventual development of relevant interventions to prevent and reduce opioid use disorders among fishing industry workers. Qualitative interviews (n = 21) were conducted to assess: (1) knowledge and attitudes about opioid use disorders; (2) features of fishing work that might affect use and/or access to treatment; and (3) community and organizational capacity for prevention and treatment. Participants reported numerous pathways connecting commercial fishing with opioid use. The combination of high stress and physically tasking job duties requires comprehensive workplace interventions to prevent chronic pain and MSDs, in addition to tailored and culturally responsive treatment options to address opioid use disorders in this population. Public health programs must integrate workplace health and safety protection along with evidence-based primary, secondary, and tertiary interventions in order to address opioid use disorders, particularly among workers in strenuous jobs (Walter 2018).

An organisation in Massachusetts - RIZE Massachusetts Foundation in 2017, announced funding committed to zero deaths related to opioid use disorder. RIZE's approach is to prevent death and improve care for people suffering from opioid use disorder and integrate them with access to clinical addiction treatment programs. The objectives of the funding program proposal were:

- Harm reduction services be coupled with immediate access to effective, low-threshold opioid use disorder treatment
- Clear path to increasing harm reduction services to the target populations
- Partnerships with clinical partners that will provide easy access to treatment for physical and mental health care, as well as addiction treatment
- Tracking and assessment tools to measure effectiveness of the services in improving health and advancing patients into clinical treatment.

To continue to influence trends in opioid abuse, insurers and other claim professionals must invest in and leverage the latest pain management interventions, technologies, training programs, and alternative medicines and continue to push for new and different treatments and processes that not only have the most promise for reducing harms associated with opioid use.

Overall clinical implications: Recommendations and Quality of evidence

Commonly used Opioids for treating pain

Weak Opioids	Strong Opioids
Codeine	Morphine
Tramadol	Oxycodone
Tapentadol	Hydromorphone
Buprenorphine patch	Fentanyl Patch
	Methadone

Opioid Indications *(ACI Pain Management Network)*:

- Acute pain (limited nature of treatment, needs to be clearly stated): *strong evidence*
- Chronic non-cancer pain: *limited evidence*
- Cancer pain, palliation toward end of life, opioid dependency: *strong evidence*

Opioid Prescribing:

- Prescribing recommendations in non-cancer pain *(Manchikanti 2012b):*
    - Maximum 90 days treatment duration
    - ≤ 40mg daily oral morphine equivalent

- Prescribing recommendations in cancer pain (*Fallon M 2018)*:
    - ≤ 300mg daily oral morphine equivalent

- Choice of opioids (*Craig 2019*; *ACI Pain Management Network 2019)*:
    - Short acting agents for acute pain or cancer breakthrough pain
    - Long acting agents for chronic non-cancer pain
    - Injectable opioids are not recommended for long term use
    - Use lower dose with old age and co-morbidities: "start low and go slow"
    - Beware increased opioid sensitivity in hepatic impairment
    - Beware accumulation of opioid metabolites in renal impairment; fentanyl has no active metabolites, oxycodone has only weakly active metabolites.
    - Beware accumulation of opioid metabolites in renal impairment.
    - Long-acting opioids formulation are often preferable to short-acting formulations.
    - Pethidine should be avoided because of the availability of other effective opioids, the high risk of dependence and the possibility of convulsions from the metabolite norpethidine.
    - Use methadone with caution due to long half-life and frequent drug interactions.

- Opioid misuse (*Hunter New England Integrated Pain Service 2014*)
    - Assess risk of opioid misuse: drug and alcohol history or Opioid Risk Tool.
    - In "at risk" patients adjust prescribing boundaries e.g. once or twice weekly pickup from local pharmacy. If this does not bring stability, consider Drug and Alcohol referral.

- Review of therapy includes 4 A's: **A**nalgesia, **A**ctivity, **A**dverse effects and **A**berrant behaviour (*FSMR 2017*).

- Opioid rotation can be used to treat tolerance or other adverse effects; start the new opioid at 50% of equivalent dose (see table below) (*Fine 2009*).

- If weaning maintenance opioids negotiate an appropriate time frame to limit opioid withdrawal and minimise patient distress. A typical plan reduces the opioid by 10 - 25% of the starting dose each month. This achieves cessation within 3 - 9 months (*ACI Pain Management Network 2019)*.

Opioid dose equivalence (approximate):

Drug	Dosage					
Morphine (oral)	5 mg	10 mg	20 mg	40 mg	100 mg	300 mg
Codeine (oral)	40mg	80 mg	160 mg	320mg	800 mg	2400mg
Oxycodone (oral)	-	7 mg	14 mg	28 mg	66 mg	200 mg
Buprenorphine (patch)	-	5 mcg/hr	10 mcg/hr	20 mcg/hr	-	-
Fentanyl (patch)	-	-	-	12 mcg/hr	37 mcg/hr	100 mcg/hr
Hydromorphone (oral)	-	2 mg	4 mg	8 mg	20 mg	60 mg

Adapted from ACI pain website

Adverse effects:

- Tolerance and hyperalgesia limit opioid effectiveness with long term use (*Lee 2011)*.
- There is growing evidence of harm: constipation, cognitive impairment, worsening sleep apnoea, sexual impairment and other endocrine dysfunction, immunosuppression, driving impairment (*ACI Pain Management Network 2019).*
- A focus on opioid therapy can distract both patient and prescriber from the evidence based active self-management strategies which lead to sustained long-term pain reduction (Craig 2019).

Overall quality of evidence (for adverse event)

Opioids compared to placebo (*Els 2017b***)**

- Any adverse event: moderate quality of evidence
- Any serious adverse event: moderate quality of evidence
- Withdrawal due to adverse events: moderate quality of evidence
- Constipation: moderate quality of evidence
- Dizziness: moderate quality of evidence
- Drowsiness or somnolence: moderate quality of evidence
- Fatigue: very low quality of evidence
- Hot flushes: very low quality of evidence
- Increased sweating: moderate quality of evidence
- Nausea: moderate quality of evidence
- Pruritus: very low quality of evidence
- Vomiting: low quality of evidence

Opioids compared to active (non-opioid) pharmacological comparators (*Els 2017b***)**

- Any adverse event: moderate quality of evidence
- Any serious adverse event: very low quality of evidence
- Withdrawal due to adverse events: moderate quality of evidence

Opioids compared to non-pharmacological interventions (*Els 2017b***)**

- Any adverse event: very low quality of evidence

See ***Table 1, 2 and 3*** in Appendix A for absolute event rate, risk ratio, number needed to treat harm and GRADE rating.

Future research implications

1. Define the prevalence of chronic opioid use in people in Workers Compensation and CTP insurance in NSW.

2. Future research is needed to distinguish predictors of early opioid prescribing, which is arguably amenable to prescriber-level interventions, and predictors of long-term opioid prescribing, which may require interventions at the patient as well as the health care system levels.

3. Longer-term studies are needed to identify the patients who are most likely to benefit from treatment.

4. Number of interventions and systems-level changes aimed at reducing opioid use have been employed in Australia. These interventions include prescription drug monitoring programmes, clinician and patient education, the introduction of abuse-deterrent formulations, changes to product labelling and treatment guidelines, and pain clinic and opioid disposal legislation. However, the impact of these interventions on opioid utilization, abuse, and patient and clinician behaviours is uncertain. From a clinical and policy perspective, there is a need for further research into patterns of opioid use and misuse, both at population as well as individual level.

5. A multiple multidisciplinary research programme to be funded for pain management.

6. Knowledge of rates of initiation and prevalence of opioid treatment, duration of therapy, prescribed daily doses and patterns of extra-medical opioid use (such as excess dosing, and pharmacy/doctor shopping) is much needed and could facilitate targeted future interventions aimed at enhancing the quality use of opioids in the treatment of pain.

7. To address risks associated with opioid dependence and abuse, workers' compensation providers and claims managers need programs that require the conservative use of opioid medication for treatable pain. The primary goals should be for clinical, meaningful improvement of function and prevention of dependency and addiction to opioids.

8. Are opioids an appropriate choice?
   To address this question, it is necessary to consider patient-specific factors that contribute to a doctor's clinical decision making including:
   - Should opioids be prescribed at all?
   - Have all non-pharmacological options of management been considered?
   - Is there a plan of management in place?
   - Have the goals of treatment been defined?
   - Have all of the psychosocial factors been considered?
   - Is the patient at risk of dependence?
   - Are there potential drug interactions?
   - Have the maximum dose and exit strategy been defined?

   Before and after commencing an initial trial period of opioids, a comprehensive assessment should be performed.

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Appendix A: Tables and figures

Table 1 Absolute event rate: adverse events

Comparison	Adverse event	Opioids				Comparator			
		Number of participants		Event rate (%)		Number of participants		Event rate (%)	
		With AE	Total	Average	95% CI	With AE	Total	Average	95% CI
Opioids versus placebo	Any AE	2436	3113	78.3	76.8 to 79.7	1030	1891	54.5	52.2 to 56.7
	Any SAE	216	2893	7.5	6.5 to 8.4	57	1431	4	3 to 5
	Withdrawals*	1836	7316	25.1	24.1 to 26.1	297	4194	7.1	6.3 to 7.9
	Constipation	285	2513	11.3	10.1 to 12.6	94	1742	5.4	4.3 to 6.5
	Dizziness	284	2448	11.6	10.3 to 12.9	71	1682	4.2	3.3 to 5.2
	Drowsiness	237	2313	10.3	9 to 11.5	57	1543	3.7	2.8 to 4.6
	Fatigue	57	796	7.2	5.4 to 8.9	29	793	3.7	2.4 to 5
	Hot flushes	14	295	4.8	2.3 to 7.2	5	298	1.7	0.2 to 3.1
	Increased sweating	32	674	4.7	3.1 to 6.3	2	676	0.3	0.0 to 0.7
	Nausea	535	2556	20.9	20.9 to 20.9	151	1790	8.4	8.4 to 8.4
	Pruritus	155	1809	8.6	8.6 to 8.6	52	1056	4.9	4.9 to 4.9
	Vomiting	184	2058	8.9	8.9 to 8.9	28	1310	2.1	2.1 to 2.1
Opioids versus active pharmacological	Any AE	454	785	57.8	54.4 to 61.3	381	798	47.7	44.3 to 51.2
	Any SAE	5	54	9.3	1.5 to 17	1	54	1.9	0 to 5.4
	Withdrawals*	185	1201	15.4	13.4 to 17.4	56	1174	4.8	3.6 to 6
Opioids versus active non-pharmacological	Any AE	1	17	5.8	0 to 17.1	0	15	0	0 to 0

Abbreviation: AE, adverse events; SAE, serious adverse events
* Withdrawals due to adverse events

(Adapted and modified from Els et al 2017b)

Table 2 Risk ratio and number needed to treat: adverse events

Comparison	Adverse event	Studies	Participants	Risk ratio (95% CI)	NNTH (95% CI)
Opioids versus placebo	Anorexia	1	330	13.64 (0.77, 240.21)	-
	Constipation	4	4255	2.23 (1.39, 3.59)	16.82 (13.20, 23.19)
	Diarrhoea	1	313	2.55 (0.69, 9.43)	-
	Dizziness	4	4130	2.76 (2.15, 3.55)	13.55 (11.15, 17.28)
	Drowsiness	3	3856	2.89 (2.19, 3.83)	15.26 (12.34, 20.00)
	Fatigue	1	1589	1.96 (1.27, 3.03)	28.54 (17.48, 77.71)
	Gastrointestinal	1	98	1.77 (0.90, 3.47)	-
	Headache	1	313	0.78 (0.33, 1.84)	-
	Hot flushes	1	593	2.83 (1.03, 7.75)	32.60 (16.95, 421.76)
	Increased sweating	1	1350	16.05 (3.86, 66.69)	22.46 (16.37, 35.78)
	Infection	2	631	0.87 (0.47, 1.61)	-
	Nausea	3	4346	2.46 (2.08, 2.92)	8.00 (6.88, 9.56)
	Nervous system disorders	1	98	2.50 (0.95, 6.56)	-
	Pruritus	1	2865	1.74 (1.28, 2.36)	27.44 (18.25, 55.27)
	Sinusitis	1	318	1.56 (0.52, 4.67)	-
	Vomiting	2	3368	4.29 (2.90, 6.34)	14.70 (12.10, 18.72)
	Xerostomia	1	1668	1.10 (0.47, 2.57)	-
Opioids versus active pharmacological	Any AE	1	1583	1.21 (1.10, 1.33)	9.91 (6.67, 19.24)
	Any SAE	1	108	5.00 (0.60, 41.39)	-
	Withdrawals*	4	2375	3.23 (2.42, 4.30)	9.40 (7.69, 12.11)

Abbreviation: AE, adverse events; NNTH, number needed to harm; SAE, serious adverse events;
* Withdrawals due to adverse events

(Adapted and modified from Els et al 2017b)

Table 3 GRADE quality judgement: adverse events

Comparison	Adverse event	Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Overall QoE
Opioids versus placebo	Any AE	1583	Serious	Not serious	Not serious	Not serious	None	MODERATE
	Any SAE	108	Serious	Not serious	Not serious	Not serious	None	MODERATE
	Withdrawals*	2375	Serious	Not serious	Not serious	Not serious	None	MODERATE
	Constipation	4255	Serious	Not serious	Serious	Not serious	Strong association	MODERATE
	Dizziness	4130	Serious	Not serious	Serious	Not serious	Strong association	MODERATE
	Drowsiness	3856	Serious	Not serious	Serious	Not serious	Strong association	MODERATE
	Fatigue	1589	Serious	Not serious	Very serious	Not serious	None	VERY LOW
	Hot flushes	593	Serious	Not serious	Very serious	Not serious	None	VERY LOW
	Increased sweating	1350	Serious	Not serious	Very serious	Not serious	V. strong association	MODERATE
	Nausea	4346	Serious	Not serious	Serious	Not serious	Strong association	MODERATE
	Pruritus	2865	Serious	Not serious	Very serious	Not serious	None	VERY LOW
	Vomiting	3368	Serious	Not serious	Very serious	Not serious	Strong association	VERY LOW
Opioids versus active pharmacological	Any AE	1583	Serious	Not serious	Not serious	Not serious	None	MODERATE
	Any SAE	108	Serious	Not serious	Not serious	Very serious	None	VERY LOW
	Withdrawals*	2375	Serious	Not serious	Not serious	Not serious	None	MODERATE
Opioids versus active non-pharmacological	Any AE	32	Very serious	Not serious	Not serious	Not serious	None	VERY LOW

Abbreviation: AE, adverse events; SAE, serious adverse events;
* Withdrawals due to adverse events

(Adapted and modified from Els et al 2017b)