Cochrane Library

Cochrane Database of Systematic Reviews

High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews (Review)

Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, Straube S

Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, Straube S.
High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews.
Cochrane Database of Systematic Reviews 2023, Issue 3. Art. No.: CD012299.
DOI: 10.1002/14651858.CD012299.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Overview of Reviews]

High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews

Charl Els[1,2], Tanya D Jackson[3], Reidar Hagtvedt[4], Diane Kunyk[5], Barend Sonnenberg[6], Vernon G Lappi[3], Sebastian Straube[3]

[1]Department of Psychiatry, University of Alberta, Edmonton, Canada. [2]College of Physicians and Surgeons of Alberta, Edmonton, Canada. [3]Department of Medicine, Division of Preventive Medicine, University of Alberta, Edmonton, Canada. [4]Accounting and Business Analytics, Alberta School of Business, University of Alberta, Edmonton, Canada. [5]Faculty of Nursing, University of Alberta, Edmonton, Canada. [6]Medical Services, Workers' Compensation Board - Alberta, Edmonton, Canada

Contact: Sebastian Straube, straube@ualberta.ca.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2023.

Citation: Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, Straube S. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2023, Issue 3. Art. No.: CD012299. DOI: 10.1002/14651858.CD012299.pub3.

ABSTRACT

Background

This overview was originally published in 2017, and is being updated in 2022.

Chronic pain is typically described as pain on most days for at least three months. Chronic non-cancer pain (CNCP) is any chronic pain that is not due to a malignancy. Chronic non-cancer pain in adults is a common and complex clinical issue, for which opioids are prescribed by some physicians for pain management. There are concerns that the use of high doses of opioids for CNCP lacks evidence of effectiveness, and may increase the risk of adverse events.

Objectives

To describe the evidence from Cochrane Reviews and overviews regarding the efficacy and safety of high-dose opioids (defined as 200 mg morphine equivalent or more per day) for CNCP.

Methods

We identified Cochrane Reviews and overviews by searching the Cochrane Database of Systematic Reviews in The Cochrane Library. The date of the last search was 21 July 2022. Two overview authors independently assessed the search results. We planned to analyse data on any opioid agent used at a high dose for two weeks or more for the treatment of CNCP in adults.

Main results

We did not identify any reviews or overviews that met the inclusion criteria. The excluded reviews largely reflected low doses or titrated doses, where all doses were analysed as a single group; we were unable to extract any data for high-dose use only.

Authors' conclusions

There is a critical lack of high-quality evidence, in the form of Cochrane Reviews, about how well high-dose opioids work for the management of CNCP in adults, and regarding the presence and severity of adverse events.

No evidence-based argument can be made on the use of high-dose opioids, i.e. 200 mg morphine equivalent or more daily, in clinical practice. Considering that high-dose opioids have been, and are still being used in clinical practice to treat CNCP, knowing about the efficacy and safety of these higher doses is imperative.

PLAIN LANGUAGE SUMMARY

High doses of opioid medicines for the management of chronic non-cancer pain

Bottom line

There is no high-quality evidence to show how well high doses of opioids work, or what side effects they cause, when they are used for adults with chronic pain that is not due to cancer.

Studies usually used doses below our cutoff. We need to know how well high-dose opioid medicine works for chronic non-cancer pain, and what side effects there may be.

Background

Opioids are a type of pain medicine related to morphine. Opioids have been used for many years as painkillers for moderate or severe chronic pain, which is pain that lasts for a long time (usually longer than three months).

Study characteristics

In this updated overview, we aimed to summarise the knowledge from Cochrane Reviews and overviews about opioid medicine for pain relief in adults who had chronic pain not due to cancer. We wanted to know how well opioid medicines worked when they were used at high doses (equal to 200 mg of morphine per day or more), and what side effects there might be.

Key results

Despite systematic searches, most recently conducted in July 2022, we did not find any information about this. Studies on opioids rarely reported on high-dose use. When they included them as part of a study of people using all levels of doses, they did not report separate information for people who used high-dose opioids.

BACKGROUND

Description of the condition

In 2020, the International Association for the Study of Pain updated the definition of pain to reflect "[a]n unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja 2020). The definition was contextually expanded, emphasising that pain is always a personal experience. Pain is influenced in varying degrees by biopsychosocial factors, and can become maladaptive, substantially and adversely impacting the sufferer's functional and psychosocial well-being (Raja 2020). About 49% of chronic pain sufferers in the United States reported that their pain resulted in work limitations (Yong 2022). In a Spanish study, 13.5% of chronic pain sufferers reported having lost or left their jobs because of their pain (De Sola 2016).

Chronic non-cancer pain (CNCP) is very common in adults, estimated to impact about 20% (Breivik 2006; Dahlhamer 2018; Goldberg 2011; Moore 2014). Although there are several self-report instruments to measure pain and its impact on the physical, social, emotional, and spiritual aspects of life, the personal and subjective nature of pain makes objective measurement impossible. Any assessment of pain is subjective and based on an individual's report (Breivik 2008). Notwithstanding, a person's report of an experience as pain should be respected (Raja 2020).

Chronic pain is typically described as pain that persists past normal healing time, or pain lasting or recurring for more than three to six months (Bonica 1953).

Chronic non-cancer pain is any chronic pain that is not due to a malignancy; CNCP is frequently divided into neuropathic pain, i.e. pain that appears to originate in the nerves; and non-neuropathic or nociceptive pain, which appears to often have a musculoskeletal origin and to arise in muscles, bones, or ligaments.

Description of the interventions

The treatment of pain may encompass a variety of approaches, including pharmacological management. Effective pain therapy has been described as a reduction in pain intensity of at least 50% over baseline, or sometimes as a reduction of at least 30% over baseline, along with improvement in work- and function-related outcomes. Effective pain therapy results in consistent improvements in fatigue, sleep, depression, quality of life, and work (Moore 2014).

Opioid therapy is used for the treatment of both acute and chronic painful conditions. There are numerous policies and country-specific clinical guidelines to assist with the use of opioids for the management of chronic pain. The World Health Organization's (WHO) analgesic ladder guides the use of pain medications (including opioids and non-opioids, such as non-steroidal anti-inflammatory drugs (NSAIDs)) in the management of pain (WHO 1996). Although originally formulated for cancer pain, this tool is now used for a broad range of chronic pain conditions. The American College of Occupational and Environmental Medicine (ACOEM) concludes that quality evidence does not support a superiority of opioids over NSAIDs or other medications for the treatment of CNCP (Hegmann 2014b). For acute pain, a recent systematic review and meta-analysis of randomised trials, including findings from 47 trials (N = 6607), supported the notion that opioid prescribing at surgical discharge increases the risk of adverse events but does not reduce pain intensity (Fiore 2022).

This overview addressed the use of high-dose opioids. As discussed below, we took this to mean opioids at doses of 200 mg morphine equivalent (MEQ) per day or more.

How the intervention might work

Opium is a plant-derived substance; the primary ingredients are morphine and codeine. The term 'opioids' refers to either naturally occurring compounds (opiates) or synthetic compounds. As centrally acting analgesics, opioids bring about their action in the human body by binding to opioid receptors. The mu, kappa, and delta opioid receptors are widely distributed throughout the nervous system (Rachinger-Adam 2011). Key among the opioid effects is analgesia; the focus of this overview is the use of opioids for their analgesic effect. Opioids bring about complex changes at the cellular and molecular level, decreasing pain perception and increasing tolerance to painful stimuli (Rass 2014).

A number of opioid actions besides analgesia have been described. These include euphoria (Schulteis 1996), sedation, drowsiness, and endocrine dysregulation (Vuong 2010). Opioids also alter sleep regulation, and are associated with poor sleep quality, insomnia, respiratory depression, sleep apnoea and sleep-disordered breathing (Zutler 2011). Physiological dependence on opioids may develop rapidly after the initiation of opioid use, and opioid abuse and dependence (i.e. opioid use disorders (OUD)) are a major concern with this group of medications. Opioid addiction is also a significant problem, and its neurobiology suggests that increasing doses of opioids are desired over time (Kosten 2002).

Besides other symptoms, the use of opioids is associated with the development of somnolence and sedation (Els 2017). Although each case is individually evaluated, the use of opioids is generally not recommended for people engaged in safety-sensitive work (Hegmann 2014a).

Although a number of adverse effects have been identified with the acute administration of opioids in novice users, chronic opioid use has been suggested to result in fewer medical problems (Rass 2014). However, some of these adverse effects are serious and potentially lethal, and may not decrease with long-term use. In addition, long-term opioid therapy at higher doses has been found to be associated with lower self-efficacy for pain management, and increased fear-avoidance beliefs, which are robust predictors of treatment outcome (Morasco 2017).

Why it is important to do this overview

Opioids are commonly used, and used at high doses, for the treatment of pain, including CNCP (Zutler 2011). The opioid doses used for CNCP vary between practitioners, payers, and countries. The use of opioids for CNCP has increased, despite safety concerns (Bohnert 2012; Chapman 2010; Kidner 2009), and despite a lack of clear evidence of the benefit of higher doses (Morasco 2017).

There are several studies examining the prescribing trends for opioids in recent decades for the treatment of CNCP. For example, an analysis of Workers' Compensation Board (WCB) data (where most claimants with pain would have non-malignant pain) from Manitoba, Canada demonstrated a dramatic increase in the average

opioid dose prescribed over time, from less than 500 mg MEQ per year in 1998 to over 6000 mg MEQ per year in 2010 (Kraut 2015). People using opioids at high doses may account for a significant portion of total opioid consumption. Use by the top 3% of WCB claimants on opioids in Alberta, Canada accounted for 80% of the total MEQ used (Boyko 2016). In England, there was a 34% increase in the number of opioid items prescribed between 1998 and 2016, representing a 127% increase when accounting for the oral morphine equivalency (Curtis 2019). Only 12% of strong opioids in England were prescribed for cancer pain in 2014 (Zin 2014); from 2010 to 2014, buprenorphine and codeine had the greatest increase in prescription rates (Mordecai 2018).

A recent study of 41 general practices in England found that 19.3% of the people prescribed opioids were given a dose equal to, or above 120 mg morphine a day; the most commonly cited reasons were musculoskeletal pain of the back, neck, joints, or limbs (Ponton 2018).

The use of high-dose opioids for CNCP has come under review because of questions about the effectiveness of opioids for CNCP, and the potential for adverse events, abuse, and addiction (Franklin 2014; Häuser 2014; Katz 2015; NOUGG 2010; Nuckols 2014). Three and a half decades ago, Portenoy and Foley described an addiction risk of lower than 1% (Portenoy 1986). However, evidence suggests that opioid abuse and addiction are well documented, and not uncommon among people with chronic pain, with rates of addiction averaging between 8% and 12% (Vowles 2015). Opioid addiction can potentially develop even if these drugs are used for the management of severe pain (Kosten 2002; Huffman 2015; Vowles 2015). This is further supported by a 2020 study, which found that 26.5% of people using opioids to treat CNCP met the criteria for OUD, with 9.0% meeting the criteria for moderate or severe OUD (Boscarino 2020).

With increasing opioid doses, the risk for addiction increases. Huffman and colleagues reported that a 50 mg increases in oral morphine dose almost doubled the risk of addiction; a 100 mg increase in dose was associated with a three-fold increase in risk (Huffman 2015). Furthermore, there is the potential for serious adverse events, such as sleep apnoea, sleep-disordered breathing, and respiratory depression, which may lead to opioid-associated deaths; such adverse outcomes of opioid use demonstrate a clear dose dependency (Jungquist 2012; Walker 2007).

Hegmann and colleagues summarised the substantial increase in the use of opioids, along with the increase in deaths associated with opioid use (Hegmann 2014b). Opioid-related deaths are common, and can occur even when the prescription is in accordance with guidelines. Sixty percent of opioid-related deaths in the USA occurred in people who were given prescriptions according to prescribing guidelines of medical boards (with 20% of deaths with doses up to 100 mg MEQ per day, and 40% in people prescribed dosages above that threshold). The remaining 40% of deaths occurred in people abusing the drugs (Manchikanti 2012a). Abuse of opioids includes multiple prescriptions, 'double-doctoring', and drug diversion.

A consensus has emerged that while long-term opioid therapy for non-cancer pain may be appropriate for selected individuals, it should not be the rule (Manchikanti 2012b). Further, a strong and reproducible dose-response relationship for efficacy led to the recommendation for a MEQ 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).

For people with chronic pain, at short-term follow-up, opioids are associated with small beneficial effects versus placebo, but are also associated with increased risk of short-term harms, and do not appear to be superior to non-opioid therapy. Evidence of opioid use on intermediate-term and long-term benefits remains very limited, and additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent (Chou 2020). In a recent study, opioid users reported no improvement for pain symptoms, physical function, emotional function, and social/family disability (Veiga 2019). Opioid users reported higher satisfaction with care and outcomes at one-year follow-up, but at two years, they only reported improvement in satisfaction with outcomes (Veiga 2019). Opioids showed limited effectiveness in long-term CNCP management, as opioid users presented no improvements in functional outcomes or quality of life (Veiga 2019).

Guidelines and research reports vary in what they consider to be a high opioid dose. A previous Canadian guideline designated a dose of opioids in excess of 200 mg MEQ per day as a 'watchful dose' (NOUGG 2010); this guideline has been updated, and the current Canadian guideline recommends dose limits of 90 mg and 50 mg MEQ per day (Busse 2017). This is more aligned with the dose recommendations in the ACOEM guideline (Hegmann 2014b), and the CDC guideline (Dowell 2016). Other recent guidelines recommend maximum doses in the order of 100 mg or 120 mg MEQ per day. For example, a German guideline, based on a systematic review, recommended that the morphine equivalent dose should not exceed 120 mg per day (Häuser 2014). We adopted a dose of 200 mg MEQ per day as the 'high-dose' threshold for this overview, as use at this level would generally be considered as clearly 'high dose'.

Another Cochrane overview complements this present overview, Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews (Els 2017).

In view of the ongoing prescribing of high-dose opioids for CNCP by some physicians, with its potential for serious harm, we thought it was important to search for new evidence concerning the practice; this motivated the present overview update.

OBJECTIVES

To describe the evidence from Cochrane Reviews and overviews regarding the efficacy and safety of high-dose opioids (defined as 200 mg morphine equivalent or more per day) for chronic non-cancer pain.

METHODS

We aimed to provide an overview of the evidence from Cochrane Reviews and overviews for the efficacy and safety of any opioid agent used at a high dose, administered by any route and frequency of administration, for the treatment of chronic non-cancer pain (CNCP) in adults. Typically, we expected trial durations of at least two weeks to be relevant for a chronic painful condition. Reviews including shorter trials would have been critically assessed. If a

review included a majority of data from inappropriately short trials, we might have excluded the review from the overview, depending on the condition studied.

Criteria for considering reviews for inclusion

We had planned to include all Cochrane Reviews and overviews of randomised controlled trials that assessed the efficacy and safety of opioids in adults with CNCP.

We expected the following of a Cochrane Review or overview in order to be included in our overview.

- There was a clearly defined research question relevant to the use of opioids in CNCP.
- The Cochrane Review or overview performed a systematic search for relevant evidence, providing details of databases searched and the search strategies.
- The Cochrane Review or overview detailed criteria for the inclusion of studies. Included studies in Cochrane Reviews are typically randomised controlled trials (RCT), as this study design is associated with a lower risk of bias than non-randomised study designs.
- Outcomes of interest and data on the high-dose range (200 mg morphine equivalent (MEQ) or more per day) were reported.

Outcomes of interest

When choosing outcome measures to assess the efficacy and safety of interventions in our overview, we preferred outcome measures that were of known utility. Our preferred outcome measures were based on the guidance for systematic reviews in the pain field (Moore 2010). We planned to consider group average values if no, or insufficient data for responder analyses were available. Our outcomes of interest are listed below; we planned to extract and analyse data for opioid doses of 200 mg morphine equivalent or more per day.

Pain-related outcomes

- Proportion of participants with at least 50% pain reduction over study baseline
- Proportion of participants with at least 30% pain reduction over study baseline
- Proportion of participants below 30/100 mm on the visual analogue pain scale (i.e. no worse than mild pain)
- Treatment group average scores for pain intensity or pain relief

Work- and function-related outcomes

- Work time missed
- Interference with work (subjective rating scales)
- Function (SF-36, SF-12 scales); proportion of participants with at least 30% improvement in functional abilities
- Quality of life (any scale)

Adverse event outcomes

- Proportion of participants with any adverse event
- Proportion of participants with any serious adverse event
- Proportion of participants withdrawing due to adverse events

We planned to note the imputation methods used in the trials, and discuss the limitations resulting from them. We would have preferred data with 'baseline observation carried forward' methodology over data with 'last observation carried forward', if there was a choice.

Search methods for identification of reviews

Electronic searches

Originally, we searched the Cochrane Database of Systematic Reviews (CDSR; in the Cochrane Library, Issue 4, 2017) across all years. The date of the last search for the original review was 18 April 2017, using the search strategy presented in Appendix 1. For this update, we searched the CDSR in the Cochrane Library, Issue 7, 2022, from April 2017 to 21 July 2022, using the search strategy presented in Appendix 2 (modified only to accommodate the updates to the CDSR interface).

Data collection and analysis

Selection of reviews

Two overview authors independently screened the results of the electronic search by title and abstract. We obtained the full-text versions of potentially relevant reviews and overviews, and two overview authors subsequently applied the selection criteria to determine eligibility for inclusion. Disagreements were resolved by consensus or by discussion with a third overview author.

Data extraction and management

Two overview authors planned to independently extract data, using a standardised form. We planned to resolve discrepancies by consensus, and to consult a third overview author and make a majority decision should we not have achieved resolution.

Using standardised and piloted data extraction forms, we planned to extract data on the following.

- Objectives of the Cochrane Review or overview
- Number of studies and participants included in the Cochrane Review or overview
- Study and participant baseline characteristics
- Inclusion and exclusion criteria applied in the Cochrane Review or overview
- Chronic pain conditions studied
- Opioid medication, dose and frequency of administration
- Our outcomes of interest
- Route(s) of administration covered in the Cochrane Review or overview
- Declarations of competing interest and sponsorship of the Cochrane Review or overview authors

Assessment of methodological quality of included reviews

For the original overview, two overview authors intended to independently undertake a formal quality assessment of the included Cochrane Reviews and overviews using criteria modified from the AMSTAR guidance (Assessing the Methodological Quality of Systematic Reviews (Moore 2010; Shea 2007)). For this update, we planned to use criteria modified from the AMSTAR-2 guidance (A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both (Shea 2017)). The overview authors planned

to reconcile differences through discussion, or if needed, by consulting a third overview author.

Data synthesis

Our primary aim, given the expected methodological and clinical heterogeneity between the Cochrane Reviews and overviews that we would include in our overview, was to perform a qualitative evidence synthesis. However, if feasible and appropriate, we would have conducted quantitative meta-analyses. For meta-analysis, we intended to use either a fixed-effect model or a random-effects model, as determined by between-study heterogeneity (I^2 statistic). In addition to assessing statistical heterogeneity, we planned to also consider clinical heterogeneity between the studies.

We planned to use a fixed-effect model when there was no evidence of significant between-study heterogeneity. We planned to calculate relative benefit or risk with 95% confidence intervals. We planned to calculate numbers needed to treat for an additional beneficial outcome or an additional harmful outcome from the pooled number of events, using the method of Cook and Sackett (Cook 1995). We planned to follow the guidance detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* for our overview and meta-analyses methodology (Higgins 2022). We planned to undertake our analyses across opioid agents (by conversion to mg morphine equivalent (MEQ)), and also for the individual agents. We planned to undertake separate analyses by trial duration. We defined short-term treatment as treatment lasing less than two weeks; medium-term lasted at least two weeks but less than two months; long-term was two months or longer.

We planned to assess the quality of the body of evidence with the GRADE approach as applied in Cochrane Reviews (Higgins 2022). See Appendix 3 for a further description of the GRADE system.

RESULTS

For the original version of this overview, we searched the Cochrane Library using a combination of controlled vocabulary (MeSH) and text terms (Appendix 1). The search resulted in 735 records, including 723 Cochrane Reviews and 12 Cochrane overviews. Three hundred and twenty-one of the Cochrane Reviews were duplicates, resulting in 414 records (402 reviews and 12 overviews). We excluded 362 reviews and five overviews based on the title or abstract, leaving 40 reviews and seven overviews for detailed examination.

We retrieved full texts of all 40 reviews and the seven overviews. We decided to also retrieve component studies from reviews that might have described high-dose opioid use. Therefore, we also obtained full-text copies of 27 potentially relevant component studies from five of the reviews (Chaparro 2012, Chaparro 2013, McNicol 2013, Santos 2015, Wiffen 2015a). Only one of these reviews had separate data on high-dose use (Wiffen 2015a). However, this was still ineligible, as people with and without cancer were included, and the data for those with non-cancer pain were not analysed separately (Bohme 2003).

No review or overview met our inclusion criteria. This was primarily due to three reasons. Some reviews focused on cancer or acute pain. Others did not include opioids as an intervention. Reviews that did include opioids for CNCP studied a range of opioid doses, with all doses (including those below and above our cut-off of 200 mg morphine equivalent per day) analysed as a single group, without providing separate data for high-dose use. The reasons for exclusion are detailed in Table 1 for reviews and Table 2 for overviews.

For this update, we searched the Cochrane Library using a combination of MeSH and text terms, with the syntax updated to accommodate the new Cochrane Library interface (Appendix 2). We identified 78 records, including 75 Cochrane Reviews and three Cochrane overviews. We excluded 71 reviews and one overview based on the title and abstract, leaving four reviews and two overviews to be reviewed as full-text reports. None of these six records met the inclusion criteria for our overview. Table 3 details the reasons for exclusion.

Our study selection is illustrated by the flow diagram in Figure 1, which combines data from the original overview and this update.

Figure 1. PRISMA study selection flow diagram

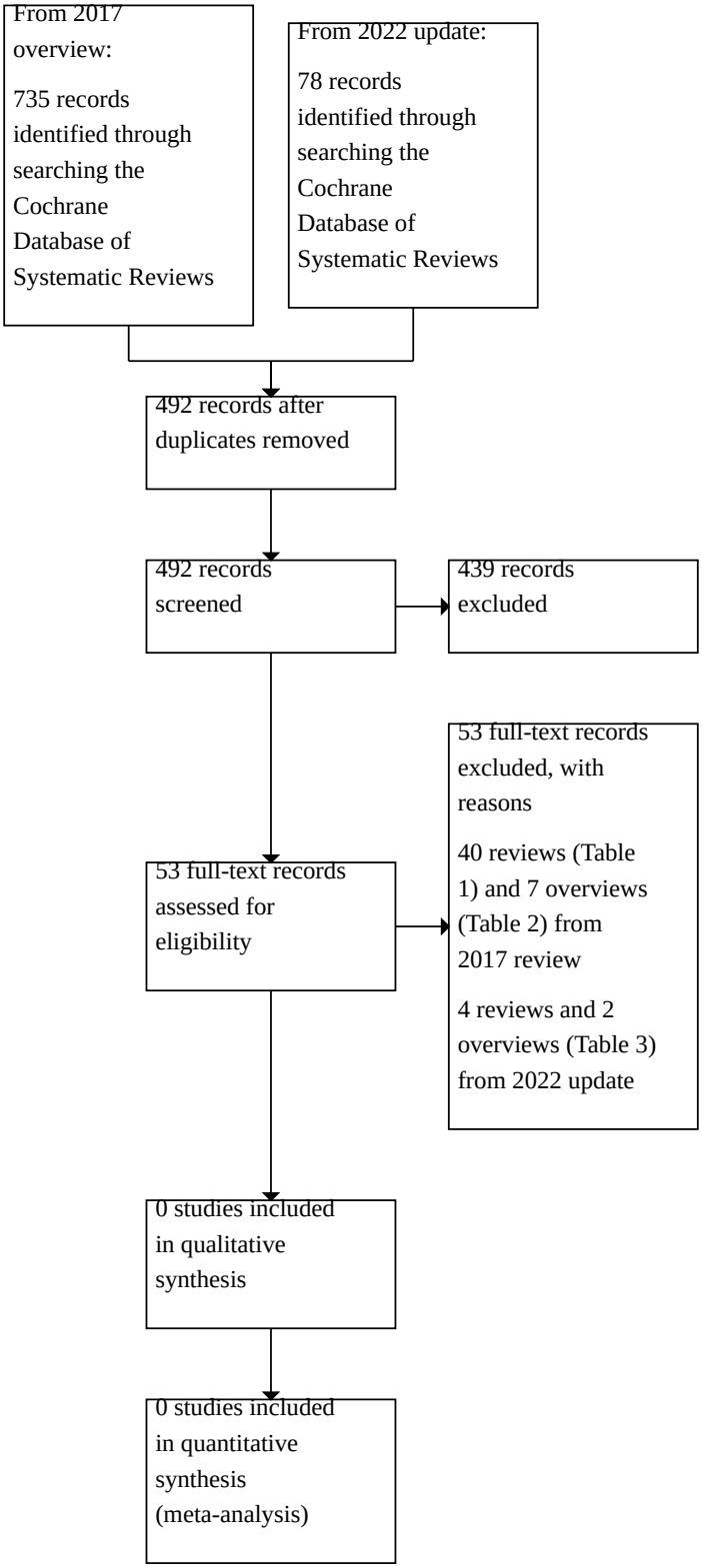

Figure 1. (Continued)

Description of included reviews

No Cochrane Reviews or overviews met our inclusion criteria.

Methodological quality of included reviews

No Cochrane Reviews or overviews were included.

Effect of interventions

No Cochrane Reviews or overviews were identified that met our inclusion criteria.

DISCUSSION

Summary of main results

No Cochrane Reviews or overviews were included in this overview.

Overall completeness and applicability of evidence

There is a lack of high-quality evidence, in the form of Cochrane Reviews, on the efficacy and safety of high-dose opioids for the management of chronic non-cancer pain (CNCP) in adults. No evidence-based statements can be made on the use of high-dose opioids in clinical practice.

Quality of the evidence

Our overview aimed to assess all the available evidence from Cochrane Reviews and overviews on the use of high-dose opioids in the management of CNCP in adults. We found no such evidence.

Potential biases in the overview process

We know of no potential biases in our overview process. It is unlikely that there is a substantial body of high-quality evidence that examines how well high-dose opioids work for CNCP, or what adverse effects they may have.

Agreements and disagreements with other studies or reviews

This overview is consistent with other reviews (Dowell 2016; Hegmann 2014b). There does not appear to be a body of dependable, high-quality clinical evidence to either support or refute the use of high-dose opioids for CNCP.

AUTHORS' CONCLUSIONS

Implications for practice

There is an absence of high-quality evidence to support or refute the use of high-dose opioids for CNCP. Opioids are associated with increased risks for adverse events, including addiction, overdose, and death (Dowell 2016).

For persons suffering from chronic non-cancer pain

When selecting a treatment modality and dosage, risks and benefits must be considered. People should be made aware of the potential risks, and the absence of evidence for benefit of high-dose opioids for CNCP. Physicians should have frank and open conversations with people in this regard, supplemented with a discussion on other, evidence-based, strategies.

For policymakers

In the absence of evidence to support or refute the efficacy of high-dose opioids, and in view of the established risks, the use of high-dose opioids for treating CNCP should not be recommended.

For funders

In the absence of evidence to support or refute the efficacy of high-dose opioids, they should not be recommended.

Implications for research

General

Although we know that opioids are commonly prescribed to people, including at high doses, for the treatment of CNCP, there is no evidence to refute or support the efficacy of this clinical practice. However, the risks associated with high-dose opioid use are well established. We do not at present have dependable information about how well high-dose opioids work, or what adverse effects may accompany their use when they are used on a long-term basis for CNCP.

Design

On the one hand, the absence of high-quality evidence for high-dose opioid use would typically call for more randomised controlled trials to be conducted, specifically addressing this question. On the other hand, the potential for significant adverse events with high-dose opioids provides an argument against conducting these studies. The ethics of conducting studies on high-dose opioids needs to be considered carefully.

Where possible, data from people receiving high-dose opioids in existing datasets should be re-analysed separately.

Measurement

Many of the outcomes of interest for high-dose opioids are the same as for opioids studied at a lower dose range. Dworkin 2005 outlined six domains that should be considered for chronic pain clinical trials, including pain, physical functioning, emotional functioning, treatment satisfaction, symptoms, and adverse events, and participant disposition.

ACKNOWLEDGEMENTS

The authors would like to gratefully acknowledge the assistance of Liz Dennett, librarian at the University of Alberta, for her assistance with the search for the overview update.

Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) supported the authors in the development of this updated overview.

Editorial contributions:

The following people conducted the editorial process for this update:

Sign-off Editor (final editorial decision): Neil O'Connell, Brunel University London; Co-ordinating Editor Cochrane Pain, Palliative and Supportive Care (PaPaS)

Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Helen Wakeford, Executive Editor, Cochrane Central Editorial Service
Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
Copy Editor (copy editing and production): Victoria Pennick, Cochrane Copy-edit Group

REFERENCES

References to excluded reviews

Alviar 2011

Alviar MJM, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No: CD006380. [DOI: 10.1002/14651858.CD006380.pub2]

Bao 2016

Bao YJ, Hou W, Kong XY, Yang L, Xia J, Hua BJ, et al. Hydromorphone for cancer pain. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No: CD011108. [DOI: 10.1002/14651858.CD011108.pub2]

Bell 2012

Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No: CD003351. [DOI: 10.1002/14651858.CD003351.pub2]

Brettschneider 2013

Brettschneider J, Kurent J, Ludolph A. Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No: CD005226. [DOI: 10.1002/14651858.CD005226.pub3]

Cepeda 2006

Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD005522. [DOI: 10.1002/14651858.CD005522.pub2]

Chaparro 2012

Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No: CD008943. [DOI: 10.1002/14651858.CD008943.pub2]

Chaparro 2013

Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD004959. [DOI: 10.1002/14651858.CD004959.pub4]

Cheong 2014

Cheong YC, Smotra G, Williams ACC. Non-surgical interventions for the management of chronic pelvic pain. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No: CD008797. [DOI: 10.1002/14651858.CD008797.pub2]

Cooper 2017

Cooper TE, Chen J, Wiffen PJ, Derry S, Carr DB, Aldington D, et al. Morphine for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No: CD011669. [DOI: 10.1002/14651858.CD011669.pub2]

da Costa 2014

da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AWS, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No: CD003115. [DOI: 10.1002/14651858.CD003115.pub4]

de Oliveira 2016

de Oliveira CO, Carvalho LB, Carlos K, Conti C, de Oliveira MM, Prado LB, et al. Opioids for restless legs syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No: CD006941. [DOI: 10.1002/14651858.CD006941.pub2]

Derry 2016

Derry S, Stannard C, Cole P, Wiffen PJ, Knaggs R, Aldington D, et al. Fentanyl for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No: CD011605. [DOI: 10.1002/14651858.CD011605.pub2]

Duehmke 2006

Duehmke RM, Hollingshead J, Cornblath DR. Tramadol for neuropathic pain. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD003726. [DOI: 10.1002/14651858.CD003726.pub3]

Eccleston 2017

Eccleston C, Fisher E, Thomas KH, Hearn L, Derry S, Stannard C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No: CD010323. [DOI: 10.1002/14651858.CD010323.pub3]

Els 2017a

Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No: CD012509. [DOI: 10.1002/14651858.CD012509.pub2]

Els 2017b

Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No: CD012299. [DOI: 10.1002/14651858.CD012299.pub2]

Enthoven 2016

Enthoven W, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No: CD012087. [DOI: 10.1002/14651858.CD012087]

Fraquelli 2016

Fraquelli M, Casazza G, Conte D, Colli A. Non-steroid anti-inflammatory drugs for biliary colic. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No: CD006390. [DOI: 10.1002/14651858.CD006390.pub2]

Gaskell 2014

Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No: CD010692. [DOI: 10.1002/14651858.CD010692.pub2]

Gaskell 2016

Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for pain in fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No: CD012329. [DOI: 10.1002/14651858.CD012329]

Hadley 2013

Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No: CD010270. [DOI: 10.1002/14651858.CD010270.pub2]

Haroutiunian 2012

Haroutiunian S, McNicol ED, Lipman AG. Methadone for chronic non-cancer pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No: CD008025. [DOI: 10.1002/14651858.CD008025.pub2]

Hróbjartsson 2010

Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No: CD003974. [DOI: 10.1002/14651858.CD003974.pub3]

Marks 2011

Marks JL, Colebatch AN, Buchbinder R, Edwards CJ. Pain management for rheumatoid arthritis and cardiovascular or renal comorbidity. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No: CD008952. [DOI: 10.1002/14651858.CD008952.pub2]

McNicol 2013

McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD006146. [DOI: 10.1002/14651858.CD006146.pub2]

McNicol 2015

McNicol ED, Strassels S, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No: CD005180. [DOI: 10.1002/14651858.CD005180.pub2]

McNicol 2017

McNicol ED, Ferguson MC, Schumann, R. Methadone for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No: CD012499. [DOI: 10.1002/14651858.CD012499.pub2]

Moore 2015

Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No: CD011407. [DOI: 10.1002/14651858.CD011407.pub2]

Moore 2015a

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No: CD011824. [DOI: 10.1002/14651858.CD011824]

Mujakperuo 2010

Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No: CD004715. [DOI: 10.1002/14651858.CD004715.pub2]

Nicholson 2017

Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No: CD003971. [DOI: 10.1002/14651858.CD003971.pub4]

Noble 2010

Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No: CD006605. [DOI: 10.1002/14651858.CD006605.pub2]

O'Connell 2013

O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No: CD009416. [DOI: 10.1002/14651858.CD009416.pub2]

Quigley 2013

Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No: CD003447. [DOI: 10.1002/14651858.CD003447.pub2]

Radner 2012

Radner H, Ramiro S, Buchbinder R, Landewé R, van der Heijde D, Aletaha D. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondyloarthritis) and gastrointestinal or liver comorbidity. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No: CD008951. [DOI: 10.1002/14651858.CD008951.pub2]

Ramiro 2011

Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, et al. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No: CD008886. [DOI: 10.1002/14651858.CD008886.pub2]

Richards 2011

Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No: CD008920. [DOI: 10.1002/14651858.CD008920.pub2]

Rubinstein 2011

Rubinstein SM, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No: CD008112. [DOI: 10.1002/14651858.CD008112.pub2]

Santos 2015

Santos J, Alarcão J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No: CD009923. [DOI: 10.1002/14651858.CD009923.pub2]

Schmidt-Hansen 2015a

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No: CD003870. [DOI: 10.1002/14651858.CD003870.pub5]

Schmidt-Hansen 2015b

Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart JS. Buprenorphine for treating cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No: CD009596. [DOI: 10.1002/14651858.CD009596.pub4]

Seidel 2013

Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD004844. [DOI: 10.1002/14651858.CD004844.pub3]

Singh 2015

Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No: CD005614. [DOI: 10.1002/14651858.CD005614.pub2]

Staal 2008

Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No: CD001824. [DOI: 10.1002/14651858.CD001824.pub3]

Stannard 2016

Stannard C, Gaskell H, Derry S, Aldington D, Cole P, Cooper TE, et al. Hydromorphone for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No: CD011604. [DOI: 10.1002/14651858.CD011604.pub2]

Stanton 2013

Stanton TR, Wand BM, Carr DB, Birklein F, Wasner GL, O'Connell NE. Local anaesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD004598. [DOI: 10.1002/14651858.CD004598.pub3]

Straube 2014

Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No: CD006601. [DOI: 10.1002/14651858.CD006601.pub4]

Thorpe 2018

Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I. Combination pharmacotherapy for the treatment of fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No: CD010585. [DOI: 10.1002/14651858.CD010585.pub2]

Whittle 2011

Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No: CD003113. [DOI: 10.1002/14651858.CD003113.pub3]

Wiffen 2015a

Wiffen PJ, Derry S, Moore RA, Stannard C, Aldington D, Cole P, et al. Buprenorphine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No: CD011603. [DOI: 10.1002/14651858.CD011603.pub2]

Wiffen 2015b

Wiffen PJ, Derry S, Naessens K, Bell RF. Oral tapentadol for cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No: CD011460. [DOI: 10.1002/14651858.CD011460.pub2]

Wiffen 2016

Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No: CD003868. [DOI: 10.1002/14651858.CD003868.pub4]

Zeppetella 2015

Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No: CD004311. [DOI: 10.1002/14651858.CD004311.pub4]

Additional references

Bohme 2003

Bohme K, Likar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomised, double-blind, placebo-controlled study. *Pain Clinic* 2003;**15**(2):193-202. [DOI: 10.1163/156856903321579334]

Bohnert 2012

Bohnert AS, Ilgen MA, Ignacio RV, McCarthy JF, Valenstein M, Blow FC. Risk of death from accidental overdose associated with psychiatric and substance use disorders. *American Journal of Psychiatry* 2012;**169**(1):64-70. [DOI: 10.1176/appi.ajp.2011.10101476]

Bonica 1953

Bonica JJ. The Management of Pain. Philadelphia: Lea & Febiger, 1953.

Boscarino 2020

Boscarino JA, Withey CA, Dugan RJ, Hu Y, Auciello J, Alfieri T. Opioid medication use among chronic non-cancer pain patients assessed with a modified drug effects questionnaire and the

association with opioid use disorder. *Journal of Pain Research* 2020;**13**:2697.

Boyko 2016

Boyko R, Els C, Lappi V, Sonnenberg B, Kunyk D, Hagtvedt R, et al. Opioid prescription analysis for Workers' Compensation Board of Alberta claimants. Poster presented at the 34th Annual Conference of the Occupational and Environmental Medical Association of Canada; 2016 Sept 25; Whistler, British Columbia, Canada.

Breivik 2006

Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European Journal of Pain* 2006;**10**(4):287-333.

Breivik 2008

Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EB, et al. Assessment of pain. *British Journal of Anaesthesia* 2008;**101**(1):17-24. [DOI: 10.1093/bja/aen103]

Busse 2017

Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* 2017;**189**(18):E659-66. [DOI: 10.1503/cmaj.170363]

Chapman 2010

Chapman CR, Lipschitz DL, Angst MS, Chou R, Denisco RC, Donaldson GW, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *Journal of Pain* 2010;**11**(9):807-29. [DOI: 10.1016/j.jpain.2010.02.019]

Chou 2020

Chou R, Hartung D, Turner J, Blazina I, Chan B, Levander X, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC011. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. Available at effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research. [DOI: 10.23970/AHRQEPCCER229]

Cook 1995

Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**(6977):452-4.

Curtis 2019

Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *The Lancet Psychiatry* 2019;**6**(2):140-50.

Dahlhamer 2018

Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. *MMWR. Morbidity and Mortality Weekly Report* 2018;**67**(36):1001-6. [DOI: 10.15585/mmwr.mm6736a2]

De Sola 2016

De Sola H, Salazar A, Dueñas M, Ojeda B, Failde I. Nationwide cross-sectional study of the impact of chronic pain on an individual's employment: relationship with the family and the social support. *BMJ Open* 2016;**6**(12):e012246.

Dowell 2016

Dowell D, Haegerich T, Chou R. CDC Guideline for prescribing opioids for chronic pain - United States, 2016. *JAMA* 2016;**315**(15):1624-45. [DOI: 10.1001/jama.2016.1464]

Dworkin 2005

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;**113**:9-19. [DOI: 10.1016/j.pain.2004.10.019]

Fiore 2022

Fiore JF, El-Kefraoui C, Chay MA, Nguyen-Powanda P, Do U, Olleik G, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet* 2022;**399**:2280-93.

Franklin 2014

Franklin GM, American Academy of Neurology. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology* 2014;**83**(14):1277-84. [DOI: 10.1212/WNL.0000000000000839]

Goldberg 2011

Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health* 2011;**11**:770.

Hegmann 2014a

Hegmann KT, Weiss MS, Bowden K, Branco F, DuBrueler K, Els C, et al. ACOEM practice guidelines: opioids and safety-sensitive work. *Journal of Occupational and Environmental Medicine* 2014;**56**(7):e46-53. [DOI: 10.1097/JOM.0000000000000237]

Hegmann 2014b

Hegmann KT, Weiss MS, Bowden K, Branco F, DuBrueler K, Els C, et al. ACOEM practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. *Journal of Occupational and Environmental Medicine* 2014;**56**(12):e143-59. [DOI: 10.1097/JOM.0000000000000352]

Higgins 2022

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Huffman 2015

Huffman KL, Shella ER, Sweis G, Griffith SD, Scheman J, Covington EC. Nonopioid substance use disorders and opioid dose predict therapeutic opioid addiction. *Journal of Pain* 2015;**16**(2):126-34. [DOI: 10.1016/j.jpain.2014.10.011]

Häuser 2014

Häuser W, Bock F, Engeser P, Tölle T, Willweber-Strumpfe A, Petzke F. Clinical practice guideline: long-term opioid use

in non-cancer pain. *Deutsches Ärzteblatt International* 2014;**111**(43):732-40. [DOI: 10.3238/arztebl.2014.0732]

Jungquist 2012

Jungquist CR, Flannery M, Perlis ML, Grace JT. Relationship of chronic pain and opioid use with respiratory disturbance during sleep. *Pain Management Nursing* 2012;**13**(2):70-9. [DOI: 10.1016/j.pmn.2010.04.003]

Katz 2015

Katz JA, Swerdloff MA, Brass SD, Argoff CE, Markman J, Backonja M, et al. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology* 2015;**84**(14):1503-4; Author Response 1504-5. [DOI: 10.1212/WNL.0000000000001485]

Kidner 2009

Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *Journal of Bone and Joint Surgery* 2009;**91**(4):919-27. [DOI: 10.2106/JBJS.H.00286]

Kosten 2002

Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Science & Practice Perspectives* 2002;**1**(1):13-20.

Kraut 2015

Kraut A, Shafer LA, Raymond CB. Proportion of opioid use due to compensated workers' compensation claims in Manitoba, Canada. *American Journal of Industrial Medicine* 2015;**58**(1):33-9. [DOI: 10.1002/ajim.22374]

Manchikanti 2012a

Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. *Pain Physician* 2012;**15**(3 Suppl):ES9-38.

Manchikanti 2012b

Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al, American Society of Interventional Pain Physicians. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain. Part 2 – guidance. *Pain Physician* 2012;**15**(3 Suppl):S67-116.

Moore 2010

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al, ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief, Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain – establishing best practice in the reporting of systematic reviews. *Pain* 2010;**150**(3):386-9. [DOI: 10.1016/j.pain.2010.05.011]

Moore 2014

Moore AR, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79-94. [DOI: 10.1111/papr.12050]

Morasco 2017

Morasco BJ, Yarborough BJ, Smith NX, Dobscha SK, Deyo RA, Perrin NA, et al. Higher prescription opioid dose is associated with worse patient-reported pain outcomes and more health care utilization. *The Journal of Pain* 2017;**18**(4):437-45.

Mordecai 2018

Mordecai L, Reynolds C, Donaldson LJ, de C Williams AC. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *British Journal of General Practice* 2018-03-01;**68**(668):e225-33. [DOI: 10.3399/bjgp18x695057]

NOUGG 2010

National Opioid Use Guideline Group (NOUGG). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. nationalpaincentre.mcmaster.ca/opioid/documents.html (accessed 12 May 2017).

Nuckols 2014

Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, Di Capua P, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Annals of Internal Medicine* 2014;**160**(1):38-47. [DOI: 10.7326/0003-4819-160-1-201401070-00732]

Ponton 2018

Ponton R, Sawyer R. Opioid prescribing in general practice: use of a two-stage review tool to identify and assess high-dose prescribing. *British Journal of Pain* 2018;**12**(3):171-82.

Portenoy 1986

Portenoy R, Foley K. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986;**25**(2):171-86.

Rachinger-Adam 2011

Rachinger-Adam B, Conzen P, Azad SC. Pharmacology of peripheral opioid receptors. *Current Opinion in Anaesthesiology* 2011;**24**(4):408-13. [DOI: 10.1097/ACO.0b013e32834873e5]

Raja 2020

Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 2020;**161**(9):1976-82. [DOI: 10.1097/j.pain.0000000000001939]

Rass 2014

Rass O, Schacht RL, Marvel CL, Mintzer MZ. Chapter 11. Opioids. In: Allen DN, Woods SP, editors(s). Neuropsychological aspects of substance use disorders: Evidence-based perspectives. New York: Oxford University Press, 2014:231-53.

Schulteis 1996

Schulteis G, Koob GF. Reinforcement processes in opiate addiction: a homeostatic model. *Neurochemical Research* 1996;**21**(11):1437-54.

Shea 2007

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic

reviews. *BMC Medical Research Methodology* 2007;**7**:1-10. [DOI: 10.1186/1471-2288-7-10]

Shea 2017

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;**358**:j4008. [DOI: 10.1136/bmj.j4008]

Veiga 2019

Veiga DR, Monteiro-Soares M, Mendonça L, Sampaio R, Castro-Lopes JM, Azevedo LF. Effectiveness of opioids for chronic noncancer pain: a two-year multicenter, prospective cohort study with propensity score matching. *The Journal of Pain* 2019;**20**(6):706-15.

Vowles 2015

Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015;**156**(4):569-76. [DOI: 10.1097/01.j.pain.0000460357.01998.f1]

Vuong 2010

Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocrine Reviews* 2010;**31**(1):98–132. [DOI: 10.1210/er.2009-0009]

Walker 2007

Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *Journal of Clinical Sleep Medicine* 2007;**3**(5):455-61.

WHO 1996

World Health Organization. Cancer pain relief: with a guide to opioid availability. 2nd edition. Geneva: World Health Organization, 1996.

Yong 2022

Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. *Pain* 2022;**163**(2):e328-32.

Zin 2014

Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain* 2014;**18**(9):1343-51. [DOI: 10.1002/j.1532-2149.2014.496.x]

Zutler 2011

Zutler M, Holty JE. Opioids, sleep, and sleep-disordered breathing. *Current Pharmaceutical Design* 2011;**17**(15):1443-9.

References to other published versions of this review

Els 2017

Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No: CD012509. [DOI: 10.1002/14651858.CD012509]

Els 2017c

Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No: CD012299. [DOI: 10.1002/14651858.CD012299.pub2]

ADDITIONAL TABLES

Table 1. Characteristics of excluded reviews

Study	Reason for exclusion
Alviar 2011	Opioids studied but not at high doses specifically
Bao 2016	Cancer pain
Bell 2012	Cancer pain
Brettschneider 2013	No opioids studied
Cepeda 2006	Opioids studied but not at high doses specifically
Chaparro 2012	Opioids studied but not at high doses specifically
Chaparro 2013	Opioids studied but not at high doses specifically
Cheong 2014	No opioids studied
de Oliveira 2016	Opioids studied but not at high doses specifically

Table 1. Characteristics of excluded reviews *(Continued)*

Duehmke 2006	Opioids studied but not at high doses specifically
Enthoven 2016	Opioids studied but not at high doses specifically
Fraquelli 2016	Acute pain
Gaskell 2014	Opioids studied but not at high doses specifically
Gaskell 2016	Review with no included studies
Hadley 2013	Cancer pain
Hróbjartsson 2010	No opioids studied
Marks 2011	No opioids studied
McNicol 2013	Opioids studied but not at high doses specifically
McNicol 2015	Withdrawn from publication
Moore 2015a	No opioids studied
Mujakperuo 2010	No opioids studied
Nicholson 2017	Cancer pain
Quigley 2013	Withdrawn from publication
Radner 2012	No opioids studied
Ramiro 2011	Opioids studied but not at high doses specifically
Richards 2011	Opioids studied but not at high doses specifically
Santos 2015	Opioids studied but not at high doses specifically
Schmidt-Hansen 2015a	Cancer pain
Schmidt-Hansen 2015b	Cancer pain
Seidel 2013	Opioids studied but not at high doses specifically
Singh 2015	No opioids studied
Staal 2008	Opioids studied but not at high doses specifically
Stannard 2016	Opioids studied but not at high doses specifically
Stanton 2013	No opioids studied
Straube 2014	Cancer pain
Whittle 2011	Opioids studied but not at high doses specifically
Wiffen 2015a	Opioids studied but with mixed cancer and non-cancer group

Table 1. Characteristics of excluded reviews *(Continued)*

Wiffen 2015b	Cancer pain
Wiffen 2016	Cancer pain
Zeppetella 2015	Cancer pain

Table 2. Characteristics of excluded overviews

Overview	Reason for exclusion
da Costa 2014	Opioids studied but not at high doses specifically
Derry 2016	Opioids studied but not at high doses specifically
Haroutiunian 2012	Opioids studied but not at high doses specifically
Moore 2015	No opioids studied
Noble 2010	Opioids studied but not at high doses specifically
O'Connell 2013	No opioids studied
Rubinstein 2011	Opioids studied but not at high doses specifically

Table 3. Characteristics of excluded reviews and overviews, 2022 update

Review or Overview	Reason for exclusion
Cooper 2017	Opioids studied but not at high doses specifically
Eccleston 2017	Opioids studied but not at high doses specifically
Els 2017a	Opioids studied but not at high doses specifically
Els 2017b	Previous version of this overview
McNicol 2017	Opioids studied but not at high doses specifically
Thorpe 2018	Opioids studied but not at high doses specifically

APPENDICES

Appendix 1. *Cochrane Database of Systematic Reviews* (in the Cochrane Library) search strategy

#1 MeSH descriptor: [Pain] explode all trees

#2 pain*:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Analgesics, Opioid] explode all trees

#5 opioid*:ti,ab,kw (Word variations have been searched)

#6 codeine or oxycodone or tramadol or hydromorphone or morphine or fentanyl:ti,ab,kw (Word variations have been searched)

#7 meperidine or pethidine or dextropropoxyphene or methadone or buprenorphine or pentazocine or hydrocodone or opium or butorphanol:ti,ab,kw (Word variations have been searched)

#8 tapentadolol or papaveretum or meptazinol or dipipanone or dihydrocodeine or diamorphine:ti,ab,kw (Word variations have been searched)

#9 #4 or #5 or #6 or #7 or #8

#10 #3 and #9

Appendix 2. *Cochrane Database of Systematic Reviews* (in the Cochrane Library) updated search strategy

#1 MeSH descriptor: [Pain] explode all trees

#2 (pain*):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Analgesics, Opioid] explode all trees

#5 (opioid*):ti,ab,kw (Word variations have been searched)

#6 (codeine or oxycodone or tramadol or hydromorphone or morphine or fentanyl):ti,ab,kw (Word variations have been searched)

#7 (meperidine or pethidine or dextropropoxyphene or methadone or buprenorphine or pentazocine or hydrocodone or opium or butorphanol):ti,ab,kw (Word variations have been searched)

#8 (tapentadolol or papaveretum or meptazinol or dipipanone or dihydrocodeine or diamorphine):ti,ab,kw (Word variations have been searched)

#9 {OR #4-#8}

#10 #3 and #9

#11 #10 in Cochrane Reviews

#12 #11 with Cochrane Library publication date Between Apr 2017 and Jul 2022

Appendix 3. GRADE Assessment

The GRADE system uses the following criteria for assigning grade of evidence.

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

Grade of evidence is decreased further if the following are present.

- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

WHAT'S NEW

Date	Event	Description
23 March 2023	New search has been performed	Updated overview
23 March 2023	New citation required but conclusions have not changed	Updated overview

HISTORY

Protocol first published: Issue 7, 2016
Review first published: Issue 10, 2017

Date	Event	Description
4 January 2018	Amended	Minor amendment to Declarations of interest section.

CONTRIBUTIONS OF AUTHORS

SS conceived of the idea. CE, RH, DK, BS, VL, and SS contributed to the protocol for this overview. TJ joined the project after the protocol was published. TJ did the searching with the help of the PaPaS Review Group and the assistance of Liz Dennett. CE, TJ, BS, and VL screened the abstracts. CE, TJ, BS, RH, and DK assessed Cochrane Reviews and overviews for inclusion, with guidance from SS. CE, TJ, and SS drafted the full overview. CE, TJ, BS, and SS drafted the overview update. All overview authors approved the current version of the overview.

DECLARATIONS OF INTEREST

Charl Els: none known; he is an addiction psychiatrist and occupational physician, employed in a regulatory setting

Tanya D Jackson: none known; she is a clinical psychologist whose practice includes people with chronic pain

Reidar Hagtvedt: none known

Diane Kunyk: none known

Barend Sonnenberg: none known; he is a family physician and a medical consultant at the Workers' Compensation Board, Alberta, primarily assessing claims where opioids are prescribed to workers

Vernon G Lappi: he is a retired specialist occupational medicine physician. He discloses that he is the former Director of Medical Services of the Workers' Compensation Board - Alberta, and that he has personal equity holdings in Berkshire Hathaway and Procter and Gamble.

Sebastian Straube: none known; he is a specialist occupational medicine physician and some of the people he assesses have chronic pain. He is a Cochrane editor but was not involved in the editorial process for this overview.

SOURCES OF SUPPORT

Internal sources

- National Institute for Health and Care Research, UK

  This project was supported by the National Institute for Health and Care Research, via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

External sources

- WCB Alberta, Canada

  We acknowledge funding from the Workers' Compensation Board - Alberta (Edmonton, Alberta) for the project 'Effectiveness and safety of high dose opioid therapy in WCB Alberta claimants', of which the original version of this overview was part. This overview update

was supported by a program grant from the Workers' Compensation Board - Alberta (Edmonton, Alberta), 'Program of research and training in Preventive Medicine'.

- Alberta School of Business, Canada

We acknowledge funding from the Alberta School of Business, University of Alberta, for the project "Effectiveness and safety of high dose opioid therapy in WCB Alberta claimants", of which the original version of this overview was part.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

TJ joined as an author after the protocol was published.

We considered both Cochrane overviews and Cochrane Reviews to be eligible for this overview. We did this be inclusive of both these forms of Cochrane evidence synthesis products.

INDEX TERMS

Medical Subject Headings (MeSH)

*Analgesics, Opioid [adverse effects]; *Chronic Pain [drug therapy]; Morphine [adverse effects]; Pain Management; Systematic Reviews as Topic

MeSH check words

Adult; Humans