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Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews

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ABSTRACT

This is a protocol for a Cochrane Review (Overview). The objectives are as follows:

To assess adverse events associated with medium- and long-term use of opioids for CNCP.

BACKGROUND

Description of the condition

Pain is described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey 1994). 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. CNCP is frequently divided into neuropathic pain (i.e. pain originating in nerves) and non-neuropathic or nociceptive pain (which is often musculoskeletal in origin and arises from structures such as muscles, bones, or ligaments).

CNCP is very common in adults. One review estimated the prevalence of CNCP (of moderate or severe intensity, lasting more than three months) at approximately 20%, with considerable variation between studies (Moore 2014). The impact of CNCP on life is substantial; it affects quality of life and activities of daily living, social life, and work - approximately 20% of people with chronic pain are unable to work because of the pain (Moore 2014).

The personal and subjective nature of pain makes objective measurement impossible; an adequate assessment of pain is subjective and based on individual report (Breivik 2008). Different instruments are used to measure pain and to determine its impact on the physical, social, emotional, and spiritual aspects of life.

Description of the interventions

The treatment of pain may encompass a variety of approaches, including pharmacological management. Effective pain therapy has been described in terms of a reduction in pain intensity of at least 50% over study baseline, and results in consistent improvements in fatigue, sleep, depression, quality of life, and work ability (Moore 2014). Opioid therapy is used for the treatment of both acute and chronic pain conditions. There are large numbers of policies and 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 (opioids and non-opioids such as non-steroidal anti-inflammatory drugs (NSAIDs)) (WHO 1996). Although originally formulated for cancer pain, this tool is now utilised for a broad range of chronic pain conditions.

Long-term opioid use may be associated with problematic patterns of use, leading to clinically significant impairment or distress, including substance use disorders (i.e. abuse and dependence). Opioid use may also be associated with somatic and psychological sequelae, including depressive disorders, anxiety disorders, sleep disorders, sexual dysfunction, and delirium (APA 2013). Further, chronic opioid use is associated with a risk of fatal and non-fatal overdose, as well as cardiovascular events, endocrinological harms, and motor vehicle accidents (CDC 2016). High quality evidence demonstrates that an increased risk of vehicle crashes exists with the use of opioids (Hegmann 2014a). Operating a vehicle is considered a surrogate for safety-sensitive work tasks, and hence the use of opioids is usually deemed incompatible with working in safety-sensitive positions (Hegmann 2014a), and may also be incompatible with decision-critical tasks. Opioid use may therefore have direct implications on ability to work and economic productivity.

The American College of Occupational and Environmental Medicine concludes that quality evidence (which we understand to mean moderate or high quality evidence) does not support the concept of superiority of opioids over NSAIDs or other medications for the treatment of CNCP (Hegmann 2014b). Estimates of efficacy may also be inflated by inappropriate imputation methods (McQuay 2012). There is, furthermore, a relative dearth of literature available on how to discontinue opioid use in high-dose users (Windmill 2013).

In view of the absence of dependable high-quality evidence for long-term benefits with the use of opioids for CNCP, the Centers for Disease Control and Prevention suggest utilising the lowest effective dose, and careful reassessment of benefits versus risks when increasing the dose to 50 morphine milligram equivalents or more per day (CDC 2016).

How the intervention might work

This overview will focus on the use of opioids for their key function

of analgesia. Opium is a plant-derived substance, with pharmacologically active ingredients including morphine and codeine. The term 'opioids' can refer to either naturally occurring compounds ('opiates') or synthetic compounds. Opioids act by binding to opioid receptors; mu, kappa, and delta opioid receptors are widely distributed throughout the nervous system (Rachinger-Adam 2011). Opioids bring about complex changes at the cellular and molecular level, decreasing pain perception and increasing tolerance to painful stimuli (Borg 2014).

Other opioid actions include euphoria (Schulteis 1996), sedation, drowsiness, and endocrine dysregulation (Vuong 2010). Opioids 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 leading to opioid abuse and dependence (opioid use disorders). Increasing doses of opioids over time are a common and significant concern with this group of medications (Kosten 2002).

A number of effects have been identified with the acute administration of opioids or in opioid-naive people; chronic opioid use has been suggested to result in fewer medical problems (Rass 2014). However, there are serious and potentially lethal adverse effects, which may still occur with long-term use.

Why it is important to do this overview

Opioids are now commonly and increasingly used for the treatment of pain, including CNCP (Zutler 2011). In fact, there has been a large increase in the use of opioids for CNCP in recent years despite safety concerns and a lack of convincing evidence of effectiveness (Kidner 2009; Chapman 2010; Bohnert 2012). Evidence of utilisation of larger doses of opioids for the treatment of CNCP is emerging. For example, one analysis of Workers' Compensation Board (WCB) data (where the vast majority of claimants with pain would have non-malignant pain) from Manitoba, Canada, has demonstrated a dramatic increase in the average opioid dose prescribed over time from less than 500 morphine milligram equivalents per year in 1998 to over 6000 morphine milligram equivalents 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 often continues postclaim, and both duration and dose of postclaim opioid use are correlated to the dose during the claim (Shafer 2015). The rate of dispensing high-dose opioids at doses of 200 morphine milligram equivalents per day or greater increased in Canada by 23% between 2006 and 2011 (Gomes 2014). Similar increases are now commonly seen across the world, including in the US and in the UK (Zin 2014).

The use of opioids for CNCP has come under scrutiny due to questions about their effectiveness and the potential for adverse events, abuse, and addiction (NOUGG 2010; Franklin 2014; Häuser 2014; Nuckols 2014; Katz 2015). In the 1980s, Portenoy

and Foley described an addiction risk of lower than 1% (Portenoy 1986). However, 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 drugs are used for the management of severe pain (Kosten 2002; Huffman 2015; Vowles 2015).

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

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 US (60%) occur in people given prescriptions based on prescribing guidelines by medical boards (with 20% of deaths for doses of at most 100 morphine milligram equivalents per day, and 40% in people receiving dosages above that threshold). The remaining 40% of deaths occurred in people abusing the drugs (e.g. multiple prescriptions, double-doctoring, drug diversion) (Manchikanti 2012a).

A consensus is emerging that long-term opioid therapy for CNCP may be appropriate only for well-selected populations (Manchikanti 2012b).

OBJECTIVES

To assess adverse events associated with medium- and long-term use of opioids for CNCP.

METHODS

We will provide an overview of the evidence from Cochrane Reviews for adverse events with any opioid agent used at any dose, and administered by any route and frequency of administration, for the treatment of CNCP in adults.

Medium- and long-term opioid use have been variably defined. For our overview, we will define opioid use between two weeks and two months as medium-term, and two months or longer as long-term use.

Typically, we would expect trial durations of at least two weeks to be relevant for a chronic painful condition. We will critically assess reviews including shorter trials, and if the majority of data

are from inappropriately short trials, we will exclude these reviews, depending on the condition studied.

Criteria for considering reviews for inclusion

We will include all Cochrane Reviews that assess medium- or long-term opioid use for CNCP due to any condition in adults. The reviews will have to report our specified adverse event outcomes. We plan to analyse data from randomised controlled trials and other study designs separately.

Search methods for identification of reviews

We will search the most recent issue of the Cochrane Database of Systematic Reviews (the Cochrane Library). The search strategy is presented in Appendix 1.

Data collection and analysis

Selection of reviews

Two review authors will independently screen the results of the electronic search by title and abstract. We will obtain the full-text versions of the reviews that are deemed potentially relevant and will subsequently apply the selection criteria to determine final inclusion. We will resolve disagreements by discussion; or in the event of failing to achieve consensus, by contacting a third review author; we will then decide by majority vote.

Data extraction and management

Two review authors will independently extract data using a standardised and piloted (on 3 reviews) data extraction form. We will resolve discrepancies by consensus. When we cannot achieve resolution, we will consult a third review author and make a majority decision.

We will extract data on the following:

- citation details;
- conditions studied;
- number of included studies;
- study and participant characteristics;
- opioid medications used, doses, and frequencies of administration;
- adverse event outcomes.

The adverse event outcomes will be:

- number of participants with any adverse event;
- number of participants with any serious adverse event;
- number of deaths;

- number of participants who withdrew from the studies due to adverse events;
- number of participants experiencing the following specific adverse events (of any severity):
 - constipation;
 - respiratory depression;
 - sleep apnoea or sleep-disordered breathing;
 - infection;
 - cognitive dysfunction;
 - hypogonadism or other endocrine dysfunction;
 - xerostomia;
 - depressive symptoms or other mood disturbances;
 - sexual dysfunction;
 - addiction.

Specific adverse events and categories of adverse events may be variably named between the trials and reviews; we will accept different terminology as long as it pertains to these concepts. In the overview, we will detail which terms are considered to describe the same concept. Should we discover that other adverse events are described frequently, we will add them to our list. Where the reporting of adverse events is specific by sex or ethnicity, such data will also be extracted. We primarily aim to compare opioids to control groups receiving placebo; comparisons of opioids versus non-opioid treatments will be a supplementary analysis, if there are sufficient data.

We will include an outcome matrix to show which outcomes were extractable from which reviews.

Assessment of methodological quality of included reviews

One overview of Cochrane Reviews on adverse events associated with treatments for acute pain has established appropriate criteria (adapted from the AMSTAR guidance (Assessing the Methodological Quality of Systematic Reviews; [Shea 2007](#))) for the quality assessment of the Cochrane Reviews to be included in an overview ([Moore 2015](#)). Following this example, we will assess the reviews with the following questions.

- Was an a priori design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Were published and unpublished studies included irrespective of language of publication?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?

- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was a conflict of interest stated?

Data synthesis

We will perform qualitative and quantitative evidence syntheses, as appropriate. For meta-analysis, we will use a fixed-effect model or alternatively a random-effects model as determined by between-study heterogeneity (I^2 statistic). In addition to assessing statistical heterogeneity, we will also consider clinical heterogeneity between the studies. A fixed-effect model will be used when there is no evidence of significant heterogeneity of either type. We will calculate risk ratios with 95% confidence intervals. We will calculate numbers needed to treat for an additional harmful outcome from the pooled number of events using the method of Cook and Sackett ([Cook 1995](#)). The methodology for our overview and for meta-analyses will be according to the guidance detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will perform our analyses across opioid agents (by conversion to morphine equivalents) and for the individual drugs. We plan to conduct separate analyses by trial duration.

We will assess the quality of evidence on adverse events associated with medium- and long-term use of opioids for CNCP using the GRADE approach as applied in Cochrane Reviews ([Higgins 2011](#)). See [Appendix 2](#) for a further description of the GRADE system.

ACKNOWLEDGEMENTS

This protocol complements another Cochrane overview protocol titled “High-dose opioids for chronic non-cancer pain: an overview of Cochrane reviews” ([Els 2016](#)). For consistency and following discussion with the Cochrane Pain, Palliative and Supportive Care editorial office, we have re-used text from that protocol for the present protocol.

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* Indicates the major publication for the study

APPENDICES

Appendix 1. The Cochrane Library search strategy

#1 MeSH descriptor: [Pain] explode all trees

#2 pain*:ti,ab,kw

#3 #1 or #2

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

#5 opioid*:ti,ab,kw

#6 codeine or oxycodone or tramadol or hydromorphone or morphine or fentanyl:ti,ab,kw

#7 meperidine or pethidine or dextropropoxyphene or methadone or buprenorphine or pentazocine or hydrocodone or opium or butorphanol:ti,ab,kw

#8 tapentadolol or papaveretum or meptazinol or dipipanone or dihydrocodeine or diamorphine:ti,ab,kw

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

#10 #3 and #9

Appendix 2. 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).

CONTRIBUTIONS OF AUTHORS

All authors have contributed to drafting this protocol.

DECLARATIONS OF INTEREST

Charl Els: none known.

Diane Kunyk: none known.

Vernon G Lappi: none known; Vernon G Lappi is a specialist occupational medicine physician and the retired Director of Medical Services at the Workers' Compensation Board of Alberta. Since his retirement, he has been a consultant to the Workers' Compensation Board of Alberta. His past practice has included patients with chronic pain.

Barend Sonnenberg: none known; Barend Sonnenberg is a Medical Consultant for the Workers' Compensation Board of Alberta and has been involved with the Workers' Compensation Board of Alberta's opioid project since 2006, which includes file reviews of cases where opioid analgesics have been prescribed.

Reidar Hagtvedt: none known.

Sangita Sharma: none known.

Fariba Kolahdooz: none known.

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External sources

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