Nonopioid drug combinations for cancer pain: protocol for a systematic review

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Abstract

Introduction: Pain related to cancer, and its treatment, is common, may severely impair quality of life, and imposes a burden on patients, their families and caregivers, and society. Cancer-related pain is often challenging to manage, with limitations of analgesic drugs including incomplete efficacy and dose-related adverse effects.

Objectives: Given problems with, and limitations of, opioid use for cancer-related pain, the identification of nonopioid treatment strategies that could improve cancer pain care is an attractive concept. The hypothesis that combinations of mechanistically distinct analgesic drugs could provide superior analgesia and/or fewer adverse effects has been tested in several pain conditions, including in cancer-related pain. Here, we propose to review trials of nonopioid analgesic combinations for cancer-related pain.

Methods: Using a predefined literature search strategy, trials—comparing the combination of 2 or more nonopioid analgesics with at least one of the combination’s individual components—will be searched on the PubMed and EMBASE databases from their inception until the date the searches are run. Outcomes will include pain intensity or relief, adverse effects, and concomitant opioid consumption.

Results/Conclusions: This review is expected to synthesize available evidence describing the efficacy and safety of nonopioid analgesic combinations for cancer-related pain. Furthermore, a review of this literature will serve to identify future research goals that would advance our knowledge in this area.

Keywords: Cancer pain, Drug combinations, Opioid therapy, Analgesic therapy, Clinical trials, Systematic review

1. Introduction

Cancer is a leading cause of morbidity and mortality, accounting for nearly 10 million deaths annually worldwide.7,36 Up to 80% of cancer patients experience pain as a symptom of their cancer or related to treatment modalities.22,37 Pain often interferes with physical, emotional, social, and occupational functioning, is multifactorial in nature, and is difficult to manage. Hence, pain poses a significant burden to patients’ activities of daily living, relationships, and overall quality of life. Although considerable clinical activity and research is devoted to cancer-related pain, many knowledge and treatment gaps remain. Pain related to cancer, and its treatment, may be related to various different etiologies including: (1) tumour infiltration or compression of bone, viscera, soft tissues, and/or nerves; (2) damage or irritation of tissues or nerves by various chemotherapeutic agents and also by radiation therapy; and (3) persistent nociceptive or neuropathic pain after cancer surgery.33 As such, underlying pathophysiology of cancer-related pain may be nociceptive, neuropathic, or mixed.4,6

Multimodal, multidisciplinary approaches are often used to manage cancer-related pain,2,12,26 and analgesic drug therapy continues to play a substantial role starting, historically, from the World Health Organization’s “analgesic stepladder” algorithm—starting with acetaminophen or a nonsteroidal anti-inflammatory drug, and adding mild opiates (e.g., codeine) and then strong opiates (e.g., morphine) as needed.21,27 A growing understanding of different pain pathophysiologies (eg, nociceptive vs neuropathic) and development of drugs to treat neuropathic pain (eg, antidepressants and anticonvulsants) has expanded diversified pharmacological approaches to the treatment of various cancer-related pain conditions.3,12,33
As introduced above, opioids have long been used to manage cancer-related pain.\(^8\,26\,30\) Their effective implementation and prescribing requires a balance between reducing moderate-to-severe pain and managing dose-related side effects such as sedation, cognitive dysfunction, and opioid-induced bowel dysfunction.\(^32\) Earlier use of opioids for cancer-related pain was quite often associated with end-of-life care; however, over the past 2 decades, we have seen the emergence of: (1) increasing cancer survivorship due to introduction of more effective cancer treatments\(^36\); and (2) a crisis of oversupply and overuse of opioids in some parts of the world (particularly North America)—largely in the setting of chronic noncancer pain and opioid misuse.\(^23\) Thus, several regions, particularly in North America, have seen increased scrutiny and regulation over opioid prescribing—even for cancer-related pain.\(^1\,11\,27\) These issues have had an impact on the delivery of pain management to patients suffering from cancer-related pain and—in addition to finding more effective pain therapies as well as minimizing opioid-related problems—have also emphasized the need to develop new nonopioid pain treatment strategies.\(^31\)

In the setting of chronic noncancer pain, a considerable number of trials have evaluated analgesic drug combinations.\(^10\,13\,17\,20\,30\,35\) In theory, combinations of 2 mechanistically distinct analgesic drugs may have additive, or sometimes even synergistic, interactions with regards to analgesia, such that a lower dose of each drug would be needed to achieve the same, or possibly greater, analgesic effect, which may also reduce the incidence of adverse effects.\(^5\,18\,29\,34\) In support of this theory, several clinical trials have demonstrated superior pain reduction with certain combinations of analgesic drugs in the setting of chronic noncancer pain treatment.\(^10\,13\,17\,20\,30\,35\) Of note, several of these trials involved combinations of nonopioid analgesic drugs.\(^13\,15\,20\)

Various nonopioid analgesic drugs (including antidepressants and anticonvulsants) that were initially developed for noncancer pain have been evaluated in treating cancer-related pain with varying degrees of success.\(^22\) Observations of sometimes modest effects of such agents could be, in part, because many studies are conducted in an “add-on” fashion such that trial participants are already receiving substantial doses of opioids and cannot tolerate the addition of high enough doses of the study analgesic, which may have side effects additive to those of opioids (eg, sedation).\(^9\) If nonopioid analgesic drugs can be initiated earlier in a patient’s pain management course and thus at a lower opioid dose, the potential to tolerate and receive higher doses of the nonopioid could result in a more favourable opioid-to-nonopioid drug dose ratio.\(^16\) Furthermore, there is a potential for even greater efficacy with double-drug combinations of nonopioid analgesics and this has led to related clinical trials in the setting of cancer-related pain. Thus, the present systematic review seeks to synthesize available evidence on the safety and efficacy of nonopioid drug combinations for the management of cancer-related pain.

### 2. Methods

This protocol was developed in accordance with PRISMA-P guidelines\(^23\) and is in the process of being registered in the PROSPERO registry (protocol number pending).

#### 2.1. Sources of evidence

We will conduct a detailed search on PubMed (Medical Literature Analysis and Retrieval System Online), the Cochrane Central Register of Controlled Trials, and EMBASE databases—from their inception until the date the searches are run—as per a predefined search strategy (Appendix 1, available at http://links.lww.com/PR9/A88). The literature search was developed and will be conducted in collaboration with an expert library scientist. We will also review the bibliographies of any systematic reviews and randomized controlled trials (RCTs) identified for relevance, as well as search clinical trial databases (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform to identify additional published or unpublished data.

#### 2.2. Report selection

##### 2.2.1. Types of studies

The review will include RCTs, published in any language, comparing the combination of 2 or more nonopioid analgesics to at least one of the combination’s individual components, and/ or placebo in reducing cancer-related pain.

##### 2.2.2. Types of participants

We will include studies with adults aged 18 years and older reporting pain directly related to any type of cancer and/or cancer treatment, such as chemotherapy, radiation therapy, and cancer surgery.

##### 2.2.3. Types of interventions

We will focus on all systemically administered combinations of 2 or more nonopioid analgesics. Drugs of interest will include, but not be limited to: anticonvulsants (ie, gabapentin, pregabalin), antidepressants (ie, duloxetine, imipramine), and nonsteroidal anti-inflammatory drugs (ie, diclofenac, paracetamol).

##### 2.2.4. Comparators

We will focus on studies that compare the combination of interest to at least one of the combination’s individual components, and/ or placebo.

#### 2.3. Data collection, extraction, and management

Two reviewers will independently evaluate studies for eligibility. Screening will be performed on titles and abstracts, and full-text screening will be performed on citations felt to be potentially eligible. Disagreements between the reviewers will be resolved by discussion and consensus. If necessary, a third reviewer will be consulted. Data from selected studies will be extracted independently by 2 reviewers using standardized extraction forms. Information regarding the study design and methodology, numbers of participants, intervention, comparator, primary and secondary outcomes, and other study characteristics will be extracted. In particular, we will extract the following data from each study included: study drug name(s), dose(s), route(s), and study/treatment duration; proportion of participants (1) reporting ≥30% pain
reduction from baseline OR ≥ moderate pain relief OR ≥ moderate global improvement (note: “moderate pain relief” and “moderate global improvement” will be recorded based on each trial’s individual definition of these terms, if relevant. We will take note of the definition in each trial if this is the case, and consider this in our analysis); (2) dropping out of the study due to treatment-emergent adverse effects; (3) reporting each specific adverse effect (eg, sedation, dizziness).

2.4. Outcomes
We will include participant-reported measures of pain intensity or pain relief using validated methods. The primary outcome will be the proportion of participants reporting ≥30% pain reduction from baseline OR ≥ moderate pain relief OR ≥ moderate global improvement. Secondary outcomes will be: (1) continuous measures of pain intensity or pain relief using validated measures (eg: use of a visual analogue scale measure of pain intensity, or similar methods); (2) the proportion of participants dropping out of the study due to treatment-emergent adverse effects; (3) the proportion of participants reporting each specific adverse effect (eg, sedation, dizziness); and (4) opioid consumption as measured by the morphine equivalent daily dose.

2.5. Analysis plan
2.5.1. Assessment of risk of bias
Risk of bias for each study will be independently assessed by 2 reviewers using the Cochrane Collaboration’s Risk of Bias tool for RCT studies.19 Disagreements between reviewers will be resolved with discussion and consensus. If necessary, a third reviewer will be consulted. We will assess the following for each study: (1) random sequence generation for possible selection bias; (2) allocation concealment for possible selection bias; (3) blinding of participants and personnel for possible performance bias; (4) blinding of outcome assessment for possible detection bias; (5) incomplete outcome data for possible attrition bias; (6) selective reporting for possible reporting bias; and (7) size of study for possible biases confounded by small sample size. Each category will be assigned a low, unclear, or high risk of bias, and presented with a “Risk of bias” graph and “Risk of bias” summary.

2.5.2. Measures of treatment effect
The primary comparison of interest, for all outcomes of interest, is between study drug(s) and one or both single-agent comparators. We will also search for comparisons of each two-drug combination and any other placebo and/or active treatment comparators. We will combine studies if they evaluated the same drug class combination at roughly similar doses and durations of treatment and in similar clinical conditions/settings. We will use RevMan 5 (RevMan 2014) to analyse study data for binary outcomes.

2.5.3. Measures of adverse events
We will record the nature and incidence of adverse events experienced by patients in each included trial to understand the safety profile of the trial drug combination and comparators. In addition, we are interested in the proportion of patients within each trial group who drop out of the study due to adverse events as an indication of severity.

2.5.4. Assessment of heterogeneity
We will only combine studies evaluating similar conditions for analysis so as to avoid clinical heterogeneity. We will use visual data assessment with L’Abbé plots24 and to calculate the I² statistic to explore statistical heterogeneity when the I² is greater than 50%.

3. Discussion
To the best of our knowledge, this will be the first systematic review of evidence on the safety and efficacy of nonopioid drug combinations in the treatment of cancer-related pain. As discussed above, cancer-related pain is a highly burdensome disease-related or treatment-related symptom and may benefit from a multimodal treatment approach. We expect that completion of this systematic review will help to consolidate our understanding of current best practices in treating cancer-related pain. Given the possibility that 2 different analgesic drug classes may provide additive analgesia, but may also result in additive adverse events, careful examination of evidence from included trials could help provide estimates of the risk–benefit profiles for drug combinations that have been studied to date. Because one of our planned secondary outcomes is concomitant opioid use, we also anticipate that included evidence may describe any opioid-sparing effects for studied combinations. This could help guide approaches to both reducing opioid doses as well as improving analgesia and side-effect profiles during the management of cancer-related pain.

We recognize that evidence may be lacking for some specific drug combinations and also for some specific cancer-related pain conditions. Thus, conducting our planned broad search of the literature will further serve to develop an agenda of future research needs in the study of nonopioid analgesic combinations for cancer-related pain. Such needs may include the study of new drug combinations not previously studied, certain understudied cancer-related pain conditions, and also methodological challenges for trials in this area.

In conclusion, given the many challenges and knowledge gaps associated with cancer pain management, this planned systematic review will serve to synthesize available evidence on nonopioid analgesic drug combination for cancer-related pain. Furthermore, careful review of this literature will serve to identify future research goals that will advance our knowledge in this area.

Disclosures
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