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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,[2,12,28] 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 (eg, codeine) and then strong opiates (eg, 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.[3,32,33]

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As introduced above, opioids have long been used to manage cancer-related pain.[8,26,38] 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.[33] 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[25] 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 analgesic drugs. 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 plots[24] and to calculate the I^2 statistic to explore statistical heterogeneity when the I^2 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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References

[1] Asthana R, Goodall S, Lau J, Zimmermann C, Diaz PL, Wan AB, Chow E, De Angelis C. Framing of the opioid problem in cancer pain management in Canada. Curr Oncol 2019;26:e410–13.
[2] Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. Pain. 1991;47(2):129-128.; Soares LG, Chan VW. The rationale for a multimodal approach in the management of breakthrough cancer pain: a review. Am J Hosp Palliat Care 2007;24:430–9.
[3] Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. PAIN 2001;92:147–57.
[4] Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. PAIN 2019;160:38–44.
[5] Berenbaum MC. What is synergy? Pharmacol Rev 1989;41:93–141.
[6] Bouhassira D, Luporsi E, Krakowski I. Prevalence and incidence of chronic pain with or without neuropathic characteristics in patients with cancer. PAIN 2017;158:1118–25.
[7] Cancer—key facts: World Health Organization, 2018. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed March 19, 2020.
[8] Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58–68.
[9] Caraceni A, Zecca E, Bonezzi C, Arcuri E, Yaya Tur R, Maltoni M, Visentin M, Gorni G, Martini C, Tirelli W, Barbieri M, De Conno F. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004;22:2909–17.
[10] Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev 2012;7:CD008943. doi: 10.1002/14651858.CD008943.pub2. Review.
[11] Dalal S, Bruera E. Pain management for patients with advanced cancer in the opioid epidemic era. Am Soc Clin Oncol Educ Book 2019;39:24–35.
[12] Feldstain A, Bultz BD, de Groot J, Abdul-Razzak A, Herx L, Galloway L, Chary S, Sinnarajah A. Outcomes from a patient-centered, interprofessional, palliative consult team in oncology. J Natl Compr Canc Netw 2018;16:719–726.
[13] Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 2009;374:1252–61.
[14] Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324–34.
[15] Gilron I, Chaparro LE, Tu D, Holden RR, Milev R, Towheed T, DuMerton-Shore D, Walker S. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. PAIN 2016;157:1532–40.
[16] Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013;12:1084–95.
[17] Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. PAIN 2015;156:1440–8.
[18] Guan J, Tanaka S, Kawakami K. Anticonvulsants or antidepressants in combination pharmacotherapy for treatment of neuropathic pain in cancer patients: a systematic review and meta-analysis. Clin J Pain 2016;32:719–25.
[19] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928.
[20] Holbech JV, Bach FW, Finnerup NB, Brøsen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. PAIN 2015;156:958–66.
[21] Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA 1995;274:1870–3.
[22] Kane CM, Mulvey MR, Wright S, Craigs C, Wright JM, Bennett MI. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: systematic review and meta-analysis. Palliat Med 2018;32:276–86.
[23] Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health 2015;36:559–74.
[24] L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987;107:224–33.
[25] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[26] Moulin DE, Kreeft JH, Murray-Parsons N, Bouquillon AI. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. Lancet 1991;337:465–8.
[27] Paice JA. Cancer pain management and the opioid crisis in America: how to preserve hard-earned gains in improving the quality of cancer pain management. Cancer 2018;124:2491–7.
[28] Peng WL, Wu GJ, Sun WZ, Chen JC, Huang AT. Multidisciplinary management of cancer pain: a longitudinal retrospective study on a cohort of end-stage cancer patients. J Pain Symptom Manage 2006;32:444–52.
[29] Raffa RB, Clark-Vetri R, Tallarida RJ, Wertheimer AI. Combination strategies for pain management. Expert Opin Pharmacother 2003;4:1697–708.
[30] Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, Landewé RB. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev 2011;10:CD008886. doi: 10.1002/14651858.CD008886.pub2.
[31] Schenker Y, Merlin JS, Quill TE. Use of palliative care earlier in the disease course in the context of the opioid epidemic: educational, research, and policy issues. Jama 2018;320:871–2.
[32] Singh VK, Shetty YC, Salins N, Jain P. Prescription pattern of drugs used for neuropathic pain and adherence to NeuPSIG guidelines in cancer. Indian J Palliat Care 2020;26:13.
[33] Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, Chwistek M, Cleeland C, Craig D, Gafford E, Greenlee H. Adult cancer pain, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2019;17:977–1007.
[34] Tallarida RJ. Drug synergism: its detection and applications. J Pharmacol Exp Ther 2001;298:865–72.
[35] Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I. Combination pharmacotherapy for the treatment of fibromyalgia in adults. Cochrane Database Syst Rev 2018;2:CD010585.
[36] Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.
[37] van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51:1070–90.e9.
[38] Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain – an overview of Cochrane reviews. Cochrane Database Syst Rev 2017;7:CD012592.