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Nonopioid drug combinations for cancer pain: a systematic review

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Abstract

Pain is highly prevalent in patients with cancer—nearly 40% report moderate-severe pain, which is commonly treated with opioids. Increasing cancer survivorship, opioid epidemics in some regions of the world, and limited opioid access in other regions have focused attention on nonopioid treatments. Given the limitations of monotherapy, combining nonopioids—such as antiepileptics and antidepressants—have shown promise in noncancer pain. This review seeks to evaluate efficacy of nonopioid combinations for cancer-related pain. Systematic searches of PubMed, EMBASE, and Cochrane CENTRAL were conducted for double-blind, randomized, controlled trials comparing a nonopioid combination with at least one of its components and/or placebo. This search yielded 4 randomized controlled trials, published between 1998 and 2019 involving studies of (1) imipramine + diclofenac; (2) mitoxantrone + prednisone + clodronate; (3) pentoxifylline + tocopherol + clodronate; and (4) duloxetine + pregabalin + opioid. In the first 3 of these trials, trends favouring combination efficacy failed to reach statistical significance. However, in the fourth trial, duloxetine + pregabalin + opioid was superior to pregabalin + opioid. This review illustrates recognition for the need to evaluate nonopioid drug combinations in cancer pain, although few trials have been published to date. Given the growing practice of prescribing more than 1 nonopioid for cancer pain and the need to expand the evidence base for rational combination therapy, more high-quality trials in this area are needed.

Keywords: Cancer pain, Analgesia, Adjuvants, Opioids, Pain medicine

1. Introduction

Cancer accounts for an increasingly large proportion of the global disease burden with approximately 18 million new cases diagnosed each year.[3] Pain resulting from malignant processes or their treatment—cancer pain—is extremely common, affecting up to 80% of patients with cancer.[20,36] It can have debilitating psychological, physical, and social effects, profoundly affecting patients' quality of life and functioning. Cancer pain may result from many possible etiologies, including local and distant effects of the neoplasm and side effects of cancer treatment, and is thus complicated to treat. There is currently no gold standard management available, despite significant research efforts and funds directed at improving quality and quantity of life of patients with cancer.[29,30]

Broadly, chronic cancer pain is classified by the International Association for the Study of Pain based on its etiology as tumour related or treatment related. Chronic tumour-related cancer pain may be either visceral or somatic, bony or nonbony, and neuropathic or nociceptive in nature, whereas chronic posttreatment cancer pain is related to medication, radiation, or surgery.[1] Chronic pain is that which lasts at least 3 months.[1] As a result of these mechanisms, patients with cancer experience pain through the nociceptive or neuropathic pathways, or both.[2,20]

The current mainstay of therapy for chronic cancer pain follows the World Health Organization's "analgesic stepladder' approach, whereby mild, moderate, and severe pain are treated primarily with drug therapies of increasing potency.[6,20] The designations of pain severity are based on a 10-point self-reported pain score, whereby mild pain is rated at 1 to 3, moderate at 4 to 7, and severe at 8 or higher.[35] Recommended treatment begins with nonopioid medications (acetaminophen,

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nonsteroidal anti-inflammatory agents [NSAIDs]) for mild–moderate pain. Moderate–severe pain is treated first with weak opioids (ie, codeine) and is then titrated to the minimally effective dose of strong opioids, if needed.[6,12] Controversy exists surrounding the value of weak opioids in cancer pain management. Recent evidence suggests that patients may benefit from the omission of this step, although it remains important in certain countries where access to strong opioids is limited.[32]

A 2016 systematic review and meta-analysis reported that 38% of all patients with cancer experience at least moderate pain and patients are often started on opioid medications early in their clinical course.[36] Although widely acknowledged as effective analgesics, opioid medications are not without risk. Common adverse effects include sedation, cognitive dysfunction, physical dependency, and opioid-induced constipation. Opioids also have a propensity for addiction due to their neurobiological effect on endogenous opioid receptors and activation of the brain's reward system.[22] As new therapies are developed to increase survival years with cancer, it becomes increasingly important to preserve quality of life for long-term survivors suffering from chronic pain. The public health epidemic of overdose deaths in North America and elsewhere has drawn attention to opioid-prescribing practices at every level of the health care system, including for patients with cancer and has brought attention to the need for alternate means of therapy.[21,23,36] This "opioid crisis" creates challenges in the management of cancer pain, including potentially limited access to strong opioids, the need for strategies to prevent substance use disorder, and guidelines for pain management in cancer patients who are current or former substance users.[28] These factors may contribute to suboptimal pain management for patients with cancer.

Several nonopioid drugs have demonstrated efficacy in the management of chronic pain. For example, antidepressant and anticonvulsant medications have long been prescribed for the management of neuropathic pain in cancer and noncancer settings.[7,8,14–17] More recently, evidence has emerged for the benefit of combining drugs to treat pain.[15] Two or more mechanistically different analgesics could have additive or synergistic effects when used together, lowering the dose of each and the intensity of their respective side effect profiles.[15,17] This hypothesis has been evaluated in several clinical trials conducted in a noncancer setting, with promising results. The present systematic review aims to summarize the findings of clinical trials that have evaluated nonopioid drug combinations for cancer pain treatment. We will report on the availability and quality of current evidence and synthesize information on the safety and efficacy of nonopioid drug combinations for cancer pain management.

2. Methods

The protocol for this review has been published previously[34] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42020183689 on August 20, 2020. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to in preparing this review.

2.1. Study selection

The review included double-blinded, randomized controlled trials (RCTs), published in any language, comparing a 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. Both parallel and crossover study designs were considered. Nonrandomized and/or nonblinded studies were excluded.

2.2. Participants

We included studies of adults (aged 18 years and older) reporting pain of any etiology directly related to cancer and/or cancer treatment, such as chemotherapy, radiation therapy, and cancer surgery.

2.3. Interventions

This review included orally administered combinations of 2 or more nonopioid analgesic drugs.

2.4. Comparators

We focused on studies which compared the nonopioid combination of interest (the intervention) with at least one of its individual components and/or placebo.

2.5. Primary outcome

The outcome of included trials was patient-reported cancer pain intensity or pain relief, measured using a validated instrument or scale, such as a visual analog scale. Our study's primary outcome was the proportion of participants reporting ≥30% pain reduction from baseline OR at least moderate pain relief OR at least moderate global improvement.

2.6. Secondary outcomes

Data about the following variables were also extracted, when available: (1) continuous measures of pain intensity or pain relief using validated measures; (2) the proportion of participants dropping out of the study due to treatment-emergent adverse effects; and (3) the proportion of participants reporting each specific adverse effect (eg, sedation, dizziness). We also recorded the incidence and nature of adverse events.

2.7. Identification of studies

We conducted a detailed search of the PubMed (Medical Literature Analysis and Retrieval System Online), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception point to the date the search was completed (June 5, 2020). The literature search strategy was developed iteratively in collaboration with an expert library scientist (S.H.). An example search strategy is attached (Appendix 1, available as supplemental digital content at http://links.lww.com/PR9/A152). The search strategy included terms specific to etiologies of cancer pain (eg, "neuropathic"), pain syndromes (eg, mucositis), and broad categories of nonopioid analgesics (eg, "anticonvulsants") to ensure that all relevant articles would be retrieved in our search. We also hand searched the reference lists of all RCTs we chose to include in our study, as well as those of relevant systematic reviews on the subject.[10,12–19] Finally, expert clinicians in the fields of anaesthesiology, pain medicine, oncology, and palliative care were consulted for their knowledge of any ongoing or recently published studies. All citations were then exported to Covidence© software for review.

2.8. Study evaluation

Two reviewers (G.S. and N.L.) independently evaluated study eligibility in 2 phases. First, titles/abstracts were screened; citations were excluded if they clearly were irrelevant to our study or did not satisfy our eligibility criteria. The full texts of any citations marked for further review were then evaluated. Disagreements between reviewers were resolved through discussion and consensus; if necessary, the senior author (I.G.) made final decisions. A PRISMA flow chart detailing this process is below (**Fig. 1**).

2.9. Excluded studies

In nearly all cases, the reason for excluding any given study was that it did not follow our criteria for study designs of interest (double-blinded RCTs). Additionally, we found that many studies were necessarily excluded because they failed to compare a drug combination of interest to either an individual component drug or placebo in isolation. Finally, studies were also excluded if the intervention also included procedural analgesic methods (ie, nerve blocks).

2.10. Data extraction

Data extraction was completed by a single reviewer (G.S.) in consultation with the senior author (I.G.). A standardized data extraction form on Microsoft Excel was adapted for this study. We extracted information about the study design, patient population, study drug combination and comparators, routes of administration, dosages, trial duration, pain control, any secondary outcomes reported, and the nature and incidence of adverse events.

2.11. Assessment of risk of bias

Two blinded reviewers (G.S. and I.G.) independently assessed risk of bias for each of the included studies using criteria outlined in the Cochrane Handbook for Randomized Controlled Trials.[19] Both reviewers provided evidence to substantiate their assessment of bias from the text of each study, and disagreements were resolved through consensus. The standard categories for risk of bias as outlined by the Cochrane guidelines were assessed. We also evaluated the sample size, having decided a priori that a study with fewer than 50 individuals per treatment arm would be considered at high risk of bias.[8,27] Each domain was assigned a risk of bias score (low/unclear/high); we summarized these data and present a corresponding graph (**Fig. 2**).

2.12. Method of analysis and assessment of heterogeneity

We decided a priori to only combine sufficiently similar studies (ie, if they evaluated the same drug class combination at roughly similar doses and durations of treatment and in similar clinical conditions/settings) in order to avoid clinical heterogeneity. We planned to use visual data assessment with L'Abbé plots and to calculate the I^2 statistic to explore statistical heterogeneity when the I^2 is greater than 50%. However, given the extremely small number of studies included in our final results, it became evident that they were far too distinct to summarize accurately. Based on this qualitative assessment of heterogeneity, we chose to forego meta-analysis and present results as they were reported in each study. No subgroup analyses were planned for the present study.

3. Results

The systematic search retrieved a total of 9823 studies across 3 databases (PubMED, EMBASE, CENTRAL). The references were imported to Covidence, and 1680 duplicates were removed. Thirty additional citations were retrieved through hand-searching–relevant reference articles. This left 8143 citations to review for inclusion, many of which were obviously irrelevant from the title. Given this large volume of titles and abstracts to review and the specific eligibility criteria for our study, the reviewers decided via consensus to conduct title/abstract and full-text screening concurrently. Twenty-seven articles were assessed in full, and 4 were suitable for inclusion in this review.[9,10,25,26] Most

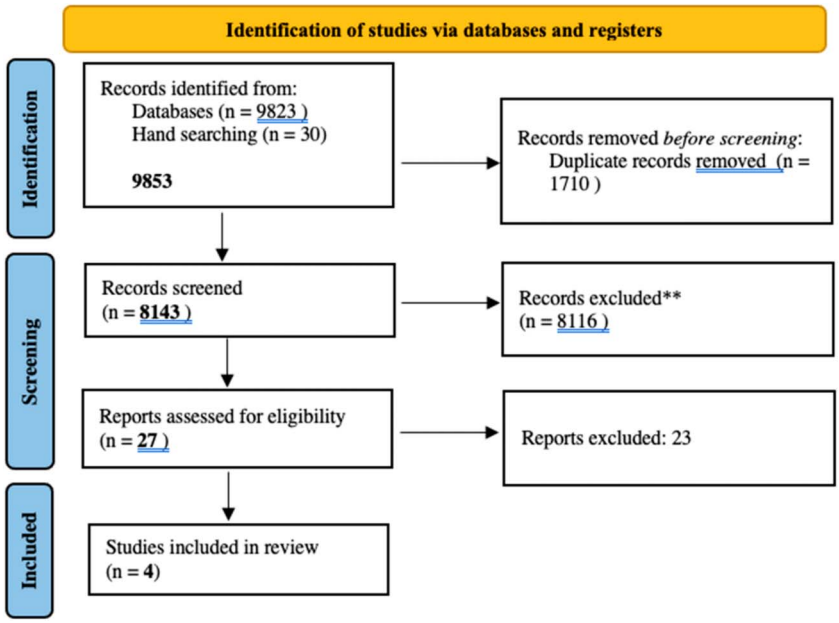

Figure 1. PRISMA flow chart showing study inclusion for this systematic review.

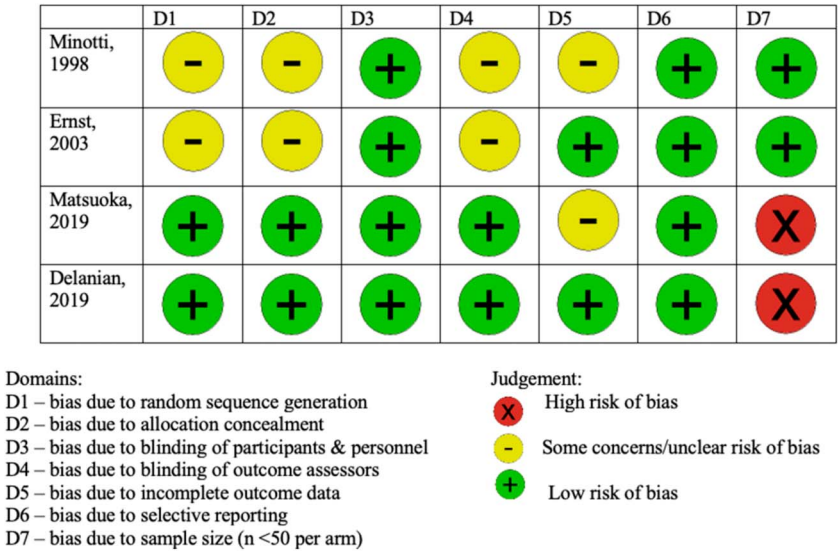

Figure 2. Risk of bias visual summary for included studies.

studies were excluded at this stage if they were not double blinded or if they did not compare the drug combination of interest to either an individual component drug or placebo. The study selection process is illustrated in **Figure 1**.

Table 1 describes the studies included in this systematic review. Minotti et al.[26] evaluated the efficacy and tolerability of the NSAID diclofenac sodium (50 mg 4 times a day) with placebo, vs in combination with codeine phosphate (40 mg 4 times a day) or imipramine (10 or 25 mg 3 times a day) in treating chronic cancer pain.[26] The trial was conducted between 1989 and 1993 and included 184 patients with tumour-related cancer pain at a single centre. Pain relief was measured 8 days after enrolment, defined by the investigator's global assessment of a patient's pain on a 4-point scale ("unsatisfactory = 1", "moderate = 2", "good = 3", "excellent = 4"). Adequate pain control was defined as a 50% reduction in pain intensity from baseline. There were no significant differences in pain scores at the midpoint or at study end; pain control was inadequate in all 3 study arms. The diclofenac/imipramine combination provided at least moderate pain relief in 68.9% of patients; 65.6% of diclofenac/codeine patients and 56.5% of the diclofenac/placebo patients experienced moderate pain relief after 8 days of treatment. The incidence of adverse events was high: gastrointestinal discomfort, dry mouth, and neurologic symptoms were reported by patients in all 3 groups but were most common in the diclofenac/codeine group (90.7%). This group also experienced the highest attrition rate due to adverse events (13.3%, compared with 2.3% in the imipramine group and 5.3% in the placebo group).[26]

Ernst et al.[10] compared a combination of mitoxantrone (12 mg/m^2, once every 3 weeks) and prednisone (5 mg, 2 times a day) (MP) with clodronate (1500 mg, intravenously once every 3 weeks) with MP and placebo in patients with boney cancer pain from hormone-refractory prostate cancer. This trial had an average follow-up duration of 21 months, and 227 patients were included across 17 Canadian sites. At the primary trial end point (reduction in pain without an increase in analgesic use or reduction in analgesic use without an increase in pain), 45% of patients in the MP clodronate group and 39% of patients in the MP placebo group achieved adequate pain control, which was not statistically significant.[10] The rate of adverse events was similar between the 2 groups (44% in the clodronate group and 43% in the placebo group).

Matsuoka et al.[24] compared a combination of duloxetine with an opioid/pregabalin combination to opioid/pregabalin alone for neuropathic or nociceptive chronic pain from cancer.[25] Patients with both tumour-related and treatment-related pain were included, although the authors did not describe pain etiology for each patient. Seventy patients were enrolled across 12 centres in Japan—patients were eligible if they were experiencing moderate-to-severe pain within the past 24 hours and were either intolerant of, or nonresponsive to, opioid–pregabalin combination therapy. The active intervention group received a starting dose of 20-mg duloxetine per day, titrated up to 40 mg; the trial duration was 10 days. In the duloxetine group, 44.1% of patients reported meaningful pain reduction (a decrease in pain score of at least 30% from baseline) compared with 18.2% in the placebo group. Similarly, 32.1% of patients in the duloxetine group reported pain reduction of greater than 50% from baseline, whereas only 3.0% of patients in the placebo group reported the same. There was a statistically significant change in mean pain score between the 2 groups (mean between-group score difference of −0.85, 90% confidence interval [−1.69 to 001], $P = 0.048$). Nausea was more than twice as common in the duloxetine group as it was in the placebo group (41.2% vs 20.5%). One patient withdrew due to severe adverse events, although these were related to disease rather than the study medications. The authors concluded that the addition of duloxetine to pregabalin/opioid combination therapy was clinically beneficial, although further evidence was needed to substantiate these findings.[25]

Delanian et al. [9] compared a combination of pentoxifylline (800 mg), tocopherol (1000 mg), and clodronate (1600 mg) taken daily for 5 days (weekdays), followed by prednisone for 2 days (weekends) (PENTOCLO arm) to a triple placebo. The trial was conducted at a single centre in France and included 59 patients with cancer experiencing radiation-induced plexopathy.[9] After 18 months, there was no significant difference in pain relief, sensitivity, or motor function between the 2 groups. Several secondary outcomes were also assessed, including quality of life and biomarkers. There was a nonsignificant trend toward reduced pain severity and fewer neuropathic pain symptoms in

Table 1

Summary of included studies.

Author and year	Results	Adverse events	Proportion of patients reporting >30% pain relief or moderate pain relief	Proportion of patients dropping out due to adverse events
Minotti 1998	No significant differences in pain scores at day 4 Inadequate pain control was noted in all groups	GI discomfort, dry mouth, CNS disturbance - reported in all 3 groups, most commonly in DC	DI: 68.9% (42/61) DC: 65.6% (40/61) DP: 56.5% (35/62)	DI: 2.3% DC: 13.3% DP: 5.3%
Ernst 2003	No significant differences in pain scores were noted	DP + clodronate: 44% experienced severe (Grade 3 or 4) adverse events DP + placebo: 43% experienced severe adverse events The nature of toxicity was similar amongst the 2 groups, except patients in the placebo group experienced more cardiovascular adverse events	MP/clodronate: 44% MP/placebo: 39%	5% global attrition rate due to adverse events. Rates were similar in the 2 groups
Matsuoka 2019	D had better pain relief ($P = 0.053$) more patients in D achieved 30% and 50% reduction in pain vs P	Group D: 1 patient withdrew consent due to toxicity, 1 deteriorated; Group P: 1 patient suffered toxic events, 1 withdrew consent due to toxicity, 2 deteriorated AEs: appetite loss and anorexia were important in group D; somnolence was prevalent in both groups	D: 44.1% (15/34) P: 18.2% (6/33) reported >30% pain reduction at d 10	D: 1/35 = 2.90% P: 1/35 = 2.90%
Delanian 2019	No significant differences in SOMA score at 18 mo No significant change from baseline (0 points—3P vs 1 point PENTOCOLO) at 18 mo	81% of all patients reported AEs; no significant between-group differences were reported AEs attributed to PENTOCLO regimen—gastrointestinal events, vascular events	Proportion of patients reporting pain relief not given; median pain scores at the end of the trial demonstrated no significant treatment effect	PENTOCOLO: 4/30%–13.3% Placebo: 4/29%–13.8%

DI, diclofenac & imipramine); DC, diclofenac & codeine; DP, diclofenac & placebo; MP, mitoxantrone & prednisone; D, duloxetine; P, pregabalin; PENTOCOLO, pentoxifylline, tocopherol, clodronate.

the intervention group after 18 months; however, this group also reported lower quality of life at trial completion. Rates of adverse events were not significantly different between the intervention and control groups: in this trial, 81% of patients across both groups experienced adverse events, with similar treatment-related dropout rates between the 2 groups (13.3% PENTOCLO, 13.8% placebo). Although there was no significant difference in adverse event incidence, gastrointestinal and vascular symptoms were more prominent in the PENTOCLO arm.[9]

An assessment of risk of bias in the included studies is outlined in **Figure 2**. Studies by Ernst et al., Matsuoka et al., Delanian et al. were considered to be at low risk of bias overall. Ernst et al. had 4 of 7, Matsuoka et al. had 5 of 7, and Delanian et al. 6 of 7 domains ranked as "low risk". The most noteworthy potential source of bias in the latter trials was small sample size. The study by Minotti et al. was considered to have an "unclear" risk of bias overall, due to the lack of documentation of certain aspects of their trial methodology.

4. Discussion

The present study sought to summarize all evidence from RCTs of nonopioid drug combinations in the management of cancer pain, reporting on the efficacy and safety profile of each intervention. Drug regimens, including adjuvant analgesics (ie,: antidepressants, antiepileptics), were expected to have been thoroughly evaluated against standard care with opioids for the treatment of cancer pain. However, our results reflect that the relevant literature on the subject is limited: a mere 4 studies fit our search criteria. Furthermore, differences in patient populations, methodology, and interventions tested precluded a quantitative meta-analysis.

Chronic cancer pain may be tumour or treatment related; within each of these categories, the nature of the painful insult gives rise to various pain sensations. Neuropathic pain was the most common type of chronic pain evaluated in this systematic review: Delanian et al. and Matsuoka et al. studied only patients with neuropathic cancer pain, and 24.4% of the patients in the study by Minotti et al. trial reported tumour-related neuropathic pain symptoms. The mixed results of these trials demonstrated that pain etiology and classification should be considered carefully in evaluating patient populations in clinical trials on chronic cancer pain. Pain is both a syndrome and a symptom of an underlying physiological process—in this case, nerve damage—which ought to be considered in deciding treatment.[33] The terminology "cancer pain" or "cancer related pain" is not sufficient to identify, even in broad terms the patient pain syndrome.[4] Pain caused from different tumor lesions should be described as potentially mixed, nociceptive, or neuropathic pain pathophysiologies.[28] In the study by Matsuoka et al., neuropathic pain is identified using the International Association for the Study of Pain algorithm, but whether pain due to treatment or cancer and if nociceptive and neuropathic pains are treated together is unknown. The application of the International Association for the Study of Pain criteria to cancer-induced neuropathic pain deserves specific attention.[4]

All 4 trials that we included used different drug combinations, although the trials by Matsuoka et al. and Minotti et al. included antidepressant medication. In these 2 trials, which included patients with neuropathic pain, these agents showed the most promise as evidenced by the rates of patient-reported pain relief. These results are consistent with previous research supporting the use of adjuvant medications (ie, frequently antidepressants and gabapentanoids) for neuropathic pain both within and outside of the context of cancer pain.[6,17]

The findings of our study warrant comparison with other pain trials, particularly those specific to chronic noncancer pain, for which there is a larger body of evidence that is currently being used to support analgesic trends in practice. For example, a 2015

meta-analysis of double-blinded RCTs of pharmacotherapy for neuropathic pain included 229 studies, of which 2 exclusively included patients with cancer pain.[11] In their analysis, the authors identified the strongest evidence in favour of duloxetine, pregabalin, and gabapentin and discussed limitations in the methodology of several trials to explain the moderate overall effect size.[11,13] Similar issues, of large placebo responses and heterogenous inclusion criteria, amongst others, were noted for the 4 trials in our current study, in addition to small sample sizes. No systematic review study has examined nonopioid drug combinations for any indication to the best of our knowledge. However, 2 meta-analyses of nonopioid drugs for cancer pain and in palliative medicine independently concluded that although some agents showed promise as effective analgesics, there is a dearth of the literature on the subject and that many relevant studies have insufficient follow-up to make recommendations for the management of chronic cancer pain.[24,31]

There is an opportunity for the further study of promising agents that will improve treatment options. A recent comprehensive search of ongoing and unpublished clinical trials found only 1 study of nonopioid drug combinations for cancer pain currently in progress.[18] Our analysis of the existing literature may help guide the design of future studies of this unfortunately underrecognized topic. The few studies addressing this subject have significant methodological limitations; future research should be designed to avoid the shortcomings described here. Of the trials described here, the study of Matsuoka et al. add-on that duloxetine and pregabalin was the most efficacious routine evaluated.[25] Some important weaknesses of this trial include the small sample size, and the dose of the trial drug administered and that patients also received opioid analgesics: patients received duloxetine titrated to 40 mg per day for a study period of 10 days, which is considered a subtherapeutic dose and an inadequate trial duration. Duloxetine should be titrated to a 60-mg dose over a period of at least 2 weeks to achieve therapeutic effect, as established in a 2011 guideline.[5,25] In this trial, duloxetine was added to a pregabalin opioid; therefore, the opioid effect cannot be disregarded. This may suggest the usefulness of duloxetine as an alternative adjuvant when a pregabalin/opioid regime is not tolerated. This could be a rational consequence of a partial analgesic effect of opioids, benefitting of an adjuvant for neuropathic pain in cases of pain due to cancer with combined nociceptive and neuropathic pain. As hypothetical as it is, this consideration leaves unanswered the question on how duloxetine and pregabalin combination compare with opioid alone, with pregabalin alone or duloxetine alone in cancer pain (nociceptive, neuropathic or both) management. There is a similar deficiency in the trial by Minotti et al. using imipramine in which the trial duration was only 8 days. Further research in a different cancer pain setting is needed to provide evidence for duloxetine's efficacy and to overcome the limits of the small sample size used in this trial. Our review indicates that this work may be a useful baseline for designing future trials in cancer pain management, although methodological improvements would be necessary.

The use of nonopioid drug combinations for cancer pain is particularly relevant in the current climate of the opioid crisis. Although this crisis has particularly affected patients with chronic noncancer pain, there are risks associated with opioid reliance in special populations such as cancer survivors and few guidelines exist for pain management in this population.[28,30] A multimodal approach could be beneficial, and our study lays important groundwork to better understanding which specific agents may be the best.

Another issue well worth consideration is that of the benefits vs consequences of combination drug therapy. Evidence exists for the benefits of multidrug combination therapy working additively or synergistically.[17] However, the risks of polypharmacy must not be ignored. A 2014 European study examined the prevalence of polypharmacy and its relationship with potential side effects amongst patients with advanced cancer.[23] In this study, patients were taking opioids with additional adjuvants or other analgesics and nearly half of all patients were prescribed redundant or unnecessary medications that may have contributed to adverse health outcomes.[23] Our study evaluated adverse events and analgesic efficacy. Combinations including an antidepressant agent appeared to be relatively safe: the adverse event–related dropout rate was only 2.9% for the duloxetine group in the study by Matsuoka et al. and only 2.3% for the imipramine group in the study by Minotti et al.[9,10,25,26] Additionally, the adverse events experienced by these patients were relatively mild, including gastrointestinal discomfort, appetite loss, somnolence, and nausea across the 2 studies. We hope that future research on this subject further clarifies risks and benefits of combination drug therapy.

Several factors limit the findings of this work. First, the extremely small number of eligible studies made it impossible to put forth a comprehensive synthesis of efficacy and safety data for the relevant topic. Similarly, the studies that were summarized demonstrated significant heterogeneity, which prevented a quantitative meta-analysis from being performed. Thus, no measure of treatment effect was derived, and the findings reported in each individual study reviewed must be applied with caution to future research and clinical practice. Finally, it must be acknowledged that the generalizability of this study is low; the conclusions of each included article are applied to a select population only. This is particularly true of the study by Delanian et al. as radiation-induced plexopathy is a highly specific and unique cancer pain condition.

The present review study was conducted with the intent of summarizing RCT evidence for the efficacy and safety of nonopioid medication combinations in cancer pain treatment. We report that the available data is scant and heterogenous; further research on this topic is necessary to recommend options for combinations of drugs to manage cancer pain that would reduce reliance on opioid medications. A call for high-quality evidence is clear, such that patients with cancer can be better treated to improve symptoms and relieve suffering.

Disclosures

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A152.

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