Article:
Kane, CM, Mulvey, MR orcid.org/0000-0002-6357-3848, Wright, S et al. (3 more authors) (2018) Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. Palliative Medicine, 32 (1). pp. 276-286. ISSN 0269-2163

https://doi.org/10.1177/0269216317711826

Title

Opioids combined with antidepressants or antiepileptic drugs for cancer pain: systematic review and meta-analysis.

Authors

Chris M. Kane[1], Matthew R. Mulvey[1], Sophie Wright[1], Cheryl Craigs[1], Judy M. Wright[2], Michael I Bennett[1]

Affiliations

[1]Academic Unit of Palliative Care, Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, UK

[2] Academic Unit of Health Economics, Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, UK;

Corresponding author

Chris M. Kane, Academic Unit of Palliative Care, Leeds Institute of Health Sciences, Level 10 Worsley Building, Clarendon Way, Leeds, LS2 9NL

Email: C.M.Kane@leeds.ac.uk, Tel: +44(0)113 3436949

Short title

Opioid plus adjuvants for cancer pain: systematic review and meta-analysis

Keywords

Cancer pain, neuropathic pain, opioids, amitriptyline, gabapentin, pregabalin, adjuvant prescribing, meta-analysis, systematic review.

Abstract

Background: Combining antidepressant or antiepileptic drugs with opioids has resulted in increased pain relief when used for neuropathic pain in non-cancer conditions. However evidence to support their effectiveness in cancer pain is lacking.

Aim: To determine if there is additional benefit when opioids are combined with antidepressant or antiepileptic drugs for cancer pain.

Design: Systematic review and meta-analysis. Randomised control trials comparing opioid analgesia in combination with antidepressant or antiepileptic drugs versus opioid monotherapy were sought. Data on pain and adverse events were extracted. Data were pooled using DerSimonian-Laird random-effects meta-analyses, and heterogeneity was assessed.

Results: Seven RCTs that randomised 605 patients were included in the review. Patients' pain was described as neuropathic cancer pain, cancer bone pain and non-specific cancer pain. Four RCTs were included in the meta-analysis in which combination of opioid with either opioid in combination with gabapentin or pregabalin was compared with opioid monotherapy. The pooled standardised mean difference was 0.16 (95%CI -0.19, 0.51) showing no significant difference in pain relief between the groups. Adverse events were more frequent in the combination arms. Data on amitriptyline, fluvoxamine and phenytoin were inconclusive.

Conclusion: Combining opioid analgesia with gabapentinoids did not significantly improve pain relief in patients with tumour-related cancer pain compared with opioid monotherapy. Due to the heterogeneity of patient samples, benefit in patients with definite neuropathic

cancer pain cannot be excluded. Clinicians should balance the small likelihood of benefit in patients with tumour-related cancer pain against the increased risk of adverse effects of combination therapy.

Key statement

What is already known about the topic?

- Combining adjuvant analgesia to opioids provided no additional benefit for tumour-related cancer pain
- What this paper addsThere are important risks of bias within the included studies: overall the assessment of the evidence quality was low
- Based on the available low quality evidence, the analyses demonstrated no additional benefit when adding adjuvant analgesia to opioids for tumour-related cancer pain

Implications for practice

- The benefit-harm trade-offs remain uncertain when combining opioid and adjuvant for treatment-related cancer pain

Background and Objective

Pain affects up to two thirds of patients with cancer.[1] Pain is the symptom most feared by patients with this disease as well as by those that care for them.[2] Approximately 80% of cancer pains are caused by the cancer itself (tumour-related cancer pain)[3, 4] and is regarded as a mixed-mechanism pain as nociceptive, inflammatory and neuropathic mechanisms commonly co-exist, particularly in bone metastases.[5, 6] Increasingly, pain caused by exposure to anti-cancer therapies (such as chemotherapy, surgery or radiotherapy) is recognised as an important cause of pain in patients with cancer. Treatment-related cancer pain is considered more similar to classic peripheral neuropathic pain mechanism and character.[6, 7] A recent systematic review estimated that 40% of cancer patients with pain experience pain dominated by neuropathic mechanisms.[3] Neuropathic cancer pain is associated with greater analgesic requirements and poorer quality of life.[3, 8]

Strong opioids remain the mainstay treatment for tumour-related cancer pain.[9-11] When given per-protocol in a research setting 73-75% of cancer patients can experience good pain relief using this approach.[9, 12] However, in clinical practice at least a third of cancer patients report inadequate treatment of their pain.[13] Evidence based pharmacotherapy for neuropathic mechanisms include tricyclic antidepressants (TCAs) such as amitriptyline, and antiepileptic drugs such as gabapentin.[14] These agents target non-opioid pathways that are involved in neuropathic pain.[15] Combining these drugs with opioids has resulted in clinically modest but statistically significant benefits for neuropathic pain in non-cancer conditions.[16] Consequently opioid plus an adjuvant combination therapy is recommended for tumour-related cancer pain.[17-19]

However, systematic review evidence suggests that there is a lack of strong evidence to support the effectiveness of opioid plus an adjuvant combination therapy in cancer pain management.[20] Furthermore, opioid monotherapy is only effective in around three-quarters of patients with tumour-related cancer pain, potentially because of inadequate recognition and management of neuropathic mechanisms. We wanted to determine the effectiveness of opioids combined with antidepressant or antiepileptic drugs for tumour-related cancer pain, compared to opioid monotherapy.

Methods

We undertook a systematic review and meta-analysis of randomised controlled trials of as part of an update to the European Association for Palliative Care guidelines on opioids for cancer pain.[17] This review was conducted in accordance with Centre for Reviews and Dissemination Guidelines[21] which include the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance on reporting study selection.[22]

Criteria for considering studies for this review

Types of studies and intervention

Randomised controlled trials (RCTs) that evaluated opioid therapy combined with antidepressants or antidepressants, versus the same opioid as monotherapy. We excluded case reports, case series, and observational studies.

Types of patients

Studies that included patients with a diagnosis of cancer and a clinical judgement of tumour-related cancer pain. All tumour-related cancer pains were considered eligible because of the mixed-mechanism pathology. Studies that included only patients with treatment-related pain, or where data on tumour-related cancer pain were not reported separately from treatment-related cancer pain, were excluded.

Types of outcome

We included studies that measured outcome at baseline at least once after starting intervention. Primary outcomes included outcomes reporting an assessment of pain intensity using a recognised pain scale (e.g. Visual Analogue Scale or Numeric Rating Scale), or the numbers of patients achieving a specified reduction in pain (e.g. a 50% or 30% reduction).

Search methods

Electronic databases MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (Ebsco) were searched from inception to December 2014 and updated in July 2016 using text words, their synonyms and index terms (e.g. MeSH) for the search concepts (search strategy for MEDLINE reported in Appendix 1). Reference lists of studies found were searched for any additional studies. We also searched on-going trials databases, the Cochrane library and Pub-Med for any other potentially includable studies. National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Association for Palliative Medicine and the European Association for Palliative Care (EAPC) websites and databases were also searched for potential studies.

Selection of studies

Two review author (CK and MB) independently assessed for inclusion all the potential studies identified as a result of the search strategy. The Full text were obtained for any articles identified that appeared to meeting the inclusion criteria, or lacked sufficient information to make a decision based on title and abstract summary. Final decisions were made by consensus after reading full text of articles. Any disagreements were resolved through discussion.

Data extraction

For eligible studies the following data were extracted: trial design (including blinding or open-label), details of experimental and control treatment, dose regimens, duration of treatment before final pain assessment, numbers of patients in each trial arm, pain description (whether neuropathic cancer pain was specified or not) and the pain scale used to assess pain.

The following primary outcome data for each arm of each study, where available: mean pain score at baseline and at final assessment, with its standard error or standard deviation; mean change in pain from baseline, with its standard error or standard deviation; numbers of patients achieving the specified reduction in pain.

Assessment of risk of bias in included studies

We assessed risk of bias for each included study using a modified version of the seven criteria outline in the Cochrane Handbook for Systematic Review of Intervention.[23] A full description of the assessment of risk of bias methodology is reported in Appendix 2.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants or study personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (bias due to incomplete outcome data)
6. Selective reporting (reporting bias)
7. Other bias was assessed for each included study, any important concerns we had about other possible sources of bias.

Statistical analyses

Pain scores reported at baseline and time of outcome assessment were converted into changes in pain score from baseline, with its standard error. These changes in pain score were compared across treatments arms to calculate mean differences in changes in pain score across arms. Where differences in pain scores occurred in different trials mean differences were converted into standardised mean differences for analysis as per the Cochrane Handbook for Systematic Reviews.[23] It was intended that where trials reported median pain scores and interquartile ranges these were used to directly estimate the means and standard deviations for trials when the sample size was larger the 25 and by assuming a normal distribution for the pain scores.[24]

Trials were pooled using DerSimonian-Laird random-effects meta-analyses, with heterogeneity assessed using I^2. We undertook an analysis by type of adjuvant drug used (amitriptyline, gabapentin or pregabalin). Lastly, we pooled all trials to determine the effectiveness of combining adjuvants with opioids compared to opioid monotherapy. It was intended that further analyses to investigate funnel plot asymmetry, potential for publication bias and to further analyse the sources of heterogeneity was be undertaken if sufficient numbers of studies were found to be eligible.

Results

Description of studies

Our search returned 5771 results of which 1881 duplicates were removed (Figure 1). A total of 3890 recorded were screened, 3865 were excluded and 25 full text reports were assessed for eligibility. In total seven studies were included in our qualitative synthesis and four in the meta-analysis. In total there were 605 patients included across all seven studies, 319 in the experimental arms and 286 in the control arms. The mean follow up was 19.2 days, range 7-28 days; 403 of 605 patients completed the trial period.

Table 1 presents the characterises of included studies. The seven included studies comprised two trials of gabapentin,[25, 26] two of pregabalin,[27, 28] one of amitriptyline,[29] one of phenytoin[30] and one of fluvoxamine.[31] Four RCTs were double blind[25, 27, 29, 30] and three were open-label.[26, 28, 31] Six studies were parallel design and one was a cross-over design

(Table 1). The doses of amitriptyline and gabapentin were within recommended ranges for monotherapy: amitriptyline 25-150mg daily, gabapentin 900-3600mg daily.[14] However, doses of pregabalin in the two included studies were lower than recommended for monotherapy (minimum of 150mg in Sjolund et al,[27] and between 25-150mg in Mercadante 2013[28]), compared with minimum of 300 mg as recommended.[14] Opioid comparators included morphine, oxycodone, buprenorphine and tramadol. We standardised opioid doses as oral morphine equivalents using clinical conversion tables.[32] The drug and dose regimens for these trials are shown in Table 2.

Assessment of risk of bias

There was low risk of bias associated with random sequence generation, incomplete outcome data reporting, selective reporting of outcome data (Table 3). For all studies there was high or unclear risk of bias associated with allocation concealment, blinding of participants and study personnel, and blinding of outcome assessor. Overall the methodological and reporting quality of included studies was low.

Primary outcome

Pooled data by type of adjuvant drug

For amitriptyline combined with opioid, only one crossover trial of 16 patients met the inclusion criteria and no significant difference between trial arms was demonstrated.[29] The mean difference (with standard error) in VAS was 0.7 (0.86). The standardized mean difference (SMD) was 0.3 (-0.42, 1.01). Xiao[31] shows a reduction in NRS for severe pain when fluvoxamine was combined with opioids that is greater than control, however the authors did

not perform a head-to-head comparison, therefore it is not possible to state if this difference is significant or not.

For gabapentin combined with opioid, only two trials, total 196 patients, met the inclusion criteria.[25,26] No significant benefit was demonstrated when the trials were pooled: SMD was 0.32 (-0.25, 0.89). We found two studies of pregabalin combined with opioid, total 222 patients.[27, 28] The pooled data showed no significant benefit: SMD was -0.02 (-0.62, 0.58). We found one trial of 50 patients that combined phenytoin with opioid.[30] This used percentage reduction in pain as its outcome measure. This showed that 21/25 (84%) of patients achieved >50% pain relief with opioid alone compared with 22/25 (88%) gaining >50% when this was combined with phenytoin. This difference was not significant.

Meta analysis

We excluded three trials from the meta-analysis. Yajnik et al.[30] could not be included in the meta-analysis because the outcome measure of percentage reduction in pain score could not be compared with the other trial outcome measures (absolute pain scores). Furthermore, the authors evaluated the analgesic effect of Phenytoin which is rarely used in clinical practice for neuropathic pain.[30] Mercadante et al.[29] was not included as it studied a drug from a different class to the other included studies and it would not be a reasonable comparison. Although the study by Xiao et al. did present NRS pain scores, it could not be included because the data were divided into moderate and severe pain groups without detailed pain ratings.[31] The data were therefore not comparable to the other included studies. We contacted the authors for further information but they did not respond.

Included in the meta-analysis were two studies of gabapentin[25, 26] and two studies of pregabalin.[27, 28] The trial by Keskinbora et al. included 10 patients with treatment-related pain, we included this because the majority of patients (n=65) had tumour-related pain.[26] The final meta-analysis therefore included 419 patients (218 experimental, 201 control) of which 333 (76%) provided outcome data. When all Gabapentinoid studies were pooled, no significant differences were found between the combination treatments versus opioid monotherapy. The pooled SMD was 0.16 (-0.19, 0.51); data are shown in Figure 2. There was moderate heterogeneity across trials (I^2 = 56%).

Adverse events

All papers reported adverse events but there was wide variation in the way this was reported. The most commonly reported adverse events were somnolence, dizziness and nausea (Table 2). In general, the frequency of adverse events in the combination arms was greater than in the monotherapy arms; two studies found these differences to be significant.[28, 29] It was not possible to perform a meta-analysis of adverse events, as there was no consistent reporting between the trials.

Discussion

The analyses presented here demonstrates no additional benefit when adding adjuvant analgesia to opioids for tumour-related cancer pain. However, there appears to be an increase in adverse events associated with adjuvant analgesia.[28, 29, 31] We identified

important risks of bias within each study, and overall our assessment of the evidence quality was low. Consequently the benefit-harm trade-offs remain uncertain when combining opioid and adjuvant for treatment-related cancer pain.

There are likely to be several potential explanations for the observed lack of effect within most of the individual studies and particularly when assessed overall as pooled data. First, although we specified cancer pain as a broad inclusion criterion because it commonly includes mixed pain mechanisms, the sample only included three studies specifically in neuropathic cancer pain. One of these was positive[26] and two were negative.[25, 29] Overall, 212 (44%) of the total number of patients in the meta-analysis had neuropathic cancer pain. Adjuvants may be expected to work better when definite neuropathic mechanisms are present. Second, although doses of adjuvants were within recommended ranges for amitriptyline and gabapentin, the two studies that examined pregabalin may have been under-dosed. This is particularly relevant as despite the lack of a clear dose-response relationship for amitriptyline and gabapentin, higher doses (600mg) of pregabalin have been shown to be more effective than lower doses (300mg) when used as monotherapy.[14] Third, the relatively short duration of treatment (10-28 days) and the 21% attrition during the trials overall (24% for data used within meta-analysis) may have meant that the studies were underpowered to detect a true difference. The moderate heterogeneity (I^2 = 56%) in the pooled data also suggests important differences that may have obscured any clear treatment effect.

Despite these methodological considerations, it is also plausible that adjuvants may have much less effect in cancer patients who are often older and frailer than patients with non-cancer neuropathic pain, upon which much of the existing evidence is based. Cancer patients in these studies were already taking significant doses of opioids and the frequency of reported adverse events (more common in combination arms) points to poor tolerance of drug treatment with potentially limited scope for further dose increases.

Detailed examination of the evidence base in non-cancer contexts reveals that the efficacy of combining opioids and adjuvants is inconsistent and highly dependent on the choice of both comparator and outcome measure. For example, Gilron et al. demonstrated superiority of morphine combined with gabapentin over either monotherapy arm based on average daily pain intensity.[33] Although there remained a significant difference when the numbers of patients experiencing >30% pain relief were compared between combination and gabapentin monotherapy (78% versus 61%), there was no significant difference when combination was compared with morphine monotherapy (78% versus 79.5%).[33] Khoromi et al. demonstrated no significant differences between nortriptyline, morphine, their combination or active placebo (benztropine) based on proportions of responders.[34] Hanna et al. found a significant benefit of combining oxycodone with gabapentin compared to gabapentin alone, but the trial contained no oxycodone monotherapy arm, preventing any direct comparison with our results.[35] Zin et al. found no benefit of combining low dose oxycodone with pregabalin compared to pregabalin alone, and the lack of oxycodone monotherapy arm also prevented direct comparison.[36]

Two further studies also show inconsistent evidence. Gatti et al. found greater benefit of combining oxycodone and pregabalin compared to either monotherapy based on average daily pain scores.[37] However, in this open label study, absolute pain intensity fell by 80% in the combination arm, by 76% with oxycodone monotherapy, and only by 46% with pregabalin monotherapy.[37] Effective or very effective pain relief was experienced by 91.2% of patients in the combination arm, 95.6% with oxycodone monotherapy arm, and by less than 20% with pregabalin monotherapy.[37] More recently, Gilron et al. demonstrated the superiority of combined morphine plus nortriptyline therapy over both morphine monotherapy and nortriptyline monotherapy based on average daily pain scores.[38] However, when their analysis was based on proportions of patients experiencing >30% pain relief, there were no significant differences between combination (71.1%), morphine (51.3%) or nortriptyline (65.8%) arms.[38] In summary then, our findings are in line with the evidence base in non-cancer conditions.

Although inconsistently and often poorly reported, adverse events were more common in the combination arms. It is therefore important that there should be clear and demonstrable benefit to the patient if they are to be used. At present, the efficacy of these drugs in addition to opioid analgesia has not been clearly demonstrated. Our data suggests that routine use of these drugs for tumour-related cancer pain therefore has the potential to cause more harm than benefit for patients.

Strengths and weaknesses

This systematic review and meta-analysis adhered to the CRD guidance as closely as possible. We believe we have identified all appropriate studies. It is the first time a meta-analysis of adjuvant analgesia in combination with opioids for tumour-related cancer pain has been attempted and we believe our analysis adds significant knowledge to inform clinical practice. The search strategies used in the three databases were sensitive and likely to retrieve relevant trials within those databases.

The studies included were heterogeneous and required adjustment to allow comparison of pain outcomes. Use of standardised pain outcomes for all clinical trials in cancer pain would enable more reliable comparisons in future. There is a significant risk of bias in the studies because of small size and lack of blinding in some. However we would expect that any bias would have favoured the intervention. Despite this, we have shown no clear evidence of efficacy. This is supported by the finding that five of the six trials we identified reported no differences between intervention and control arms. One weakness is that not all studies specifically included patients with predominantly neuropathic cancer pain. The potential for clinical benefit in this group of patients cannot be excluded with certainty, though this benefit was not apparent in two of the three RCTs that specified neuropathic cancer pain.[25, 27]

Implications for practice

Low quality evidence suggest that adding gabapentinoids to stable opioid analgesia did not improve pain relief in patients with tumour-related cancer pain, while the case for amitriptyline, fluvoxamine and phenytoin remains inconclusive. The findings from this review are consistent with a more detailed analysis of the evidence base in non-cancer contexts. The latter highlight a number of negative studies and a lack of consistent benefit when combination treatment is directly compared with opioid monotherapy or when outcomes are based on proportion of responders.

Therefore adjuvant analgesia may be used with caution provided more rigorous identification of neuropathic pain is undertaken with early reassessment of benefit and adverse outcomes, and the medication being stopped if there is no overall benefit. This is not the first time adjuvant analgesia in addition to opioids for cancer pain has come under a higher level of scrutiny in recent years. A recent RCT of ketamine, previously thought to be effective, has demonstrated a lack of benefit with a moderate risk of harm, not dissimilar to the results here.[39]

Some studies have compared triple combinations (antiepileptic, antidepressant and opioid) with dual combinations (antiepileptic OR antidepressant, with opioid) in patients with cancer pain.[40, 41] These studies reported significantly better pain scores with triple combination over dual combination therapy. Unfortunately none of these studies included an opioid alone arm, and so do not meet the inclusion criteria for this review. Nevertheless, their findings are

in keeping with non-malignant chronic neuropathic pain research and warrants further investigation.[42]

Author contributions:

- Kane CM: Conceived, designed, extract and analysed data, drafted and approved final manuscript.
- Mulvey MR: Drafted and revised content of final manuscript. Approved final manuscript.
- Wright S: Extracted and analysed data, drafted and approved final manuscript.
- Craigs C: Extracted data, designed and conducted meta-analysis, drafted and approved final manuscript.
- Wright JM: Designed search strategy and extracted data, drafted and approved final manuscript
- Bennett MI: Conceived and designed study, assisted with data extraction and analysis, drafted and approved final manuscript

Declaration of conflict of interest

The Authors declare that there is no conflict of interest.

References

1. van den Beuken-van Everdingen, M. H., de Rijke, J. M., Kessels, A. G., Schouten, H. C., van Kleef, M., Patijn, J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 2007 Sep;18(9):1437-49.
2. (BMA), British Medical Association. End-of-life care and physician-assisted dying. London: BMA; 2016.
3. Bennett, M. I., Rayment, C., Hjermstad, M., Aass, N., Caraceni, A., Kaasa, S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain 2012 Feb;153(2):359-65.
4. Grond, S., Radbruch, L., Meuser, T., Sabatowski, R., Loick, G., Lehmann, K. A. Assessment and treatment of neuropathic cancer pain following WHO guidelines. Pain 1999 Jan;79(1):15-20.
5. Falk, S., Dickenson, A. H. Pain and nociception: mechanisms of cancer-induced bone pain. J Clin Oncol 2014 Jun 1;32(16):1647-54.
6. Baron, R., Maier, C., Attal, N., Binder, A., Bouhassira, D., Cruccu, G., Finnerup, N. B., Haanpaa, M., Hansson, P., Hullemann, P., Jensen, T. S., Freynhagen, R., Kennedy, J. D., Magerl, W., Mainka, T., Reimer, M., Rice, A. S., Segerdahl, M., Serra, J., Sindrup, S., Sommer, C., Tolle, T., Vollert, J., Treede, R. D. Peripheral Neuropathic Pain: A mechanism-related organizing principle based on sensory profiles. Pain 2016 Nov 03.
7. Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., Colvin, L. A., Fallon, M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain 2014 Dec;155(12):2461-70.
8. Rayment, C., Hjermstad, M. J., Aass, N., Kaasa, S., Caraceni, A., Strasser, F., Heitzer, E., Fainsinger, R., Bennett, M. I., European Palliative Care Research, Collaborative. Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European Palliative Care Research Collaborative-Computerised Symptom Assessment study. Palliative Medicine 2013 Sep;27(8):714-21.
9. Zech, D. F., Grond, S., Lynch, J., Hertel, D., Lehmann, K. A. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain 1995 Oct;63(1):65-76.
10. Caraceni, A. Evaluation and assessment of cancer pain and cancer pain treatment. Acta Anaesthesiol Scand 2001 Oct;45(9):1067-75.
11. Pigni, A., Brunelli, C., Caraceni, A. The role of hydromorphone in cancer pain treatment: a systematic review. Palliat Med 2011 Jul;25(5):471-7.
12. Riley, J., Branford, R., Droney, J., Gretton, S., Sato, H., Kennett, A., Oyebode, C., Thick, M., Wells, A., Williams, J., Welsh, K., Ross, J. Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. J Pain Symptom Manage 2015 Feb;49(2):161-72.
13. Greco, M. T., Roberto, A., Corli, O., Deandrea, S., Bandieri, E., Cavuto, S., Apolone, G. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014 Dec 20;32(36):4149-54.
14. Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., Gilron, I., Haanpaa, M., Hansson, P., Jensen, T. S., Kamerman, P. R., Lund, K., Moore, A., Raja, S. N., Rice, A. S., Rowbotham, M., Sena, E., Siddall, P., Smith, B. H., Wallace, M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015 Feb;14(2):162-73.
15. Baron, R., Binder, A., Wasner, G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010 Aug;9(8):807-19.
16. Chaparro, L. E., Wiffen, P. J., Moore, R. A., Gilron, I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev 2012 Jul 11(7):CD008943.
17. Caraceni, A., Hanks, G., Kaasa, S., Bennett, M. I., Brunelli, C., Cherny, N., Dale, O., De Conno, F., Fallon, M., Hanna, M., Haugen, D. F., Juhl, G., King, S., Klepstad, P., Laugsand, E. A., Maltoni, M., Mercadante, S., Nabal, M., Pigni, A., Radbruch, L., Reid, C., Sjogren, P., Stone, P. C., Tassinari, D., Zeppetella, G. Use of opioid analgesics in the treatment of cancer

pain: evidence-based recommendations from the EAPC. The lancet oncology 2012 Feb;13(2):e58-68.

18. Ripamonti, C. I., Santini, D., Maranzano, E., Berti, M., Roila, F., Group, Esmo Guidelines Working. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2012 Oct;23 Suppl 7:vii139-54.
19. Garcia de Paredes, M. L., del Moral Gonzalez, F., Martinez del Prado, P., Marti Ciriquian, J. L., Enrech Frances, S., Cobo Dols, M., Esteban Gonzalez, E., Ortega Granados, A. L., Majem Tarruella, M., Cumplido Buron, J. D., Gasco Hernandez, A., Lopez Miranda, E., Ciria Santos, J. P., de Castro Carpeno, F. J. First evidence of oncologic neuropathic pain prevalence after screening 8615 cancer patients. Results of the On study. Annals of Oncology 2011 Apr;22(4):924-30.
20. Bennett, M. I. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med 2011 Jul;25(5):553-9.
21. Dissemination, Centre for Reviews and. Guidance for undertaking reviews in health care. CRD, editor. York: University of York; 2009.
22. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Group, Prisma. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul 21;6(7):e1000097.
23. Higgins, J., Green, S. . Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011;Available from www.handbook.cochrane.org.
24. Hozo, S. P., Djulbegovic, B., Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology 2005 Apr 20;5:13.
25. 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 Jul 15;22(14):2909-17.
26. Keskinbora, K., Pekel, A. F., Aydinli, I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. J Pain Symptom Manage 2007 Aug;34(2):183-9.
27. Sjolund, K. F., Yang, R., Lee, K. H., Resnick, M. Randomized study of pregabalin in patients with cancer-induced bone pain. Pain and therapy 2013 Jun;2(1):37-48.
28. Mercadante, S., Porzio, G., Aielli, F., Ferrera, P., Codipietro, L., Lo Presti, C., Casuccio, A. The effects of low doses of pregabalin on morphine analgesia in advanced cancer patients. Clin J Pain 2013 Jan;29(1):15-9.
29. Mercadante, S., Arcuri, E., Tirelli, W., Villari, P., Casuccio, A. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. Tumori 2002 May-Jun;88(3):239-42.
30. Yajnik, S., Singh, G. P., Singh, G., Kumar, M. Phenytoin as a coanalgesic in cancer pain. J Pain Symptom Manage 1992 May;7(4):209-13.
31. Xiao, Y., Liu, J., Huang, X. E., Ca, L. H., Ma, Y. M., Wei, W., Zhang, R. X., Huang, X. H., Chang, J., Wu, Y. J. Clinical study on fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. Asian Pacific journal of cancer prevention : APJCP 2014;15(23):10445-9.
32. Mercadante, S., Caraceni, A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. Palliat Med 2011 Jul;25(5):504-15.
33. Gilron, I., Bailey, J. M., Tu, D., Holden, R. R., Weaver, D. F., Houlden, R. L. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005 Mar 31;352(13):1324-34.
34. Khoromi, S., Cui, L., Nackers, L., Max, M. B. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007 Jul;130(1-2):66-75.
35. Hanna, M., O'Brien, C., Wilson, M. C. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain 2008 Aug;12(6):804-13.

36. Zin, C. S., Nissen, L. M., O'Callaghan, J. P., Duffull, S. B., Smith, M. T., Moore, B. J. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. The journal of pain : official journal of the American Pain Society 2010 May;11(5):462-71.

37. Gatti, A., Sabato, A. F., Occhioni, R., Colini Baldeschi, G., Reale, C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. Eur Neurol 2009;61(3):129-37.

38. Gilron, I., Tu, D., Holden, R. R., Jackson, A. C., DuMerton-Shore, D. Combination of morphine with nortriptyline for neuropathic pain. Pain 2015 Aug;156(8):1440-8.

39. Hardy, J., Quinn, S., Fazekas, B., Plummer, J., Eckermann, S., Agar, M., Spruyt, O., Rowett, D., Currow, D. C. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. J Clin Oncol 2012 Oct 10;30(29):3611-7.

40. Nishihara, M., Arai, Y. C., Yamamoto, Y., Nishida, K., Arakawa, M., Ushida, T., Ikeuchi, M. Combinations of low-dose antidepressants and low-dose pregabalin as useful adjuvants to opioids for intractable, painful bone metastases. Pain Physician 2013 Sep-Oct;16(5):E547-52.

41. Arai, Y. C., Matsubara, T., Shimo, K., Suetomi, K., Nishihara, M., Ushida, T., Kobayashi, K., Suzuki, C., Kinoshita, A., Kondo, M., Matsubara, S., Hayashi, R., Tohyama, Y., Nishida, K., Arakawa, M. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. Journal of anesthesia 2010 Jun;24(3):407-10.

42. Holbech, J. V., Bach, F. W., Finnerup, N. B., Brosen, K., Jensen, T. S., Sindrup, S. H. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain 2015 May;156(5):958-66.