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ORIGINAL ARTICLE

# Use of non-opioid analgesics as adjuvants to opioid analgesia for cancer pain management in an inpatient palliative unit: does this improve pain control and reduce opioid requirements?

**Shivani Shinde · Pamela Gordon · Prashant Sharma · James Gross · Mellar P. Davis**

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**Abstract**
*Background* Cancer pain is complex, and despite the introduction of the WHO cancer pain ladder, few studies have looked at the prevalence of adjuvant medication use in an inpatient palliative medicine unit. In this study, we evaluate the use of adjuvant pain medications in patients admitted to an inpatient palliative care unit and whether their use affects pain scores or opiate dosing.
*Methods* In this retrospective observational study, patients admitted to the inpatient palliative care unit over a 3-month period with a diagnosis of cancer on opioid therapy were selected. Data pertaining to demographics, diagnosis, oral morphine dose equivalent of the opioid at the time of discharge, adjuvant analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and pain scores as reported by nurses and physicians were collected.
*Results* Seventy-seven patients were eligible over a 3-month period, out of which 65 (84 %) were taking an adjuvant medication. The most commonly prescribed adjuvant was gabapentin (70 %). Fifty-seven percent were taking more than one adjuvant. There were more women in the group receiving adjuvants (57 vs. 17%, $p$=0.010). Those without adjuvants compared with those on adjuvants did not have worse pain scores on discharge as reported by physicians (0.8±0.8 vs. 1.0±0.7, $p$=0.58) or nurses (2.0±2.7 vs. 2.1±2.6, $p$=0.86). There was no difference in morphine equivalent doses of the opioid in both groups (median (min, max); 112 (58, 504) vs. 200 (30, 5,040)) at the time of discharge; 75–80 % of patients had improvement in pain scores as measured by a two-point reduction in numerical rating scale (NRS).
*Discussion* This study shows that adjuvant medications are commonly used for treating pain in patients with cancer. More than half of study population were on two adjuvants or an adjuvant plus NSAID along with an opioid. We did not demonstrate any benefit in terms of improved pain scores or opioid doses with adjuvants, but this could reflect confounding variables and physician choice. Larger prospective studies are needed to define the opioid-sparing effects of adjuvants.
*Conclusion* Adjuvant agents are used in over 80 % of those treated for cancer pain.

**Keywords** Adjuvants · Opioid · Cancer pain

## Introduction

Cancer pain has a complex pathophysiology requiring comprehensive assessment and use of several pharmacologic and non-pharmacologic interventions. Opioids are the cornerstone of cancer pain management [1, 2]. The World Health Organization (WHO) three-step ladder, published in 1986, provides a framework for cancer pain management [1, 2]. The guideline recommends non-opioid analgesic for mild pain, a "weak" opioid for moderate pain, and a potent opioid for severe pain or inadequately controlled pain with a weak opioid. Non-opioid adjuvants, defined as drugs with other indications but have analgesic effect in certain pain conditions, are recommended to be added at all steps of the ladder based on the type of pain and clinical context. Commonly used adjuvant analgesics are a diverse group of medications which include

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S. Shinde · P. Gordon · P. Sharma · J. Gross · M. P. Davis (✉)
The Harry R Horvitz Center for Palliative Medicine, Division of Solid Tumor, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Avenue, R35, Cleveland, OH 44195, USA
e-mail: davism6@ccf.org
URL: http://www.clevelandclinic.org/palliative

corticosteroids, antidepressants, and anticonvulsants [3–6]. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as adjuvants to opioids, even though they are primarily analgesics [7, 8].

Of the adjuvant analgesics, antidepressant, anticonvulsant, and corticosteroid medications have been established for neuropathic pain; however, their use in cancer pain is less well studied [9–13]. Gabapentinoids are known to reduce bone and visceral pain [14–17], and there is evidence that cancer-induced bone pain has a neuropathic mechanisms [18–23]. Amitriptyline has been shown to improve neuropathic pain and reduces opioid dose requirements in animal models [24–27]. Amitriptyline also improves visceral pain [28–30]. Both gabapentinoids with amitriptyline or imipramine have been effective in relieving cancer pain [31–44]. Selective norepinephrine serotonin reuptake inhibitors (SNRIs) have also been approved for use in neuropathic pain. Duloxetine has been used to treat neuropathic cancer pain [45] and has been found to be effective in treating arthritis and visceral pain [46–49]. Combinations of adjuvant analgesics with or without opioids have been used successfully to manage difficult-to-treat pain syndrome in humans and animal models [39, 50–53]. The therapeutic goals for combining opioids with adjuvant analgesics include improved pain control relative to opioids alone, reduced opioid doses, potentially reduced opioid-related side effects, and improved function [4]. Combinations of appropriate adjuvant analgesics and opioids have been reported to improve pain control in the majority of cancer pain syndromes [40, 54, 55]. Dosing strategies with oxycodone and pregabalin have been investigated in a recent randomized trial [56]. Maintaining the dose of oxycodone and increasing the pregabalin dose improved pain control and reduced side effects relative to oxycodone dose titration with maintenance of pregabalin dose [56]. Despite the evidence, adjuvant medications are underutilized in practice, and in certain series, adjuvants were used in less than 50 % of patients treated for cancer pain [57–59]. A systematic review of eight prospective clinical studies showed that the combination of adjuvant analgesic drugs (such as antidepressants or antiepileptic) with opioids for cancer pain is not as effective as it is in non-cancer neuropathic pain [60]. In at least one cross-sectional study, the use of adjuvant analgesics was associated with more pain, greater pain interference, more symptoms, and lower function [61]. Most randomized control trials looking at the role of non-opioid adjuvants in cancer pain management are of shorter duration (less than 30 days) [60].

The objective of this study was to retrospectively compare pain severity and morphine equivalent doses of opioid analgesics on an inpatient palliative unit in patients receiving opioids and adjuvants with patients on opioid analgesics alone.

## Methods

In this retrospective observational study, electronic medical records of patients admitted to the Harry R. Horvitz Center for Palliative Medicine inpatient unit at the Cleveland Clinic from January 1, 2012, to March 31, 2012, were reviewed, in accordance with an IRB exemption. Patients included in the study had a diagnosis of cancer, cancer pain treated with opioids, and able to give a verbal pain score on admission and discharge.

Demographic data collected included age, gender, and diagnosis. The initial opioid and dose on admission was collected and recorded as well as pain severity by numerical rating scale (NRS) and categorical scale (CAT). On discharge, the final opioid and dose were converted to oral morphine equivalence using a standard protocol (Table 1, conversion table). The adjuvant medications at the time of discharge were also recorded. For the purpose of this study, adjuvants included were NSAIDs, tricyclic antidepressants (TCA), selective norepinephrine reuptake inhibitors (SNRI), corticosteroids, and anticonvulsants.

The nursing staff assessed pain severity using a NRS on day 1 of admission and on the day of discharge. The scale was a standard 0–10 scale with 0 being no pain and 10 being severe pain. The treating physician also assessed pain on day 1 of admission and on the day of discharge. Physicians rated pain using a modified Edmonton Symptom Assessment Scale as none, mild, moderate, or severe (CAT), which was converted to a corresponding numerical scale of 0–4. A one-point decrease in the CAT or a two-point decrease in the NRS was considered a response [15]. The choice and opioid dosing strategy was based on the standard protocol of the inpatient unit, clinical context, physician discretion, and patient-related goals [16].

## Statistics

Comparisons were made between those receiving opioids alone and those receiving opioids and adjuvant analgesics in regards to opioid dose and pain response. A responder's analysis was performed based upon a two-point reduction in a numerical rating scale (0 is no pain, 10 is severe pain) [62]. Categorical

**Table 1** Opioid conversion table

| Opioid | IV | PO/SL |
|---|---|---|
| Morphine | 1 mg | 3 mg |
| Oxycodone | – | 4.5 mg |
| Fentanyl | 25 mcg | – |
| Transdermal | 25 mcg | – |
| Hydromorphone | 0.2 mg | 0.4 mg |
| Buprenorphine | 35 mcg | 70 mcg |
| Methadone | | 0.2 mg |
| Oxymorphone | – | 1 mg |

variables are summarized as frequency counts and percentages. Continuous variables are summarized as the mean, standard deviation, median, and range. Gender was compared between groups using the chi-square test. All other variables were compared using the Wilcoxon rank sum test. Data were analyzed using JMP software. All statistical tests were two-sided, and $p<0.05$ was used to indicate statistical significance.

## Results

In total, 201 patients were admitted, 124 were excluded (see Fig. 1), and 77 charts were abstracted. Of the excluded patients, 55 died during the admission, 10 were unable to give a pain score due to confusion, 46 were not treated with opioids, and 13 had a diagnosis other than cancer. Of those recruited, 65 were on adjuvants at discharge and 12 were not. The most common diagnosis in those without adjuvants was hepatobiliary or pancreatic cancer whereas those on adjuvants were lung cancer (Table 2).

A wide variety of adjuvants were used although gabapentin was the most common (Tables 3 and 6). Thirty-seven patients (57 %) were on more than one adjuvant medication, and the most commonly used combination was corticosteroid plus gabapentin in 16 patients (20 %).

There were 39 females and 38 males; mean (SD) age for those on opioids alone was 61 (13) and for those on opioids plus adjuvants was 57 (13). There was a higher percentage of females on adjuvant analgesics (57 vs. 17 %, $p=0.010$). There was no association between age and adjuvant analgesics ($p=0.3$).

**Table 2** Primary diagnosis

| Diagnosis | On no adjuvants (12) | | On adjuvants (65) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Lung | 1 | 8.3 | 21 | 32.3 |
| Breast | – | – | 7 | 10.8 |
| Kidney | – | – | 5 | 7.7 |
| Pancreas | 2 | 16.7 | 3 | 4.6 |
| Prostate | 1 | 8.3 | 4 | 6.2 |
| Cervix | – | – | 4 | 6.2 |
| CUP | 1 | 8.3 | 2 | 3.1 |
| Cholangiocarcinoma | 2 | 16.7 | 1 | 1.5 |
| Esophagus | 1 | 8.3 | 2 | 3.1 |
| Lymphoma | 1 | 8.3 | 2 | 3.1 |
| Myeloma | – | – | 3 | 4.6 |
| Appendix | – | – | 2 | 3.1 |
| Penis | – | – | 2 | 3.1 |
| Sarcoma | – | – | 2 | 3.1 |
| Uterus | – | – | 2 | 3.1 |
| Bladder | 1 | 8.3 | – | – |
| Colon | – | – | 1 | 1.5 |
| Liver | 1 | 8.3 | – | – |
| Melanoma | 1 | 8.3 | – | – |
| Polycythemia rubra vera | – | – | 1 | 1.5 |
| Skin | – | – | 1 | 1.5 |

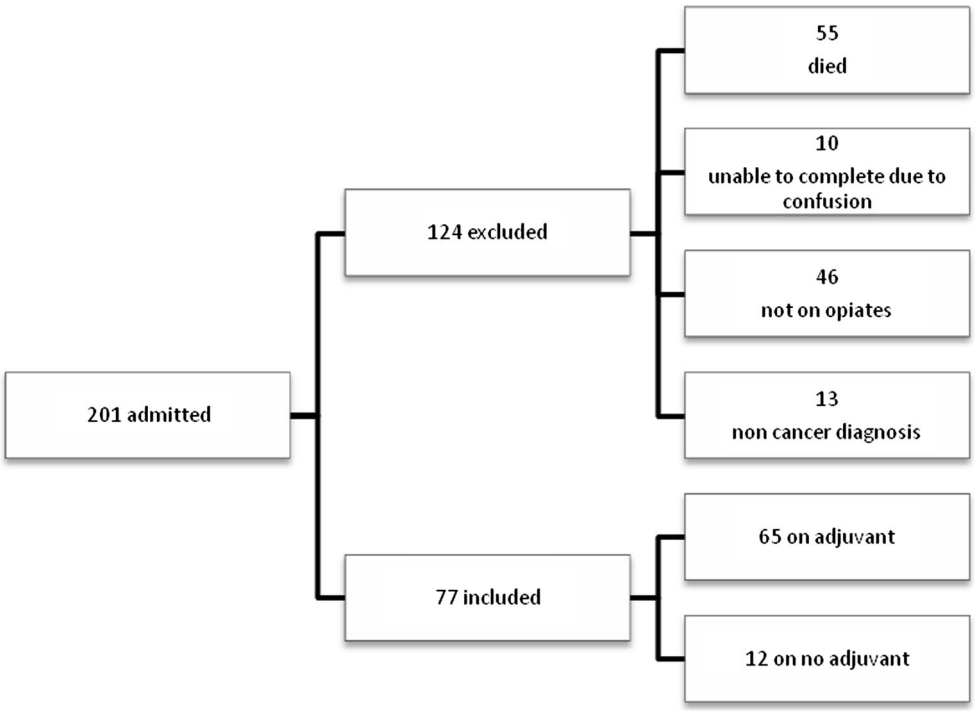


**Fig. 1** Exclusion criteria

**Table 3** Adjuvant medications used

| Non-opioid adjuvants used | Opioid+adjuvant (65) | |
|---|---|---|
| | *N* | % |
| Gabapentin | 45 | 70 |
| Dexamethasone | 23 | 35 |
| NSAID | 14 | 21 |
| Acetaminophen | 5 | 8 |
| Pregabalin | 4 | 6 |
| Duloxetine | 3 | 5 |
| Lidocaine patches | 2 | 3 |
| Prednisone | 1 | 1.5 |
| Carbamazepine | 1 | 1.5 |
| Divalproex | 1 | 1.5 |
| Citalopram | 1 | 1.5 |
| Amitriptyline | 1 | 1.5 |
| Venlafaxine | 1 | 1.5 |

Oral morphine equivalents at discharge were not statistically different between the two groups: those on opioids alone (median 112 mg; range 58–504) and those on adjuvants (median 200 mg; range 30–5,040) ($p$=0.19).

Pain scores, as rated by nursing staff and physicians, were not different between the groups on admission or on discharge and the improvement in pain scores was also the same (Tables 4 and 5).

We also performed a responder's analysis. There was no difference between the two groups with 9 (75 %) responders among the patients on opioids alone and 52 (80 %) among those on adjuvants plus opioids ($p$=0.69).

## Discussion

Previous studies evaluating the use of adjuvant analgesics in the cancer population have focused on the treatment of neuropathic pain [17]. Our study is unique in examining the use of adjuvants in all cancer patients. We showed in this retrospective study that 84 % of cancer patients admitted to our inpatient palliative medicine unit were discharged on adjuvant analgesics. Increasingly, a neuropathic pathophysiology is being recognized as an important factor with entities such as bone cancer pain. It is unclear from this study if the high proportion of patients on adjuvants represents a high proportion of patients with pain secondary to neuropathic causes or whether adjuvant medications are being prescribed for non-neuropathic pain. Patients with cancer frequently have more than one pain syndrome, one of which will be responsive to an adjuvant analgesics [63].

In our study, gabapentin was the most frequently prescribed adjuvant. This is different from other studies for which gabapentin were available. The use a gabapentin ranged from 0 to 30 % of patients treated for cancer pain [57, 64, 65]. Gabapentinoids benefit neuropathic cancer pain but may also reduce visceral and bone pain. Several studies involving treatment of neuropathic cancer pain found gabapentin to be the most commonly prescribed adjuvant [24, 66–71]. Gabapentin is also effective in a multitude of other symptoms including insomnia [72–74], cough [75–77], hiccough [78–80], nausea [81–83], and delirium [84]. The use of steroids may be for multiple reasons, i.e., as an adjuvant but also for non-pain symptoms such as fatigue and anorexia [85, 86]. Because steroids are prescribed for many reasons in palliative care, it was difficult from a chart

**Table 4** Nurse pain scores

| | On no adjuvant (12) | On adjuvant (65) | *p* value |
|---|---|---|---|
| Nurse pain score on admission | | | |
| Mean±SD | 3.7±3.2 | 5.0±3.3 | 0.21 |
| Median (min, max) | 4.5 (0, 8) | 6 (0, 10) | |
| Nurse pain score on discharge | | | |
| Mean±SD | 2.0±2.7 | 2.1±2.6 | 0.86 |
| Median (min, max) | 0 (0, 7) | 0 (0, 9) | |
| Change in nurse pain score | | | |
| Mean±SD | −1.7±3.5 | −3.0±3.5 | 0.18 |
| Median (min, max) | −0.5 (−8, 4) | −2 (−10, 7) | |

**Table 5** Physician pain scores

| | On no adjuvant (12) | | On adjuvant (65) | | *p* value |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | |
| Physician pain score on admission | | | | | |
| None (0) | 2 | 16.7 | 9 | 13.8 | 0.83 |
| Mild (1) | 3 | 25.0 | 16 | 24.6 | |
| Moderate (2) | 3 | 25.0 | 17 | 26.2 | |
| Severe | 4 | 33.3 | 23 | 35.4 | |
| Mean±SD | 1.8±1.1 | | 1.8±1.1 | | |
| Median (min, max) | 2 (0, 3) | | 2 (0, 3) | | |
| Physician pain score on discharge | | | | | |
| None (0) | 5 | 41.7 | 17 | 26.2 | 0.58 |
| Mild (1) | 4 | 33.3 | 35 | 53.8 | |
| Moderate (2) | 3 | 25.0 | 11 | 16.9 | |
| Severe | 0 | 0 | 2 | 3.1 | |
| Mean±SD | 0.8±0.8 | | 1.0±0.7 | | |
| Median (min, max) | 1 (0, 2) | | 1 (0, 3) | | |
| Change in physician pain score | | | | | |
| Mean±SD | −0.9±1.1 | | −0.9±1.2 | | 0.99 |
| Median (min, max) | −1.0 (−3, 1) | | −1.0 (−3, 2) | | |

**Table 6** Individual adjuvants and dosages per patient

| | Adjuvant 1 | Adjuvant dose 1 (daily) | Adjuvant 2 | Adjuvant dose 2 (daily) |
|---|---|---|---|---|
| 1 | Gabapentin | 800 mg 3× | Amitriptyline | 25 mg |
| 2 | Ketorolac | 30 mg 96 L | | |
| 3 | Gabapentin | 800 mg 3× | Dexamethasone | 8 mg 2× |
| 4 | No adjuvants | | | |
| 5 | Dexamethasone | Unknown | | |
| 6 | Meloxicam | 15 mg | Pregabalin | 50 mg 2× |
| 7 | Gabapentin | 300 mg 6× | | |
| 8 | No adjuvants | | | |
| 9 | Gabapentin | 300 mg | Dexamethasone | 4 mg 2× |
| 10 | Gabapentin | 900 3× | Naproxen | 500 mg 2× |
| 12 | Gabapentin | 900 mg 3× | | |
| 13 | No adjuvants | | | |
| 14 | Dexamethasone | 4 mg | Gabapentin | 300 mg 2× |
| 15 | Gabapentin | 300 mg 4× | Dexamethasone | 1 mg |
| 17 | Gabapentin | 300 mg 2× | Dexamethasone | 4 mg 2× |
| 18 | Gabapentin | 300 mg | Acetaminophen | 1000 mg |
| 19 | No adjuvants | | | |
| 20 | Gabapentin | 300 mg 3× | | |
| 21 | Gabapentin | 600 mg 2× | | |
| 22 | Gabapentin | 800 mg 3× | ibuprofen | 600 mg 4× |
| 23 | Venlafaxine | 75 mg | | |
| 24 | Naproxen | 375 mg 2× | | |
| 25 | Gabapentin | 800 mg 3× | | |
| 26 | Gabapentin | 600 mg a.m., 900 mg p.m. | | |
| 27 | Dexamethasone | 4 mg 2× | | |
| 28 | Pregabalin | 150 mg 3× | Dexamethasone | 8 mg 2× |
| 29 | Dexamethasone | 4 mg | Divalproex | 250 mg 2× |
| 30 | Carbamazepine | 100 mg 2× | | |
| 31 | Gabapentin | 700 mg 2× | Lidocaine patch | 5 % (700 mg/patch) |
| 32 | No adjuvants | | | |
| 33 | Gabapentin | 300 mg 3× | | |
| 34 | Gabapentin | 900 mg 2× | Dexamethasone | 4 mg 2× |
| 35 | Dexamethasone | 4 mg | | |
| 36 | Lidocaine patch | 5 % (700 mg/patch) | | |
| 37 | Gabapentin | 500 mg 3× | Duloxetine | 60 mg |
| 38 | Dexamethasone | 4 mg 2× | | |
| 39 | No adjuvants | | | |
| 40 | Gabapentin | 200 mg 3× | | |
| 41 | Gabapentin | 900 mg 3× | Dexamethasone | 4 mg 2× |
| 43 | Gabapentin | 600 mg | | |
| 44 | Citalopram | 10 mg | | |
| 45 | Gabapentin | 900 mg 3× | Diclofenac XR | 100 mg |
| 46 | Gabapentin | 700 mg 2× | Dexamethasone | 4 mg 2× |
| 47 | Gabapentin | 600 mg 4× | Acetaminophen | 650 mg 3× |
| 48 | Gabapentin | 800 mg 3× | Duloxetine | 30 mg |
| 49 | Gabapentin | 900 mg | ibuprofen | 800 mg 3× |
| 50 | Pregabalin | 150 mg 2× | | |
| 51 | Gabapentin | 800 mg 3× | Naproxen | 500 mg 2× |

**Table 6** (continued)

| | Adjuvant 1 | Adjuvant dose 1 (daily) | Adjuvant 2 | Adjuvant dose 2 (daily) |
|---|---|---|---|---|
| 52 | Gabapentin | 600 mg 3× | ibuprofen | 800 mg 3× |
| 53 | Gabapentin | 600 mg 3× | Dexamethasone | 1 mg 2× |
| 54 | Aspirin | 81 mg | | |
| 55 | Gabapentin | 300 mg | Dexamethasone | 4 mg 2× |
| 56 | Gabapentin | 300 mg 3× | Dexamethasone | 4 mg 2× |
| 57 | No adjuvants | | | |
| 58 | No adjuvants | | | |
| 59 | Naproxen | 500 mg 2× | Gabapentin | 1200 3× |
| 60 | No adjuvants | | | |
| 61 | Gabapentin | 700 mg 2× | Ketorolac | 30 mg 96 L |
| 62 | Gabapentin | 300 mg 3× | | |
| 63 | Acetaminophen | 650 mg 3× | | |
| 64 | Gabapentin | | Dexamethasone | 4 mg 2× |
| 65 | Gabapentin | 300 mg 3× | | |
| 66 | No adjuvants | | | |
| 67 | Dexamethasone | 4 mg 2× | Duloxetine | 60 mg 2× |
| 68 | Gabapentin | 600 mg 5× | Prednisone | 5 mg/48 h |
| 69 | Gabapentin | 300 mg 3× | Acetaminophen | 1000 mg 3× |
| 70 | Gabapentin | 300 mg 3× | Dexamethasone | 4 mg 2× |
| 71 | Gabapentin | 400 mg 3× | Dexamethasone | 4 mg |
| 72 | Ibuprofen | 600 mg 3× | | |
| 73 | Dexamethasone | 4 mg 2× | | |
| 74 | Pregabalin | 150 mg 2× | | |
| 75 | Gabapentin | 900 mg 3× | Acetaminophen | 650 mg 3× |
| 76 | No adjuvants | | | |
| 77 | Gabapentin | 600 mg 3× | | |
| 78 | Gabapentin | 1,200 mg 3× | | |
| 79 | Pregabalin | 150 mg 2× | | |
| 80 | Gabapentin | 600 mg 4× | Dexamethasone | 4 mg 2× |

review to clearly determine if the sole reason for prescription was pain relief.

The justification of adjuvant analgesic use in cancer pain stems from positive trials in non-cancer neuropathic pain and some studies in cancer, which have shown improved pain relief and reduced opioid requirements. Those studies which demonstrated a benefit have shown that the effect size is less than that seen in non-cancer-related neuropathic pain [17]. Our study demonstrated equal improvement in pain scores between those treated with adjuvants and those treated with opioids alone. There was no reduction in the opioid doses with the addition of adjuvant analgesics. This may reflect the small numbers of patients on this study since the effect size of adjuvant analgesics is small [60]. It is difficult to make definitive conclusion regarding the effectiveness of adjuvants based on this retrospective study; one of the limitations of our study was the low numbers of patients in the non-adjuvant group, limiting the strength of our comparisons. This is a retrospective study and hence hypothesis generating. These findings should be confirmed in a large randomized prospective study.

Other limitations of our study are that several of the adjuvant medications are used for multiple reasons rather than for pain only; it is impossible to determine that all medications were used with the sole intent of providing pain relief. Individual adjuvant dosages varied and, for some individuals, may have been subtherapeutic for pain relief (Table 6). A large number of patients were excluded due to inability to give scores or were actively dying. Exclusion due to such clinical reasons is a common limitation to trials on the inpatient palliative unit. Confounding variables are likely to have influenced the results. More women were in the group receiving adjuvant medications, indicating an imbalence between groups. This suggests that there could be other unmeasured confounding factors. It is unclear if this is an anomaly due to

the different sizes of the groups or whether there is an adjuvant prescribing bias in favor of women. Another limitation is that we did not measure side effect differences between the groups. It is possible that the addition of adjuvant analgesics may increase symptoms from drug side effects. It would also be interesting to compare patients admitted to the unit already on adjuvants with those who had adjuvant analgesics started in the hospital.

## Conclusion

Our study shows that adjuvant analgesics are commonly prescribed to cancer patients admitted with pain to our unit. Adjuvant analgesics did not appear to improve pain control or lower opioid doses in this study. However, the majority of patients in the inpatient palliative unit have improved pain control over the duration of hospitalization.

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