Brief Report

# Does cancer type and adjuvant analgesic prescribing influence opioid dose?—a retrospective cross-sectional study

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**Abstract:** Opioids are the backbone of cancer pain management. Minimal evidence exists examining the relationship between cancer type and opioid dose. Similarly, the use of adjuvant analgesics and its impact within an inpatient cancer setting is understudied. This study examined the influence of cancer type upon opioid dose, measured by oral morphine equivalent daily dose (oMEDD). The effect of adjuvant analgesics on patient oMEDD was also examined. This retrospective cross-sectional study examined records of 520 patients admitted to Royal Melbourne Hospital or Peter MacCallum Cancer Centre between 2016 and 2018 with advanced cancer. Number and dose of both opioid and adjuvant analgesics were collected along with demographic and cancer data. Comparisons of median oMEDD by cancer type [analysis of variance (ANOVA), non-parametric *t*-tests] and adjuvant analgesics (Kruskal-Wallis test) were performed. There were no statistically significant differences in oMEDD between the 12 cancer types (P=0.83; n=215). Patients co-prescribed pregabalin (n=102) and paracetamol (n=73) as adjuvant analgesics were on significantly higher daily oMEDD [60 mg (P=0.015), 90 mg (P<0.001), respectively]. Opioid dose did not differ significantly between cancer types. The observed use of adjuvant analgesics coincided with significantly higher oMEDD prescription which may relate to complex pain seen in this cohort of inpatients in a quarternary cancer centre. Future research should focus on pain type and aetiology, and pain scores in different cancer pain syndromes to determine the net effect of opioids and adjuvants in cancer pain prescribing.

**Keywords:** Opioid; palliative care; cancer pain; hospice care

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## Introduction

Pain is a common symptom in people with cancer, with almost two-thirds reporting cancer pain in advanced, terminal or metastatic disease (1). Cancer pain, particularly if poorly managed (2) can cause considerable distress and impact negatively on functional ability and quality of life.

Strong opioid analgesia forms the mainstay of treatment for moderate to severe cancer pain in the updated World Health Organisation (WHO) guidelines for cancer pain management (3). A recent Cochrane review found up to 95% of cancer patients treated with strong opioid analgesia experienced significant reductions in pain over a fortnight (4). Adjuvant analgesics are co-analgesics often utilised with opioids to achieve control of cancer pain through

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multimodal analgesic action (5) and may reduce opioid dose and adverse effects by potentiating analgesic effects through non-opioid pathways (6,7).

There is limited research on the impact of cancer type on the prevalence, intensity, and analgesic requirements in cancer pain. Unfortunately, despite encouraging progress in the treatment of cancer pain, a third of cancer pain remains undertreated (8). Anecdotally, certain cancer types may require larger opioid doses due to their typical pain presentations. For example, head and neck cancers may be more likely to present with neuropathic pain, which is less responsive to opioids than non-neuropathic pain (9). Pain from primary or secondary brain tumours result from peritumoural oedema and can be associated with nausea and vomiting, which is most effectively managed using corticosteroids, with opioid having an adjunctive analgesic role instead (10,11). The discovery of an association between cancer type and opioid requirement would provide a basis for more individualized opioid prescribing approaches and also potentially allow the stratification of patients with certain malignancies to earlier referral to palliative care or pain services. Authors have looked at prescription patters including that of opioids in various cancer types in outpatients (12), however there has been limited research on inpatients. Similarly, the use and impact of adjuvant analgesics within an inpatient cancer setting is understudied.

The primary objective of this study was to investigate any association between maintenance slow release (SR) opioid dose and cancer type in an inpatient cohort with chronic cancer pain. The secondary objective was to examine for any associations between SR opioid dose and adjuvant analgesic type and dose. This article is presented in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1296/rc).

## Methods

A retrospective cross-sectional study was undertaken of adult patients with one of 12 advanced solid organ cancer types discharged on SR opioids from either The Royal Melbourne Hospital or Peter MacCallum Cancer Centre medical oncology or palliative care units between January 1st 2016 and December 31st 2018. Advanced cancer was defined as Stage IV cancer, or locally advanced unresectable cancer. Twelve distinct solid cancer types were included to capture as many cancer types as possible. They were brain, breast, colorectal, gynaecological, head & neck, kidney/bladder, lung, melanoma, oesophageal/gastric, pancreatobiliary, prostate, and unknown primary cancer types. The classifications were chosen based on the WHO classification of cancer types (13). Certain cancer types have been grouped to anatomical location (e.g., kidney/bladder, oesophageal/gastric) due to relative limited representation to the health service.

In order to capture an equal timepoint reflecting pain control for all patients, patient records were audited on day of hospital discharge to represent stable regular opioid dose as a measure of sufficiently controlled pain. Immediate release opioids were excluded on the basis that day-to-day dosing was highly variable, thus not being a reliable indicator of stable opioid requirement that would allow a just comparison between groups, in addition to being the minority opioid requirement. Outpatients were not included as they form a different heterogenous group with various pain levels, hence the opioid dose used is not always a reflection of sufficient opioid dose required to achieve satisfactory pain control, and thus cannot be treated the same as the opioid dose of an inpatient at discharge timepoint.

As outlined in *Figure 1*, of the 7,747 patients discharged with metastatic cancer during the relevant period, 671 were eligible for enrolment. These patients were dichotomized into those that had been prescribed SR opioids at discharge and those who had not. Patient records were examined sequentially for cancer type. For the SR opioid group, recruitment for each of the 12 distinct cancer types was intended to be capped at twenty patients. This was chosen for convenience sampling, and to limit bias against certain cancer types being disproportionately represented, allowing for meaningful comparison between all included cancer types (irrespective of differing cancer prevalences). Accordingly, 151 discharges were excluded on the basis of exceeding 20 patients per cancer type. For a number of the included malignancies the number of people prescribed SR opioids did not reach 20 during the 3-year study period.

Stable doses of opioids and adjuvant analgesics were determined from patient discharge prescriptions. This study included paracetamol as an adjuvant analgesic. Steroid use was only recorded if its documented use was for pain control. SR opioid data was used to represent a stable baseline daily opioid requirement. For standardization of data analysis, SR opioid dose was converted to oral morphine equivalent daily dose (oMEDD) using a standardised evidence-based calculation which varied between opioids according to contemporary evidenced-

 

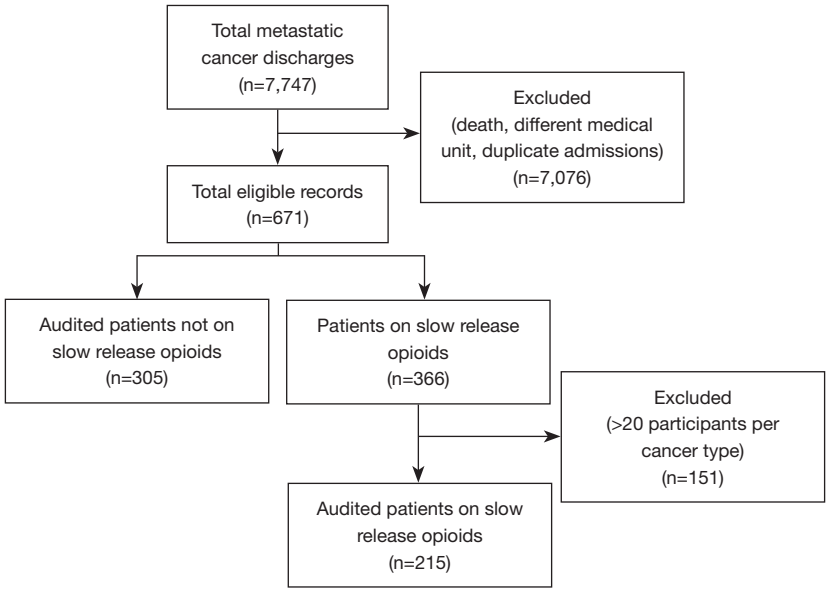


**Figure 1** Selection of patient records for audit.

based opioid dose equivalence calculation table (14).

Baseline demographic data were collected [age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, discharge unit, length of stay] as well as cancer type, and opioid and adjuvant analgesic type and dose. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Melbourne Health Office for Research (No. QA2016086). Informed consent was not conducted in the retrospective deidentified study.

### *Statistical analysis*

Descriptive statistics were performed for baseline demographics, median oMEDD and adjuvant analgesics by cancer type of patients prescribed SR opioids (n=215) *vs.* not prescribed SR opioids (n=305). Comparison of the two patient groups was performed using a chi-squared test for categorical variables, a *t*-test (assuming equal variance) for age comparison and a Wilcoxon rank-sum test for length of stay.

Analysis of variance (ANOVA) modelling was used to test the primary outcome of mean oMEDD against each cancer subtype, and oMEDD against discharge unit, following logarithmic transformation of the mean oMEDD distribution of each cancer subtype to approximately normal distribution. Participants with missing data were excluded (1 patient with melanoma without opioid type).

Comparisons of median oMEDD values by cancer type was performed using non-parametric testing to compare the difference between one cancer type against the total of all cancer types. The P value represented the null hypothesis, where $P<0.05$ was considered statistically significant. Confidence intervals for the median difference in oMEDD by cancer type were generated using bootstrapped quantile regression.

Analysis of median oMEDD considered against the top three most prescribed adjuvant analgesics in the patient cohort as an independent variable was performed using a Kruskal-Wallis test, where the P value represented the null hypothesis, with $P<0.05$ considered statistically significant. All analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX, USA).

## Results

In total, 41% (n=215) of the sample were prescribed SR opioids (*Table 1*). Of those prescribed SR opioids, the majority were prescribed only one SR opioid, at least one adjuvant analgesic, and had ECOG performance status score of 2 or 3. The commonest SR opioid prescribed was oxycodone (57%, n=123) followed by morphine (21%, n=45) (*Table 2*). Cancer patients prescribed SR opioids were significantly more likely stay in hospital for longer than those not prescribed SR opioids (6 *vs.* 4 days, P=0.01).

Within the 3-year pre-defined cohort, while most of

 

**Table 1** Participant baseline characteristics

| Characteristics | N [%] |
|---|---|
| Overall | 215 [41] |
| Age (years), mean ± SD | 64±14 |
| Length of stay (days), median [Q1, Q3] | 6 [3, 11] |
| Male | 110 [51] |
| Number of SR opioids | |
| 1 | 204 [95] |
| 2 | 11 [5] |
| ECOG performance status | |
| 0 | 2 [1] |
| 1 | 51 [24] |
| 2 | 85 [40] |
| 3 | 69 [32] |
| 4 | 7 [3] |
| Not recorded | 1 [1] |
| Number of adjuvant analgesics | |
| 0 | 58 [27] |
| 1 | 63 [29] |
| 2 | 64 [30] |
| 3 | 30 [14] |
| Discharge unit | |
| Medical oncology | 145 [67] |
| Palliative care | 70 [33] |

SD, standard deviation; SR, slow release; ECOG, Eastern Cooperative Oncology Group.

**Table 2** Median oMEDD according to opioid type

| Opioid | N [%] | Median oMEDD [Q1, Q3] (mg) |
|---|---|---|
| Oxycodone | 123 [57] | 90 [15, 150] |
| Morphine | 45 [21] | 60 [10, 120] |
| Fentanyl | 20 [9] | 111 [75, 150] |
| Buprenorphine | 13 [6] | 25 [25, 50] |
| Hydromorphone | 12 [6] | 150 [70, 280] |
| Methadone | 2 [1] | 157 [75, 240] |

oMEDD, oral morphine equivalent daily dose.

**Table 3** Median oMEDD requirement by cancer type

| Cancer type | N [%] | Median oMEDD [Q1, Q3] (mg) |
|---|---|---|
| Prostate | 20 [9] | 135 [60, 180] |
| Gynaecological | 20 [9] | 120 [75, 150] |
| Breast | 20 [9] | 90 [10, 545] |
| Kidney, bladder | 17 [8] | 90 [80, 180] |
| Pancreatobiliary | 20 [9] | 90 [60, 180] |
| Unknown primary | 20 [9] | 90 [60, 111] |
| Oesophageal/gastric | 17 [8] | 90 [40, 90] |
| Melanoma | 18 [8] | 75 [44, 180] |
| Lung | 20 [9] | 75 [30, 140] |
| Head & neck | 19 [8] | 60 [55, 120] |
| Brain | 4 [2] | 30 [–, –] |
| Colorectal | 20 [9] | 27.5 [25, 30] |
| All | 215 | 90 [60, 140] |

oMEDD, oral morphine equivalent daily dose.

the primary cancer types in the SR opioid group reached the *a priori* cap of 20, five tumour types did not reach the 20 participant sample size prescribed SR opioids (kidney/bladder, oesophageal/gastric, melanoma, head & neck, brain) (*Table 3*). In these tumour groups, all discharges were audited over the 3-year data collection period. Notably, it was observed that of the consecutive patients prescribed SR opioid analgesia on discharge, the relative proportion of SR opioid prescription varied by tumour type, even taking into account a larger sample size where auditing comprised the complete discharges for each tumour over the 3 years.

Although patients with brain and colorectal cancers had lower median oMEDD requirements (30 and 27.5 mg, respectively, compared to sample median of 90 mg), these were either statistically insignificant or consisting of small numbers (4 brain cancer patients) on opioids (*Table 3*). Excluding the brain cancer cohort, there was no statistically significant difference in mean oMEDD between the twelve cancer types (P=0.83) as determined via ANOVA modelling. There was also no statistically significant difference in median oMEDD between the twelve cancer types (P>0.08, varying) when each cancer type was compared in isolation

**Table 4** Median oMEDD by adjuvant analgesic in the SR opioid group

| Adjuvant analgesic | Prescribed adjuvant (mg), median oMEDD [Q1, Q3] | Not prescribed adjuvant (mg), median oMEDD [Q1, Q3] | P value |
|---|---|---|---|
| Paracetamol (n=102) | 60 [30, 90] | 30 [20, 90] | 0.0146 |
| Pregabalin (n=73) | 90 [60, 140] | 30 [18, 60] | <0.001 |
| Steroids (n=61) | 38 [22, 105] | 30 [60, 90] | 0.0715 |

oMEDD, oral morphine equivalent daily dose; SR, slow release.

to all other cancer types as a collective group.

All patients were prescribed either paracetamol, pregabalin, or steroids. A minority of patients were also co-prescribed non-steroidal anti-inflammatory drugs (n=5), Serotonin and norepinephrine reuptake inhibitors (e.g., desvenlafaxine, duloxetine) (n=6), and tricyclic antidepressants (e.g., nortriptyline, amitriptyline) (n=6). *Table 4* demonstrates adjuvant analgesic prescription for patients in the SR opioid group for paracetamol, pregabalin, and steroids. Patients prescribed pregabalin had significantly higher oMEDD doses {90 mg [interquartile range (IQR), 80] *vs.* 30 mg (IQR, 62)} than people not prescribed pregabalin. Similarly, patients prescribed paracetamol had significantly higher oMEDD doses [60 mg (IQR, 60) *vs.* 30 mg (IQR, 70)] than those who were not. There were no statistically significant differences in oMEDD between patients prescribed and not prescribed steroids.

## Discussion

### *Cancer type and opioid analgesic requirements*

The current study did not find any statistically significant difference in opioid analgesic dose between 12 different cancer types. This study considered an Australian patient cohort, its closest comparator an American paper that considered a larger cohort of 750 patients and similarly found no statistically significant difference in median oMEDD requirement across six cancer types (12). However, this study included only outpatients at point of referral to palliative care, and pain scores were not included to indicate whether pain was controlled or not at the censored timepoint.

Studies have shown a greater prevalence of pain in breast cancers (15,16) compared to lung or colon cancers. However, it has not been established whether those cancers that carry a greater likelihood of causing pain also have a greater likelihood of requiring a greater opioid dosage. Neuropathic cancer pain, however, which is responsible for approximately a third of cancer pain (17), is known to be less responsive to opioids, take longer to achieve pain control, require more modalities to achieve pain control, and to require higher doses of opioids and other analgesics compared to nociceptive pain (9,18,19). A large European study of 1,051 patients with incurable cancer found that patients with neuropathic pain were more likely to use strong opioids, adjuvant analgesics including corticosteroids, and have inferior functional outcomes (9). A recent study assessing 350 patients with cancer pain undergoing palliative care (15) found that the commonest pain aetiologies to elicit neuropathic pain were pain from nerve involvement combined with either bone or soft tissue association, rather than nerve involvement alone (15).

It is possible that cancer type itself does not necessarily relate to opioid dosage requirements. Rather, the pain type (neuropathic) and aetiology (nerve in combination with bone or soft tissue involvement) may be more important discriminators for opioid and adjuvant analgesic use. It is also plausible that patients with primary brain cancers would be less likely to be prescribed SR opioids, and require lower doses, given steroids hold a greater analgesic role than opioids in this situation, although our results contain a small number of patients in this cohort. Clear patterns on the likelihood of certain cancer types requiring higher doses of opioids has not been widely studied, and a larger study discriminating between types of pain (neuropathic, nociceptive, nociplastic), and examining its preponderance in different cancer types as well as response to opioids may provide more clarity.

### *Adjuvant analgesia and opioid analgesic requirements*

Consistent with international guidelines (3,20,21) on cancer pain management which support the use of adjuvant analgesics, our centre had a 73% adjuvant analgesic co-

 

prescription rate for those with cancer pain who were on opioids. This is concordant with other studies examining adjuvant analgesic use for cancer pain in the hospital setting which found a similar majority (>80%) of patients being co-prescribed adjuvant analgesics (22,23). These studies had gabapentin as the most commonly prescribed adjuvant analgesic whereas pregabalin was the commonest gabapentinoid prescribed in the current study, possibly relating to local government rebates favouring pregabalin for neuropathic pain. Additionally, although gabapentin and pregabalin are both gabapentinoids, research outcome data vary on their effect on cancer pain. Gabapentin has been shown to be effective in non-malignant neuropathic pain (24), however two randomized clinical trials concluded that gabapentin had either minimal (25) or no (26) clinical benefit in treating cancer pain. Pregabalin in contrast, when compared to gabapentin and amitriptyline in a randomized double-blind placebo controlled study (27), was shown to be effective, and superior in reducing oMEDD doses compared to the other arms.

Our study did not aim to assess effectiveness of adjuvant analgesics, thus it is not possible to make conclusions on its effects on cancer pain. However, in our cohort, pregabalin and paracetamol prescription were significantly associated with higher concurrent median oMEDD dose. This contrasts with the data from a previous smaller study into adjuvant analgesia for cancer pain in an inpatient palliative care unit, which found no difference in either oMEDD requirements or pain scores in patients prescribed adjuvant analgesia (22). The higher opioid requirements in patients co-prescribed adjuvant analgesics may represent a more complex cohort with multimodal pain in a quarternary cancer hospital and palliative care unit. Also, as discussed above, neuropathic pain is associated with greater opioid doses and adjuvant analgesic use, and this may be a reflection of that subgroup of patients.

The practice of increasing the dose and/or number of analgesics is a common part of cancer pain management. Yet the net effect (benefits and adverse events) of opioid and adjuvant analgesics experienced by individual patients is less clear. Prescription of any drug needs to be balanced with degree of frailty of the cohort; patients with advanced cancer are often frail, elderly, or both. The commonest prescribed adjuvant analgesic in our cohort was paracetamol, although a Cochrane review demonstrated no clinical efficacy for paracetamol (28) for cancer pain management. A US National Database study examining 3,268 nursing home residents with cancer pain observed intensification of opioids or adjuvants within 90 days of admission, particularly in those with cognitive impairment and advanced age, depression, and multiple comorbidities (29). When patients are prescribed several opioids and adjuvants, the net effect of each analgesic becomes less clear. Overtreatment of cancer pain is a recognized issue (30,31). Future research to explore the net effects of multiple co-prescribed analgesics in cancer pain may be worthwhile, balancing the potential issue of prescriber anxiety in adding towards counterproductive prescribing.

### *Limitations*

This was a retrospective study that did not include the assessment of various cancer pain syndromes nor standardized pain scores, as these were not routinely recorded in the medical history. This study was not randomized, therefore has potential for bias. Although this study captured a high number of cancer types, its limited patients per type meant it was difficult to achieve statistical power to compare differences. The study was performed in an inpatient cohort within a large quarternary cancer centre, thus may have included patients who had more complex pain. The inclusion of outpatients however would have included a varied cohort of patients, ranging from poorly controlled to well controlled pain, hence the opioid doses would not have been able to be equally treated. Study results may be less generalisable due to these reasons.

## Conclusions

We found no difference in maintenance opioid dosage used between cancer subtypes in a large quarternary cancer centre. The use of pregabalin and paracetamol were associated with significantly higher total daily oMEDD, which may in part reflect complex cancer pain in an inpatient cohort. Future studies should focus on pain type and aetiology, and pain scores to provide a greater indication of whether opioid dose is reflective of pain control. An understanding of the degree of difference in opioid and analgesic requirements in different cancer pain syndromes, and the potential contribution of overtreatment in contributing to potentially ineffective adjuvant analgesics would be of significant clinical value.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1296/rc

*Data Sharing Statement:* Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1296/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1296/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Melbourne Health Office for Research (No. QA2016086). Informed consent was not conducted in the retrospective deidentified study.



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