



ENhANCE trial protocol: A multi-centre, randomised, phase IV trial comparing the efficacy of oxycodone/naloxone prolonged release (OXN PR) versus oxycodone prolonged release (Oxy PR) tablets in patients with advanced cancer

Aaron K. Wong^{a,b,c,*}, Anneke Grobler^{d,e}, Brian Le^{a,b}

^a Department of Palliative Care Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, Victoria, 3000, Australia

^b The Royal Melbourne Hospital, 300 Grattan St, Parkville, Victoria, 3050, Australia

^c Department of Medicine, University of Melbourne, Eastern Hill Campus, Victoria Parade, Fitzroy, Victoria, 3065, Australia

^d Department of Paediatrics, University of Melbourne, Australia

^e Murdoch Childrens Research Institute, Melbourne, Australia

ARTICLE INFO

Keywords:

Pain
Neoplasms
Palliative care
Analgesics
Opioid
Constipation

ABSTRACT

Background: Oxycodone is a frequently used opioid in cancer. Opioid-induced constipation (OIC) is common. Oxycodone/Naloxone Prolonged Release (OXN PR) contains naloxone, which mitigates OIC. Trials have either focused on non-cancer pain, or conducted before significant experience of using OXN PR. This trial aims to demonstrate (1) analgesic equivalence between OXN PR and Oxycodone Prolonged Release (Oxy PR), and (2) superiority of constipation outcomes in OXN PR compared to Oxy PR in cancer pain. Unlike other trials, it will only include patients with at least moderate pain scores ($\geq 4/10$), allow usual laxatives, and exclude potential liver dysfunction.

Methods: This is a multi-centre, open-label, randomised, phase IV study of OXN PR vs Oxy PR in patients with cancer-related pain. The primary outcome is pain difference on Brief Pain Inventory-Short Form (BPI-SF) at 5 weeks. Secondary outcomes are comparison of other pain outcomes (BPI-SF) and neuropathic pain measures (Leeds Assessment of Neuropathic Symptoms & Signs (S-LANSS)), constipation (Bowel Function Index (BFI)), quality of life (EORTC-QLQ-C30), rescue analgesia use, total opioid dose, and total laxative dose over 5 weeks.

Conclusion: The comparison of analgesic efficacy between both arms, and superiority of constipation in the OXN PR arm will add new knowledge on the comparisons of both agents, and oxycodone independently. This trial will extend knowledge of the effectiveness, safety, and adverse effect profiles of both drugs in terms of pain, constipation, quality of life outcomes for patients with cancer pain, and provide clinicians with high quality data to guide decision making.

Trial registration: Name of the registry: ANZCTR

Trial registration number: ACTRN12619001282178

Date of registration: 17/09/2019

URL of trial registry record: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377673&isReview=true>

Protocol version 2.1.28 August 2020

Abbreviations: OXN PR, oxycodone/naloxone prolonged release; Oxy PR, oxycodone prolonged release; OIC, opioid-induced constipation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration calculation; BPI – SF, Brief Pain Inventory – Short Form; S-LANSS, Leeds Assessment of Neuropathic Symptoms & Signs; BFI, Bowel Function Index; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; PRO CoMiDa, Patient Reported Outcome Completion and Missing Data Checklist; PRO, Patient Reported Outcome; ITT, Intention To Treat; GEE, Generalised Estimating Equations.

* Corresponding author. Department of Palliative Care Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, Victoria, 3000, Australia.

E-mail address: aaron.wong@petermac.org (A.K. Wong).

<https://doi.org/10.1016/j.conctc.2022.101036>

Received 21 March 2022; Received in revised form 1 September 2022; Accepted 7 November 2022

Available online 13 November 2022

2451-8654/Crown Copyright © 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

Moderate to severe cancer pain affects up to two thirds of those with advanced cancer [1], and has a significant impact on quality of life [2,3]. Globally, the cancer burden is rising. In 2020 there were 19.3 million new cancer cases and 10 million cancer-related deaths, with these figures projected to double by 2070 [4]. The predicted rise of cancer incidence presents a follow-on increase in the burden of cancer-related pain.

Opioids are the mainstay of cancer pain treatment, and more than 50% of people living with cancer will receive a strong opioid in the course of cancer care [1]. Oxycodone is one of the most commonly used opioids [5,6], and is the commonest potent opioid prescribed in Australia, accounting for 73% of prescriptions as documented in centralised government dispensing records of 125,335 people [7]. Oxycodone consumption is greatest in the USA (57% of global use), followed by the United Kingdom (8%) and France (8%) [6].

A key mechanism of action for the analgesic effect of oxycodone is via its binding to μ -opioid receptors in the brain [8]. However, it also binds to μ -opioid receptors in the gastrointestinal tract inhibit neural pathways within the enteric nervous system that coordinate motility, thus depressing peristaltic contractions resulting in delayed gastric emptying and slowing the intestinal transit [9]. While oxycodone is effective in managing cancer pain, its use is frequently complicated by opioid-induced constipation (OIC) through this mechanism [10–12].

Up to 90% of patients on opioids suffer from opioid induced bowel dysfunction, of which OIC is reported to be most debilitating [10–12], adding to new iatrogenic symptoms in already unwell cancer patients. Naloxone is a competitive opioid receptor antagonist used to reverse the effects of oxycodone. When administered orally at low doses, naloxone antagonises peripheral opioid receptors in the gastrointestinal tract while sparing central opioid analgesic actions [13,14]. Oxycodone/Naloxone Prolonged Release (OXN PR) consists of Oxycodone: Naloxone at a 2:1 ratio, where the aim of the addition of naloxone to oxycodone is to reduce the effects of OIC [15]. Studies have shown that OXN PR provides equivalent analgesia to oxycodone PR (Oxy PR), whilst significantly reducing the impact of OIC in patients with moderate-to-severe non-cancer pain [16–20]. There are several gaps within the current literature for the use of OXN PR in cancer pain.

The characteristics and management of non-cancer pain are different compared to cancer pain in terms of pathophysiology and principles of opioid dosing and escalation, and it is important to build on the evidence in the outcomes of these medications in cancer pain. Additionally, hepatic disease is important to consider in this population.

In patients with a healthy liver, plasma naloxone concentration is only <2% when given at doses <150 mg [14]. This does not cause significant enough antagonism of the central μ -opioid receptors to reduce the central analgesic effects of oxycodone. However, in moderate to severe liver dysfunction, naloxone plasma concentrations can increase by > 100-fold [21], which counteracts the desired central analgesic effects of oxycodone. In advanced cancer, hepatic disease can be a consequence of secondary metastatic spread of the tumour to the liver, systemic treatment with chemotherapeutic agents or antiendocrine therapy, or comorbid disease [22,23]. The incidence of chemotherapy-related hepatotoxicity ranges between 12.1% and 80% depending on treatment regimens and patient population [22,24]. Existing evidence and product information place contraindication on the use of OXN PR for those with ‘moderate’ or ‘severe’ hepatic failure, based on Child-Pugh score, however this is not a standard method of assessing liver function in the cancer population [25]. The Child-Pugh score is also not a good predictor of reduced first pass metabolism [25] and does not account for other common causes of poor liver metabolism, such as liver metastases, liver cirrhosis, or portal-systemic shunting [25]. Liver dysfunction results in elevated concentrations of both unmetabolised oxycodone and naloxone, however with disproportionately higher naloxone concentrations [21]. When given alone in

liver dysfunction, oxycodone can lead to opioid toxicity at lower than expected doses. The addition of naloxone, with its disproportionately greater plasma concentrations, leads to a significantly lower analgesic response. In order to prevent this common and under-recognised confounder, this is the only trial of OXN PR and Oxy PR that carefully excludes all potential common causes of liver dysfunction in this population. Our trial pragmatically specifies acceptable cut-off values for safety of administration of OXN PR based on serum biochemistry, and the lack of liver metastases or comorbid liver disease, to reflect “real-world” practice in cancer and palliative care.

In terms of OXN PR or Oxy PR, the choice between using one or the other as first line opioid may lie in clinician preference or perception of effect. It is not always possible to pre-empt when a cancer patient may develop liver metastases. Those who are commenced on OXN PR, and subsequently develop liver metastases, will experience a worsening in analgesic efficacy necessitating an opioid conversion into Oxy PR or another suitable opioid. Are the analgesic and anti-constipating effects of OXN PR worth this potential risk? Ahmedzai et al. [15] showed improvements in constipation in the OXN PR arm compared to the Oxy PR arm. However, part of its clinical significance was based on a reduction of mean oral bisacodyl dose from 32.7 mg to 26.1 mg – a 20% decrease in dose required. This result was not statistically significant, and one could argue that the pill burden and requirement for laxatives are still present nonetheless. Furthermore, the bisacodyl dose used was several times higher than the recommended doses of 5–10 mg/day [26], meaning it may not be easily translatable to usual clinical practice, where other laxatives would be introduced earlier. Our trial allows several laxatives to reflect what is done in usual care, which are captured on a medication diary.

In terms of pain, although OXN PR and Oxy PR were shown in the pivotal trial to provide no significant differences in analgesic efficacy, average pain scores on the BFI at enrolment was low, with mean (SD) 3.42 (2.03) and 3.63 (1.76) for OXN PR and Oxy PR, respectively [15]. These patients reported low rescue medication use meaning their pain did not change significantly throughout the trial to achieve moderate or severe levels. Our trial only includes patients with pain scores of 4 or above, closer to the standard cut-off used for “moderate” cancer pain [27], which will provide important answers on pain outcomes for cancer patients with moderate to severe pain.

This study will examine the use of OXN PR in patients with any metastatic (Stage IV) or unresectable solid or non-solid organ malignancy without evidence of cirrhosis, portal hypertension, or liver metastasis. We also use standard liver biochemistry (instead of Child-Pugh score) as a clinically practical method to assess for liver function, thus employing a real-world approach to considering safety for use of OXN PR. Our novel approach will also compare any differences in response to neuropathic pain, quality of life, total opioid dose, rescue analgesia use, and total laxative use. We also evaluate maintenance of analgesia and effects on bowel function in patients who switch between treatments for 6 weeks.

2. Methods

2.1. Aims

This trial aims to demonstrate (1) equivalence in analgesic efficacy between OXN PR and Oxy PR amongst cancer patients with pain, and (2) superiority of constipation management in OXN PR compared to Oxy PR amongst cancer patients with pain. Our hypothesis is that both arms are analgesically equivalent, and that constipation outcomes are superior in the OXN PR group compared to the Oxy PR group.

2.2. Primary objective

To demonstrate analgesic equivalence amongst cancer patients with pain who are taking OXN PR compared with patients taking Oxy PR over

a 5-week period, based on average pain over last 24 h as measured by the Brief Pain Inventory- Short Form (BPI-SF). Thus, the primary outcome is pain difference on Brief Pain Inventory-Short Form (BPI-SF) at 5 weeks. The equivalence margin is defined as 1 point on the pain numeric rating scale which is the minimal clinically important difference [28,29].

2.3. Secondary objectives

- 1) To compare effects of OXN PR or Oxy PR on
 - Constipation, as measured by the Bowel Function Index over a 5-week period.
 - Quality of Life (nausea, vomiting, diarrhea, appetite, functional activity, breathlessness, insomnia, fatigue, mood, memory), as measured by the EORTC-QLQ-C30 over a 5-week period.
 - Rescue analgesia use defined as total dose and frequency of immediate release opioid
 - Total opioid dose defined as total oral morphine equivalent daily dose
 - Total laxative use defined as total dose and frequency of laxative use
- 2) To demonstrate equivalence of OXN PR and Oxy PR on other pain measures, such as worst pain over preceding 24 h, least pain over preceding 24 h, and current pain at completing questionnaire (as measured by BPI-SF) over a 5-week period.
- 3) To evaluate maintenance of analgesia and effect on bowel function in patients who switch from Oxy PR to OXN PR, and from OXN PR to OxyPR.

Secondary outcomes are comparison of other pain outcomes (BPI-SF), constipation (Bowel Function Index (BFI)), quality of life (EORTC-QLQ-C30), rescue analgesia use, total opioid dose, and total laxative dose over 5 weeks.

2.4. Trial design

This is a multi-centre, open-label, randomised, phase IV study of OXN PR or Oxy PR in patients with metastatic (Stage IV) or unresectable solid tumours or haematological malignancies with cancer-related pain.

The study flowchart is listed in Fig. 1. The study protocol and related documents were reviewed and approved by the institutional Human Research Ethics Committee (HREC/55080/PMCC-2019).

2.5. Setting

This study is conducted at 5 metropolitan hospital sites in Victoria, Australia, with large cancer and palliative care services – Peter MacCallum Cancer Centre, The Royal Melbourne Hospital, Austin Health, St Vincent's Hospital Melbourne, and Western Health.

2.6. Participant characteristics

Patients aged ≥ 18 with a diagnosis of any metastatic (stage IV) or unresectable solid tumour or haematological malignancy are eligible for participation in this study. Patients are required to have pain defined as a numeric pain rating score of ≥ 4 , and are to be clinically appropriate for Oxy PR 20–160 mg per day or OXN PR 20/10–160/80 mg per day as determined by the investigator, either as first prolonged release opioid or switched from a different opioid. Patients are allowed to be currently prescribed Oxy PR or OXN PR and willing to be randomised to either treatment. Patients must have adequate organ function as defined below within 14 days prior to randomisation: serum alanine aminotransferase $< 2.5 \times$ upper limit of normal (ULN) and/or serum bilirubin $< 2.5 \times$ ULN, serum albumin ≥ 20 g/L, estimated Glomerular Filtration Rate ≥ 50 mL/min (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation).

Patients are to be capable of swallowing oral medications and have a life expectancy of ≥ 12 weeks. Patients will be excluded if they have clinically significant gastrointestinal disease (inflammatory bowel disease, intestinal obstruction or pseudo-obstruction, active diverticular disease, gastrointestinal haemorrhage, history of bowel perforation, history of ischaemic colitis), or if they have possible difficulty metabolising the investigational product (known cirrhosis, portal hypertension or liver metastasis). Patients cannot have commenced new chemotherapy or immunotherapy treatment within 14 days prior to randomisation, nor radiotherapy to any abdominal area or site of pain within 4 weeks prior to randomisation. Patients are not allowed to be enrolled on another clinical trial with an investigational agent for pain within 30 days of randomisation.

2.7. Sample size calculation

The standard deviation used in the sample size calculation was the largest standard deviation reported (1.4) by Dupoirion et al. [30]. When the sample size in each group is 43, a two group design will have 80% power to reject both the null hypothesis that the mean BPI-SF score in OXN PR arm is not worse by more than 1 point compared to that of Oxy PR arm and the null hypothesis that the mean BPI-SF score in OXN PR arm is not better by more than 1 point compared to that of Oxy PR arm, i. e. that the two treatment arms are not equivalent in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 1.45 and that each test is made at the 5% level. This is adjusted for 10% loss to follow-up to 48 patients per arm.

This sample size also provides adequate power to detect a difference between the two treatment arms in symptoms of constipation. A sample size of 43 (or 48 if adjusted for 10% loss to follow-up) in each group has 80% power to detect a difference in means of 16 on the BFI, assuming that the common standard deviation is 26¹⁵ using a two group t-test with

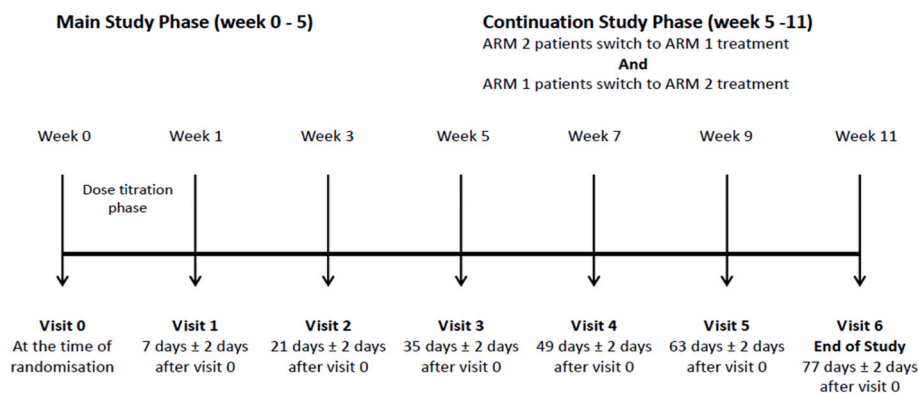


Fig. 1. Study flowchart.

a 0.05 2-sided significance level.

2.8. Randomisation

Each site will randomise consenting eligible patients electronically using an online electronic data capture system. Eligible patients will be randomised to receive in a 1:1 ratio, either:

OXN PR: Oxycodone/naloxone prolonged release for 5 weeks followed by optional switch to Oxycodone prolonged release (Oxy PR) for a further 6 weeks.

Oxy PR: Oxycodone prolonged release for 5 weeks followed by optional switch to oxycodone/naloxone prolonged release (OXN PR) for a further 6 weeks.

Approximately 96 patients will be randomised between the two arms in a 1:1 allocation ratio, stratified by site using permuted block randomisation. There are no blinding procedures for this open-label trial.

The sites planned are Peter MacCallum Cancer Centre, The Royal Melbourne Hospital, Austin Hospital, St Vincent's Hospital Melbourne, and Western Hospital. All 5 sites are located in Victoria, Australia.

2.9. Rescue medications

Immediate-release oxycodone is allowed as rescue medication for breakthrough pain, where each dose is approximately 1/6th that of the total daily dose of study medication. Patients are instructed to record all rescue medications in a medication diary provided.

If constipation occurs, patients are instructed to take oral docusate sodium with sennosides (50mg/8 mg tablets, up to 2 tablets twice daily) as a laxative rescue medication. Dose and frequency of rescue laxative use will be recorded in the medication diary. Other laxatives are also permitted and are recorded in a medication diary provided.

Compliance of study drug will be monitored via pill count and/or patient medication diary.

2.10. Study assessments

A summary of study assessments is listed in [Table 1](#). Questionnaires

Table 1
Schedule of assessments.

Trial Phase	Screening	Main Study Phase				Continuation Study Phase		
		Week 0	Week 1 7 days ± 2 days after visit 0	Week 3 21 days ± 2 days after visit 0	Week 5 35 days ± 2 days after visit 0	Week 7 49 days ± 2 days after visit 0	Week 9 63 days ± 2 days after visit 0	Week 11 77 days ± 2 days after visit 0
Assessments/Windows	Within 14 days prior to randomisation							
Clinical/Administrative Assessments								
Written informed consent	X							
Review of inclusion/exclusion criteria	X							
Demographics & medical history	X							
Review prior/concomitant medications	X	X	X	X	X	X	X	X
Australia Modified Karnofsky Performance Status (AKPS)		X	X	X	X	X	X	X
Documentation of rescue medication(s) required		X	X	X	X	X	X	X
Adverse events assessment			X	X	X	X	X	X
Review of patient diaries			X	X	X	X	X	X
Laboratory Procedures/Assessments								
Biochemistry ^a	X							
Patient Reported Outcomes								
Patient Reported Outcome Completion and Missing Data Checklist (PRO CoMiDa)		X	X	X	X	X	X	X
Bowel Function Index		X	X	X	X	X	X	X
Leeds Assessment of Neuropathic Symptoms & Signs – Self Reported (S-LANSS)		X	X	X	X	X	X	X
European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)		X	X	X	X	X	X	X
Brief Pain Inventory – Short Form	X	X	X	X	X	X	X	X

^a Biochemistry: ALT, Bilirubin, albumin, and estimated Glomerular Filtration Rate (using CKD-EPI).

used include:

- The Brief Pain Inventory – Short Form (BPI - SF) [31] is a self-administered tool consisting of 4 items relating to pain intensity (worst pain, least pain, average pain, pain right now) two items on pain relief treatment or medication, and one item on pain interference, with seven sub-items (general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life). Each item is rated on a 0–10 scale.
- The Leeds Assessment of Neuropathic Symptoms & Signs (S-LANSS) [32] is designed to identify neuropathic pain from the participant's current symptoms and signs. The S-LANSS scale has two parts; five symptom items (testing thermal sensation, autonomic changes, dysaesthesia, paroxysmal and evoked pain) and two sensory testing items assessing light touch sensation and pain sensation. Each item requires a "yes/no" response, where a score of 12 or more (out of 24) suggests pain of predominant neuropathic origin.
- The Bowel Function Index (BFI) [33] is quantitatively assesses opioid induced constipation. Three components (ease of defecation, feeling of incomplete bowel evacuation, and personal judgement of constipation) are scored by the clinician on a numerical analogue scale between 0 and 100, with the final score calculated as the mean of these three scores.
- The EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; version 3) [34] has 5 functional domains (physical, role, social emotional and cognitive functions) and 9 single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance and quality of life). Each response is rated from 0 to 4 on a Likert scale.

2.11. Statistical analyses

All analyses will be done for the main study period (Week 1 to Week 5), where the two randomised treatment arms are compared, unless stated otherwise, following the intention to treat principle.

Mean difference in BPI-SF scores between the two treatment arms

along with 95% confidence interval (CI) will be obtained from a repeated measures linear mixed effects model with fixed effects of time, treatment arm, and their interactions, and the random effects of sites and participant.

If the 95% CI for the mean difference between treatment arms excludes the equivalence margin of 1, the two treatment arms will be declared equivalent in terms of pain management. If the distribution of the data does not allow the fit of the repeated measures linear mixed models, generalised estimating equations (GEE) will be used to fit a model similar to the model described for the generalised linear mixed effects model.

2.12. Analyses of secondary outcomes

Constipation and quality of life will be analysed by the same repeated measures linear mixed effects model as described for the primary outcome.

Rescue analgesic and laxative use will be measured as the total daily dose over 24 h and will be analysed in the same way as described for constipation. Total averaged opioid dose for the week will be calculated based on data obtained from the patient diary plus rescue analgesic medication.

A subgroup analysis of the pain outcomes will be done in patients identified as having neuropathic pain according to the S-LANSS score at baseline.

2.13. Ethics, data management and monitoring

Written informed consent will be obtained from each patient before any procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. Explanation will also be provided to the patients that they are free to refuse entry into the trial and free to withdraw from the trial at any time without prejudice to future treatment. Collected data are de-identified and coded, and entered into an electronic data capture service which is designed, implemented and validated with a primary focus on data security and data integrity. A Trial Management Committee meets 6 monthly oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies. Data monitoring is conducted by an independent blinded team member. The trial sponsor is responsible for auditing of the trial, and may engage an external body to do so. Protocol amendments are submitted to the Institutional Ethics Committee and regulatory authorities for approval. The amendments are communicated to all investigators, institutional ethics committees and relevant parties on approval. Final trial data will be accessed by the investigator team only.

3. Discussion

This study protocol describes a head-to-head trial comparing the analgesic efficacy and constipation outcomes of OXN PR and Oxy PR in cancer patients. The strengths of this trial lie in its focus on “real world” practice. Building on previous trials in this area in cancer patients, our trial specifically omitted the possibility of liver dysfunction or impaired drug liver metabolism to avoid this potential and common confounding problem, which is known to impact on both the efficacy, and safety outcomes of both Oxy PR and OXN PR. We do this using a clinically pragmatic method of using liver biochemistry instead of Child-Pugh scores. This trial also places focus on only those with moderate to severe cancer pain, marked by a numerical pain score of $\geq 4/10$ at baseline. We believe this will be a more representative sample of cancer patients requiring opioids, given the recommendation for oxycodone for this demographic [35]. Finally, this trial also allows laxative use beyond a single agent (e.g. bisacodyl alone). The primary laxative used will be oral docusate sodium with sennosides. Other laxatives will also be

permitted. Our approach also compares any differences in response to neuropathic pain, quality of life, total opioid dose, rescue analgesia use, and total laxative use. We also evaluate maintenance of analgesia and effects on bowel function in patients who switch between treatments for 6 weeks.

There were several minor amendments to the inclusion criteria. Firstly, the trial initially only included patients with Stage IV disease. However, it became apparent that certain locally advanced solid cancers (e.g. head and neck cancer, pancreatic cancer), are not considered curable, where pain is treated the same way as metastatic cancers. Additionally, haematological cancers do not necessarily have a Stage IV (e.g. myeloma). We thus amended the inclusion criteria to include unresectable and/or incurable solid or haematological cancers for more accurate representation of the intended demographic. Secondly, medication compliance was initially monitored using pill count through returned blister packs at each assessment time point. However, due to COVID-19 restrictions, the trial had to adapt to a predominant telehealth model, which meant that it was difficult to do this, as some patients only had access to telephone without video. To mitigate this issue, we amended the protocol to include a patient medication diary to assess compliance. Thirdly, we initially included only patients with a better performance status, defined by Australian-modified Karnofsky Performance Status [36] of 50 or above. We later found that this had unreasonably excluded participants on the basis of mobility (e.g. lower limb pathological fracture), when the original intention had been to exclude patients who were too unwell to participate. This criterion was later on lifted to better capture the intended representative sample, and the 12-week prognosis requirement retained.

A limitation of this study is in its non-blinded nature, which may introduce bias. However, blinded trials may discourage participation [37], which is problematic in an enriched sample of already unwell cancer patients with moderate to severe pain. Blinding may also reduce the capacity to predict response accurately, since it is not reflective of routine practice [37], where clinicians and patients actually do know which drug is being used. The trial is randomised nonetheless, which eliminates selection bias and balances patient characteristics between the treatment groups.

This trial will be able to uncover new information by testing the hypothesis of analgesic equivalence between Oxy PR and OXN PR in a group of cancer patients with moderate to severe pain. It will answer the question about superiority in constipation outcomes of OXN PR compared to Oxy PR, and whether this is of clinical significance. Essentially, the data presented in the study will help to extend our knowledge of the effectiveness, safety and adverse effect profile in patients with advanced cancer.

Ethics approval and consent to participate

This study has been approved by the Human Research Ethics Committee of Peter MacCallum Cancer Centre (Reference number HREC/55080/PMCC-2019). Oral and written information about the voluntary study and all its requirements are provided to all participants, who are required to provide informed consent in writing prior to any study interventions.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This study is supported and sponsored by the Victorian

Comprehensive Cancer Centre, with partial industry funding from Mundipharma Pty Ltd. The sponsor and funding source were not involved in the study design, and the collection, analysis, management and interpretation of data, nor in the writing of the manuscript.

Authors' contributions

BL: conception; BL, AG, AW: design; AG: statistical input; BL, AW: trial supervision; AW drafted the paper and all authors read, amended, and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge Juliana Di Iulio and Daniela Surace for input into protocol writing.

References

- [1] A. Meñaca, et al, End-of-life care across Southern Europe: a critical review of cultural similarities and differences between Italy, Spain and Portugal, *Crit. Rev. Oncol. Hematol.* 82 (2012) 387–401.
- [2] J. Patijn, J. de Rijke, M. van den Beuken-van Everdingen, et al., Prevalence of pain in patients with cancer: a systematic review of the past 40 years, *Ann. Oncol.* 18 (2007) 1437–1449, <https://doi.org/10.1093/annonc/mdm056>.
- [3] M.G. Nayak, A. George, M.S. Vidyasagar, et al., Quality of life among cancer patients, *Indian J. Palliat. Care* 23 (2017) 445–450, <https://doi.org/10.4103/IJPC.IJPC.82.17>.
- [4] I.B.F. Soerjomataram, Planning for tomorrow: global cancer incidence and the role of prevention 2020–2070, *Nat. Rev. Clin. Oncol.* (2021), <https://doi.org/10.1038/s41571-021-00514-z>. Published online 2 June 2021.
- [5] *Health Alo and Welfare, Opioid Harm in Australia: and Comparisons between Australia and Canada*, AIHW, Canberra, 2018.
- [6] *International Narcotics Control Board, Narcotic Drugs: Estimated World Requirements for 2021*, United Nations, Vienna, 2020.
- [7] N. Gisev, S.-A. Pearson, B. Blanch, et al., Initiation of strong prescription opioids in Australia: cohort characteristics and factors associated with the type of opioid initiated, *Br. J. Clin. Pharmacol.* 82 (2016) 1123–1133, <https://doi.org/10.1111/bcp.13026>, 2016/07/18.
- [8] B. Lalovic, E. Kharasch, C. Hoffer, et al., Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites, *Clin. Pharmacol. Ther.* 79 (2006) 461–479, <https://doi.org/10.1016/j.clpt.2006.01.009>, 2006/05/09.
- [9] P. Holzer, Treatment of opioid-induced gut dysfunction, *Exp. Opin. Invest. Drugs* 16 (2007) 181–194, <https://doi.org/10.1517/13543784.16.2.181>.
- [10] S.J. King, C. Reid, K. Forbes, et al., A systematic review of oxycodone in the management of cancer pain, *Palliat. Med.* 25 (2011) 454–470, <https://doi.org/10.1177/0269216311401948>.
- [11] S.J. Panchal, P. Müller-Schwefe, J.I. Wurzelmann, Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden, *Int. J. Clin. Pract.* 61 (2007) 1181–1187, <https://doi.org/10.1111/j.1742-1241.2007.01415.x>.
- [12] B.J. Morlion, S.A. Mueller-Lissner, R. Vellucci, et al., Oral prolonged-release oxycodone/naloxone for managing pain and opioid-induced constipation: a review of the evidence, *Pain Pract.* 18 (2018) 647–665, <https://doi.org/10.1111/papr.12646>.
- [13] Y.S. Choi, J.A. Billings, Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation, *J. Pain Symptom Manag.* 24 (2002) 71–90, [https://doi.org/10.1016/S0885-3924\(02\)00424-4](https://doi.org/10.1016/S0885-3924(02)00424-4).
- [14] K. Smith, M. Hopp, G. Mundin, et al., Low absolute bioavailability of oral naloxone in healthy subjects, *Int. J. Clin. Pharmacol. Therapeut.* 50 (2012) 360–367.
- [15] S.H. Ahmedzai, F. Nauck, G. Bar-Sela, et al., A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain, *Palliat. Med.* 26 (2012) 50–60, <https://doi.org/10.1177/0269216311418869>.
- [16] M. Blagden, J. Hafer, H. Duerr, et al., Long-term evaluation of combined prolonged-release oxycodone and naloxone in patients with moderate-to-severe chronic pain: pooled analysis of extension phases of two Phase III trials, *Neuro Gastroenterol. Motil.* 26 (2014) 1792, <https://doi.org/10.1111/nmo.12463>. Report.
- [17] F. Guerriero, A. Roberto, M.T. Greco, et al., Long-term efficacy and safety of oxycodone–naloxone prolonged release in geriatric patients with moderate-to-severe chronic noncancer pain: a 52-week open-label extension phase study, *Drug Des. Dev. Ther.* (1) (2016) 1515–1523.
- [18] A. Sandner-Kiesling, P. Leyendecker, M. Hopp, et al., Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain, *Int. J. Clin. Pract.* 64 (2010) 763–774, <https://doi.org/10.1111/j.1742-1241.2010.02360.x>.
- [19] K. Simpson, P. Leyendecker, M. Hopp, et al., Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain, *Curr. Med. Res. Opin.* 24 (2008) 3503–3512, <https://doi.org/10.1185/03007990802584454>.
- [20] D. Vondrackova, P. Leyendecker, W. Meissner, et al., Original report: analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain, *J. Pain* 9 (2008) 1144–1154, <https://doi.org/10.1016/j.jpain.2008.06.014>. Article.
- [21] *Therapeutic Goods Administration, in: Australian Public Assessment Report for Oxycodone Hydrochloride/Naloxone Hydrochloride*, Australian Government Department of Health and Ageing, Canberra, 2010.
- [22] J. Floyd, I. Mirza, B. Sachs, et al., Hepatotoxicity of chemotherapy, *Semin. Oncol.* 33 (2006) 50–67, <https://doi.org/10.1053/j.seminoncol.2005.11.002>.
- [23] J. Qian, X. Zhang, B. Zhang, et al., Hepatotoxicity in advanced lung adenocarcinoma: a retrospective study of 2108 cases, *J. Cancer* 9 (2018) 1607–1613, <https://doi.org/10.7150/jca.24217>.
- [24] S.J. Clarke, R. Abratt, L. Goedhals, et al., Phase II trial of pemetrexed disodium (ALIMTA, LY231514) in chemotherapy-naïve patients with advanced non-small-cell lung cancer, *Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol.* 13 (2002) 737–741, <https://doi.org/10.1093/annonc/mdf115>, 2002/06/22.
- [25] B.H. Le, G. Aggarwal, C. Douglas, et al., Oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe, chronic cancer pain: challenges in the context of hepatic impairment, *Asia Pac. J. Clin. Oncol.* (2021), <https://doi.org/10.1111/ajco.13561>, 2021/03/05.
- [26] M. Corsetti, S. Landes, R. Lange, Bisacodyl: a review of pharmacology and clinical evidence to guide use in clinical practice in patients with constipation, *Neuro Gastroenterol. Motil.* (2021), e14123, <https://doi.org/10.1111/nmo.14123>.
- [27] A. Woo, B. Lechner, T. Fu, et al., Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: a literature review, *Ann. Palliat. Med.* 4 (2015) 176–183, <https://doi.org/10.3978/j.issn.2224-5820.2015.09.04>.
- [28] S. Deslauriers, J.-S. Roy, S. Bernatsky, et al., The association between waiting time and multidisciplinary pain treatment outcomes in patients with rheumatic conditions, *BMC Rheumatol.* 4 (2020) 59, <https://doi.org/10.1186/s41927-020-00157-0>.
- [29] R.H. Dworkin, D.C. Turk, K.W. Wyrwich, et al., Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMEDIATE recommendations, *J. Pain* 9 (2008) 105–121, <https://doi.org/10.1016/j.jpain.2007.09.005>, 2007/12/07.
- [30] D. Dupouiron, A. Stachowiak, O. Loewenstein, et al., Long-term efficacy and safety of oxycodone-naloxone prolonged-release formulation (up to 180/90 mg daily) – results of the open-label extension phase of a phase III multicenter, multiple-dose, randomized, controlled study, *Eur. J. Pain* 21 (2017) 1485–1494, <https://doi.org/10.1002/ejp.1050>.
- [31] C.S. Cleeland, K.M. Ryan, Pain assessment: global use of the Brief pain inventory, *Ann. Acad. Med.*, Singapore 23 (1994) 129–138, 1994/03/01.
- [32] M.I. Bennett, B.H. Smith, N. Torrance, et al., The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research, *J. Pain* 6 (2005) 149–158, <https://doi.org/10.1016/j.jpain.2004.11.007>, 2005/03/18.
- [33] P. Ducrotte, C. Caussé, The Bowel Function Index: a new validated scale for assessing opioid-induced constipation, *Curr. Med. Res. Opin.* 28 (2012) 457–466, <https://doi.org/10.1185/03007995.2012.657301>, 2012/01/13.
- [34] P.M.A.N. Fayers, K. Bjordal, M. Groenvold, D. Curran, A. Bottomley, *EORTC QLQ-C30 Scoring Manual, third ed.*, EORTC Quality of Life Group, Brussels, 2001.
- [35] M. Schmidt-Hansen, M.I. Bennett, S. Arnold, et al., Oxycodone for cancer-related pain, *Cochrane Database Syst. Rev.* 8 (2017), Cd003870, <https://doi.org/10.1002/14651858.CD003870.pub6>, 2017/08/23.
- [36] A.P. Abernethy, T. Shelby-James, B.S. Fazekas, et al., The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481], *BMC Palliat. Care* 4 (2005) 7, <https://doi.org/10.1186/1472-684X-4-7>.
- [37] R. Anand, J. Norrie, J.M. Bradley, et al., Fool's gold? Why blinded trials are not always best, *BMJ (Clinical research ed)* 368 (2020), l6228, <https://doi.org/10.1136/bmj.l6228>, 2020/01/23.