Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial

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Summary

Background Opioid analgesics are commonly used for acute low back pain and neck pain, but supporting efficacy data are scarce. We aimed to investigate the efficacy and safety of a judicious short course of an opioid analgesic for acute low back pain and neck pain.

Methods OPAL was a triple-blinded, placebo-controlled randomised trial that recruited adults (aged ≥18 years) presenting to one of 157 primary care or emergency department sites in Sydney, NSW, Australia, with 12 weeks or less of low back or neck pain (or both) of at least moderate pain severity. Participants were randomly assigned (1:1) using statistician-generated randomly permuted blocks to guideline-recommended care plus an opioid (oxycodone–naloxone, up to 20 mg oxycodone per day orally) or guideline-recommended care and an identical placebo, for up to 6 weeks. The primary outcome was pain severity at 6 weeks measured with the pain severity subscale of the Brief Pain Inventory (10-point scale), analysed in all eligible participants who provided at least one post-randomisation pain score, by use of a repeated measures linear mixed model. Safety was analysed in all randomly assigned eligible participants. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000775516).

Findings Between Feb 29, 2016, and March 10, 2022, 347 participants were recruited (174 to the opioid group and 173 to the placebo group). 170 (49%) of 346 participants were female and 176 (51%) were male. 33 (19%) of 174 participants in the opioid group and 25 (15%) of 172 in the placebo group had discontinued from the trial by week 6, due to loss to follow-up and participant withdrawals. 151 participants in the opioid group and 159 in the placebo group were included in the primary analysis. Mean pain score at 6 weeks was 2·78 (SE 0·20) in the opioid group versus 2·25 (0·19) in the placebo group (adjusted mean difference 0·53, 95% CI −0·00 to 1·07, p=0·051). 61 (35%) of 174 participants in the opioid group reported at least one adverse event versus 51 (30%) of 172 in the placebo group (p=0·30), but more people in the opioid group reported opioid-related adverse events (eg, 13 [7·5%] of 174 participants in the opioid group reported constipation *vs* six [3·5%] of 173 in the placebo group).

Interpretation Opioids should not be recommended for acute non-specific low back pain or neck pain given that we found no significant difference in pain severity compared with placebo. This finding calls for a change in the frequent use of opioids for these conditions.

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Introduction

Low back pain and neck pain are very prevalent,[1] with low back pain being the largest contributor to years lived with disability globally, and neck pain being the fourth largest.[2,3] Low back pain and neck pain also impose the highest direct costs of any medical condition.[4] The economic burden is even greater when the indirect costs are also considered.[5]

Clinical guidelines recommend opioid analgesics for people with acute low back or neck pain only when other pharmacological treatments are contraindicated or have not worked.[6] Despite these guidelines, as high as two-thirds of people in Australia receive an opioid as first-line treatment when presenting for care with low back pain and neck pain.[7] In the USA, opioid prescription rates have decreased in the previous decade, but were still dispensed at a rate of 43·3 prescriptions per 100 people in 2020.[8] The use of opioids for the management of acute low back pain and neck pain is not supported by direct and robust evidence.[9] A further concern regarding opioid use is the risks of adverse events, which can be serious (eg, dependency, misuse, and overdose) and could lead to increased mortality.[10,11] There have been recent calls to reduce the use of opioids, including guidelines from the US Centers for Disease Control and Prevention, the National Institute for Health and Care Excellence in the UK, the Stanford–*Lancet* Commission, and the Australian Commission on Safety and Quality in Healthcare.[11–14]

The aim of this research was to investigate the efficacy and safety of a judicious short course of an opioid analgesic for the management of acute non-specific low back pain and neck pain.

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See Online for appendix

Research in context

Evidence before this study

We searched electronic databases MEDLINE (via Ovid), Embase (via Ovid), Cochrane Central Register of Controlled Trials and Systematic Reviews, and the WHO International Clinical Trials Registry Platform for trials or reviews published from database inception to June 9, 2022, which contained search terms "opioid", "placebo", and "low back" or "neck pain" or both (and synonyms). We assessed the quality of trials using the Cochrane ROB 1 tool and reviewed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) ratings reported for the certainty of evidence in the systematic reviews. To our knowledge, there are no systematic reviews of opioid analgesics versus placebo for acute spinal pain. A previous review of opioids for spinal pain did not identify any studies on acute pain and found small to no effects of opioids on chronic pain. A review of opioids for acute musculoskeletal pain excluding back pain found that opioids had a small effect over placebo. We found three trials that had some degree of overlap with the OPAL trial. In one trial (low risk of bias) all participants received a non-steroidal anti-inflammatory drug besides an opioid or placebo. This trial found no benefit of adding opioids to non-steroidal anti-inflammatories. The second trial examined acute flares on chronic neck pain, and the final trial had a short follow-up (2·5 days) and was industry sponsored. These trials reported moderate effects of opioids on pain but had high risk of bias.

Added value of this study

This study is not sponsored by industry and is the first placebo-controlled trial of an opioid analgesic, without the addition of another pain medicine, for acute low back and neck pain. The study reports data on the safety and efficacy of opioids up to the 12-month follow-up, as opposed to many other studies of opioids in acute and chronic low back pain and neck pain, which had short-term follow-ups only and used an enrichment design.

Implications of all the available evidence

Our findings support the results from other studies and reviews on similar populations, which found that the effects of opioids on back and neck pain, and musculoskeletal pain in general, were probably small to none. Our findings also go further to say that not only are opioids not going to benefit individuals with back and neck pain, but they might also cause worse outcomes even after short-term judicious use.

Methods

Study design

The OPAL trial was an investigator-led, multicentre, triple-blinded, randomised controlled trial conducted across 157 primary care clinics and hospitals in Sydney, NSW, Australia. The trial protocol has been published and is summarised in this paper.[15] The trial was designed and overseen by a steering committee. The trial protocol was approved by the University of Sydney's Human Research Ethics Committee (approval number 2015/004) and the Royal Prince Alfred Hospital's Research Ethics Committee (protocol number X16-0390). The trial was done in accordance with the principles of the Declaration of Helsinki.

Participants

Participants were assessed for eligibility and recruited as they presented to general practitioners (GPs) or a hospital emergency department with a primary complaint of low back pain or neck pain (or both). An advertising campaign on social media was also trialled to identify potential participants and refer them to a trial doctor for screening, assessment, and potential enrolment.

Eligible participants had low back pain (pain between the 12th rib and buttock crease) or neck pain (pain below the occiput to the most distal cervical spine), or both, with or without radiation to the leg (for low back pain) or arm (for neck pain); a current episode of pain for 12 weeks or less and preceded by at least a 1-month period free from back and neck pain; and at least moderate pain severity (as measured by adaptations of item 7 of the 36–Item Short Form Health Survey [SF-36]—ie, how much low back pain or neck pain [none, very mild, mild, moderate, severe, or very severe] the participant had experienced in the previous week). Potential participants were excluded if they had known or suspected serious spinal pathology (eg, cauda equina syndrome, spinal fracture); contraindications to opioid analgesics based on the recruiting doctor's clinical judgment or scoring high risk on the Opioid Risk Tool;[16] taken a prescription opioid analgesic for the current episode of low back pain or neck pain at a dose higher than 15 mg of oral morphine equivalent per day for 5 or more consecutive days; spinal surgery in the preceding 6 months; scheduled or being considered for surgery or interventional procedures for low back pain or neck pain (or both) during the 6-week treatment period; younger than 18 years; insufficient English language skills or if interpretation was unavailable; and female participants who were planning conception, pregnant, or breastfeeding. All included participants provided informed written consent.

Sex was measured by self report, giving options of male or female. Changes were made to the exclusion criteria during the trial to facilitate recruitment and in response to the up-scheduling of codeine from an over-the-counter to prescription-only medicine in Australia in February, 2018.[17] The original protocol (version 1.0) states that participants must have had back or neck pain (or both) for a minimum of 2 weeks and excluded participants who had taken any prescription opioid (appendix pp 4–6).

Randomisation and masking

All participants were screened by a masked trial doctor who also obtained informed consent. Participants who were identified in emergency departments were referred to a back pain clinic in which a trained trial doctor (rheumatologist) performed the screening process as per protocol. Participants identified from social media were referred to a trial GP for screening as per protocol. The masked trial doctor then provided all participants with guideline-recommended care and a prescription for the trial medicine kit.

Participants were masked and randomly assigned (1:1) to the opioid or placebo group. The randomisation sequence was created using randomly permuted blocks by an independent statistician (who had no involvement in the rest of the trial), then shared with the trial drug manufacturer (PCI Pharma Services, Melbourne, Australia) who created identical medication kits to conceal allocation. The kits were numbered sequentially and sent to pharmacies. The participant filled their prescription at a participating blinded pharmacy to receive a trial medicine kit containing either an opioid (modified release oxycodone–naloxone) or placebo, dispensed by pharmacists. Individuals assessing outcomes and analysing the data were also masked to group assignment until the analyses were completed and interpretation was agreed upon by all study authors. Tablets were identical in appearance. Success of masking was assessed by asking participants to estimate which group they were allocated to at the week 6 survey.

Procedures

The medication regimen for those assigned to the opioid group started at an oral dose of 5 mg oxycodone and 2·5 mg naloxone as a modified release tablet, twice a day. This dose was gradually titrated up to the maximum dose of 10 mg, twice a day, on the basis of individual participant progress, tolerability, and sedation score, before down-titration to cessation. Treatment continued until adequate improvement (ie, a pain score of 0–1 out of 10 for 3 consecutive days) or for a maximum of 6 weeks. Participants were advised to return to their doctor for follow-up, including repeat prescriptions if appropriate, at weekly intervals. The oxycodone–naloxone combination was chosen to minimise the side-effect of constipation and therefore the risk of unblinding. The modified release formula was selected to allow twice daily dosing and therefore improve the ease and likelihood of compliance.

The placebo group received identical-looking tablets made of colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate, coated in brilliant blue (FCF C142090; PCI Pharma Services, Melbourne, VIC, Australia), and followed the same regimen. All participants were advised not to take non-study opioids during the intervention period. The study doctor was asked to provide guideline-recommended care to both groups. Guideline care was reassurance of a positive prognosis, advice to stay active and to avoid bed rest, and if required, other guideline-recommended treatments including non-opioid analgesics.[6] However, care was not monitored and provision of other guideline-recommended treatments could be individualised for each patient.

Trial doctors were trained in trial practices and guideline-recommended care for acute low back pain by trial staff upon joining the trial, with additional refreshers provided as needed. Monitoring visits of doctors were done regularly throughout the trial.

Data were collected at baseline, then at weeks 2, 4, 6, 12, 26, and 52 by use of a REDCap database. Outcomes and adverse events were measured via participants completing online surveys, or by research assistants over the phone if preferred by the participant. Adverse events were graded as either serious or not serious as per the Australian National Health and Medical Research Council's Safety Monitoring and Reporting in Clinical Trials guidelines.[18]

Outcomes

The primary endpoint was pain intensity (measured on a 0–10 scale by the Brief Pain Inventory Pain Severity Subscale) at 6 weeks after randomisation. The secondary outcomes and timepoints are listed in the appendix (pp 7–9).

Statistical analysis

A detailed a-priori statistical analysis plan was published before database lock.[19] A sample size of 173 participants per group (346 total) had 90% power to detect a between-group difference of 1 on a 10-point pain scale at 6 weeks assuming a SD of 2·5 and an α of 5%, and allowing for 5% dropout and 10% non-compliance. We estimated that 1 on a 10-point scale would be the minimal clinical difference.[15] All analyses were to be conducted by intention to treat—ie, by analysing all participants according to their randomised group and regardless of any departure from the protocol. The primary outcome was analysed in all randomly assigned participants who received the allocated intervention and had provided a baseline and at least one post-baseline pain score. Safety outcomes were analysed in all randomly assigned participants who received the allocated intervention.

Repeated-measures linear mixed models were used to assess the effect of treatment group on pain severity. The model included outcome data collected at every follow-up visit with fixed effects for the randomised treatment allocation, timepoint as a categorical variable, the interaction between treatment and timepoint, and the baseline pain severity score. Correlations between repeated measures were modelled using a repeated effect with a compound-symmetry structure. The primary treatment effect was estimated as the adjusted mean difference in pain severity at the week 6 visit between

groups and its 95% CI. The same model was used to estimate the effect of the treatment at weeks 12 and 52, as part of the pre-specified analyses. Continuous secondary outcomes were analysed using the same approach. Safety and health-care utilisation outcomes were reported as proportions and analysed with Fisher's exact test. Time to recovery was compared using a log-rank test and was measured from randomisation.

A prespecified subgroup analysis by site of pain and sex was done on the primary outcome. Prespecified sensitivity analyses included (1) adding duration of the current pain episode and site of pain as covariates to the main model and (2) multiple imputations of missing outcome data using fully conditional specification with 100 imputations. Post-hoc sensitivity analyses included a tipping point analysis done on the imputed data. The data and safety monitoring board met twice during the study to review safety data but there were no planned interim analyses.

Because of the clear outcome hierarchy and limited number of related secondary outcomes, we did not adjust for multiplicity; however, secondary outcome results should be interpreted as exploratory. Data were analysed and validated using SAS Enterprise Guide version 7.1. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000775516).

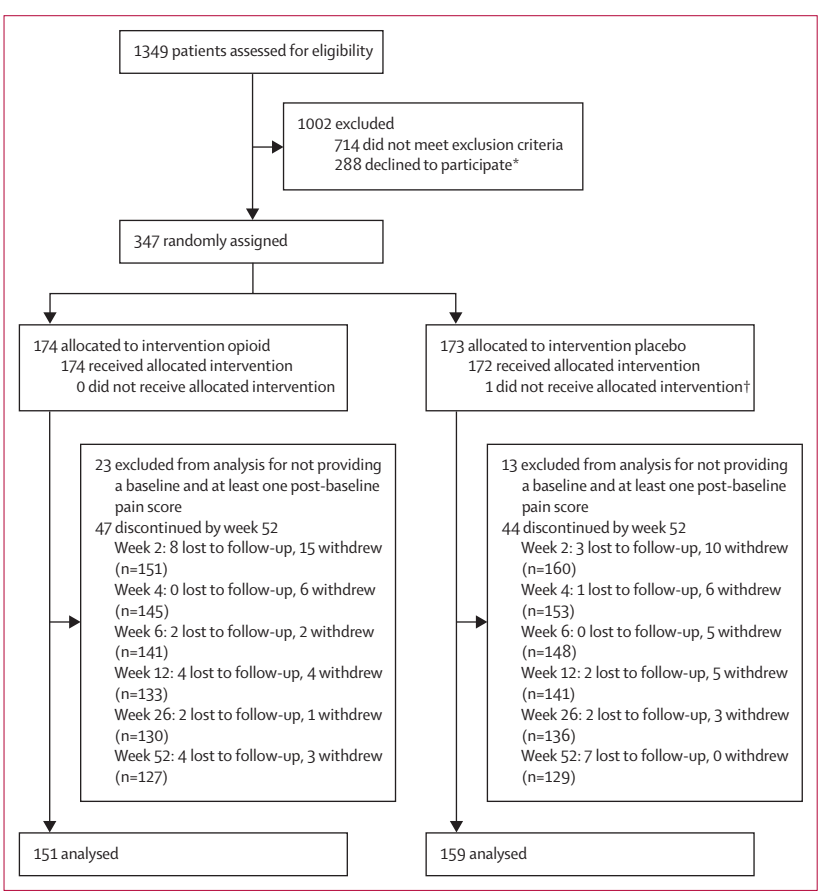

Figure 1: **Trial profile**
Participants who were lost to follow-up were those whom we were unable to contact; those who withdrew had advised trial staff they no longer wished to participate. *Reasons were collected when possible (appendix pp 10–11). †Excluded after randomisation due to a diagnosis of bony metastases.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

347 participants were randomly assigned to a treatment group between Feb 29, 2016, and March 10, 2022, when the recruitment target was reached: 174 to the opioid group and 173 to the placebo group (figure 1). One participant (from the placebo group) was diagnosed with bony metastases after randomisation and was excluded after randomisation. The mean age at baseline in the total study population was 44·7 years (SD 15·8). No major differences were found in baseline characteristics, with age, BMI, pain location, and employment status being similar across groups (table 1). The opioid group had a slightly higher proportion of female individuals than male individuals. Of the 347 participants, 335 (97%) were recruited from primary care and 12 (3%) from emergency departments; none were recruited from social media advertising. 310 (89%) participants (151 [49%] in the opioid group and 159 [51%] in the placebo group) had a baseline and at least one post-randomisation pain score, and were thus included in the primary analysis. No baseline differences in age, pain duration, or pain severity were found in participants with or without missing data at week 6, although a slightly larger proportion of female participants had missing data than male participants (appendix p 12).

No significant difference was found in pain scores at 6 weeks between the opioid plus guideline care group and the placebo plus guideline care group (adjusted mean difference 0·53, 95% CI –0·00 to 1·07, p=0·051; table 2, figure 2).

No difference was found in the primary outcome between male and female participants or between participants with low back pain or neck pain (appendix p 13). Results were consistent after further adjusting for site of pain and number of days since the onset of pain (mean difference 0·50, 95% CI –0·03 to 1·03, p=0·064). Results of multiple imputations including post-hoc tipping point analyses (appendix pp 14–15) supported main results, with the mean difference in pain score at week 6 either non-significant or favouring placebo.

Pain severity was not significantly different between groups at week 12. However, the between-group difference increased over time and by week 52 there was a small difference favouring placebo (table 2).

No significant difference was found in physical functioning measured by the generic scale (Brief Pain Inventory: pain interference) or condition-specific scale for people with neck pain (Neck Disability Index; table 2).

	Opioid (n=174)	Placebo (n=172)
Sex		
Female	93/174 (53%)	77/172 (45%)
Male	81/174 (47%)	95/172 (55%)
Age		
n	172	169
Mean (SD), years	44·0 (15·5)	45·4 (16·1)
BMI		
n	139	151
Mean (SD), kg/m²	28·4 (7·3)	28·9 (6·1)
Pain location		
Low back	136/174 (78%)	141/171 (83%)
Neck	22/174 (13%)	16/171 (9%)
Both	16/174 (9%)	14/171 (8%)
Worse pain in participants with both low back and neck pain		
Low back	7/16 (44%)	9/14 (64%)
Neck	8/16 (50%)	4/14 (29%)
Unable to determine	1/16 (6%)	1/14 (7%)
Low back pain extends to leg		
Yes	88/142 (62%)	88/145 (61%)
No	54/142 (38%)	57/145 (39%)
Neck pain extends to arm		
Yes	21/30 (70%)	11/20 (55%)
No	9/30 (30%)	9/20 (45%)
Pain duration*		
n	171	164
Mean (SD), days	21·1 (56·36)	15·9 (19·71)
Median (IQR), days	7·0 (3·0–21·0)	7·0 (3·0–21·0)
Number of episodes		
n	156	151
Mean (SD)	6·0 (13·03)	6·9 (23·59)
Median (IQR)	1·0 (0·0–6·0)	1·0 (0·0–6·0)
Currently employed		
No	55/171 (32%)	45/164 (27%)
Yes	114/171 (67%)	119/164 (73%)
Chose not to answer	2/171 (1%)	0/164
Employment classification		
Manager	17/114 (15%)	9/119 (8%)
Technician and trade worker	17/114 (15%)	17/119 (14%)
Clerical and administrative	13/114 (11%)	21/119 (18%)
Machinery operator or driver	15/114 (13%)	13/119 (11%)
Professional	17/114 (15%)	21/119 (18%)
Community or personal services worker	16/114 (14%)	13/119 (11%)
Sales worker	7/114 (6%)	11/119 (9%)
Labourer	9/114 (8%)	9/119 (8%)
Sales: self employed	0/114	1/119 (1%)
Not provided	3/114 (3%)	4/119 (3%)
Household income, AUD$ per week		
No or negative income	10/166 (6%)	8/163 (5%)
$1–799	47/166 (28%)	28/163 (17%)
$800–1999	60/166 (36%)	69/163 (42%)
$2000–3999	21/166 (13%)	18/163 (11%)

(Table 1 continues in next column)

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	Opioid (n=174)	Placebo (n=172)
$4000 or more	8/166 (5%)	9/163 (6%)
Chose not to answer	20/166 (12%)	31 (19%)
Health insurance status		
None	90/168 (54%)	74/162 (46%)
Private hospital only	14/168 (8%)	13/162 (8%)
Private ancillary (extras) only	12/168 (7%)	9/162 (6%)
Private hospital and ancillary (extras)	47/168 (28%)	61/162 (38%)
Department of Veteran Affairs†	1/168 (1%)	0/162
Chose not to answer	4/168 (2%)	5/162 (3%)
BPI pain severity		
n	174	171
Mean (SD)	5·7 (1·47)	5·6 (1·45)
BPI pain interference (0–10)		
n	167	165
Mean (SD)	5·9 (1·99)	5·7 (2·00)
RMDQ (0–24)		
n	145	148
Mean (SD)	15·7 (5·02)	15·8 (5·14)
NDI (%)		
n	35	30
Mean (SD)	39·1 (14·97)	42·0 (20·01)
Quality of life scores (SF12v2)		
Physical component		
n	156	159
Mean (SD)	35·9 (9·15)	37·1 (9·56)
Mental component		
n	156	159
Mean (SD)	45·7 (11·32)	46·0 (11·68)
Global perceived effect scale (–5 to 5)		
n	159	162
Mean (SD)	–0·4 (2·75)	–0·5 (2·74)
Participants using health services before enrolment‡		
Had imaging	8/72 (11%)	10/75 (13%)
Other health care	40/72 (56%)	49/75 (65%)
Saw a physiotherapist	24/72 (33%)	16/75 (21%)
Previous use of prescription opioid analgesic		
No	104/166 (63%)	105/160 (66%)
Yes	62/166 (37%)	55/160 (34%)

Data are n/N (%), n, mean (SD), or median (IQR). BPI-PS=Brief Pain Inventory Pain Severity. BPI-IS=Brief Pain Inventory Interference Subscale. RMDQ=Roland Morris Disability Questionnaire. N=number of participants with available data, unless otherwise stated. NDI=Neck Disability Index. *Duration of pain includes one outlier of 700 days in the opioid group. †The Department of Veteran Affairs covers the cost of health services for veterans and eligible family members in Australia. ‡Denominator is the number of participants who used any health service, and the numerator is the number of participants who used the corresponding category of service.

Table 1: **Participant baseline characteristics**

A significant difference was found in the condition-specific scale (Roland Morris Disability Questionnaire) for people with low back pain, favouring placebo at week 6 (table 2). No significant difference was found between groups for quality of life on the physical function subscale, but a small yet significant difference favouring placebo for the

	Opioid (n=174)		Placebo (n=172)		Mean difference (95% CI)	p value
	n	Mean (SE)	n	Mean (SE)		
Pain severity (BPI-PS)						
Week 2	136	3·81 (0·19)	140	3·54 (0·19)	NA	NA
Week 4	127	3·08 (0·20)	122	2·73 (0·20)	NA	NA
Week 6	132	2·78 (0·20)	138	2·25 (0·19)	0·53 (–0·00 to 1·07)	0·051
Week 12	124	2·58 (0·20)	129	2·10 (0·19)	0·48 (–0·06 to 1·02)	0·083
Week 26	121	2·67 (0·20)	126	1·87 (0·19)	NA	NA
Week 52	123	2·37 (0·20)	128	1·81 (0·19)	0·57 (0·02 to 1·11)	0·041
Physical functioning, generic (BPI-IS)						
Week 2	126	3·90 (0·22)	132	3·58 (0·21)	NA	NA
Week 4	115	2·92 (0·22)	115	2·75 (0·22)	NA	NA
Week 6	125	2·64 (0·22)	126	2·12 (0·21)	0·52 (–0·08 to 1·12)	0·088
Week 12	114	2·48 (0·22)	120	1·90 (0·22)	0·58 (–0·03 to 1·19)	0·064
Physical functioning, back (RMDQ)						
Week 6	109	8·89 (0·64)	109	6·56 (0·64)	2·33 (0·55 to 4·11)	0·011
Physical functioning, neck (NDI), %						
Week 6	23	22·70% (3·66)	19	20·98% (3·93)	1·73 (–9·16 to 12·61)	0·75
Quality of life, physical score (SF-12v2)						
Week 2	119	39·24 (0·85)	125	40·00 (0·81)	NA	NA
Week 4	112	41·44 (0·86)	113	42·28 (0·84)	NA	NA
Week 6	119	43·78 (0·85)	117	44·62 (0·83)	–0·84 (–3·17 to 1·50)	0·48
Week 12	111	45·27 (0·86)	118	45·66 (0·82)	–0·40 (–2·74 to 1·95)	0·74
Quality of life, mental score (SF-12v2)						
Week 2	119	47·46 (0·87)	125	48·50 (0·82)	NA	NA
Week 4	112	48·65 (0·88)	113	50·46 (0·86)	NA	NA
Week 6	119	48·01 (0·86)	117	51·26 (0·85)	–3·25 (–5·63 to –0·87)	0·0075
Week 12	111	48·24 (0·88)	118	51·91 (0·84)	–3·67 (–6·07 to –1·27)	0·0028
Global perceived effect scale						
Week 2	121	1·22 (0·23)	126	1·76 (0·23)	NA	NA
Week 4	114	1·81 (0·24)	114	1·93 (0·24)	NA	NA
Week 6	121	2·01 (0·23)	119	2·16 (0·23)	–0·15 (–0·80 to 0·50)	0·65
Week 12	111	2·27 (0·24)	119	2·46 (0·23)	–0·19 (–0·85 to 0·47)	0·58

For all outcomes, higher scores reflect worse outcomes except for quality of life (mental and physical) and global perceived effect, for which higher scores reflect better outcomes. BPI-PS=Brief Pain Inventory Pain Severity. BPI-IS=Brief Pain Inventory Interference Subscale. NA=not applicable. NDI=Neck Disability Index. RMDQ=Roland Morris Disability Questionnaire. SE=standard error.

Table 2: **Model results for primary and secondary outcomes**

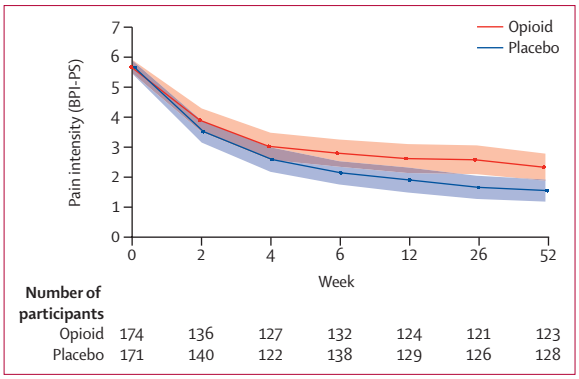

Figure 2: **Longitudinal plot of mean pain severity score**
Datapoints show mean scores at each timepoint, and the shaded areas show 95% CIs. Estimates are raw values (not modelled). BPI-PS=Brief Pain Inventory, pain severity subscale.

mental health subscale was found at 6 weeks and 12 weeks (table 2). No significant between-group difference was shown for global perceived effect scores (table 2), time to recovery (appendix pp 16–17), work absenteeism, or health-care utilisation during the treatment period (table 3). More people in the opioid group had ongoing pain at weeks 26 and 52 than in the placebo group (appendix pp 18–20). However, there was no between-group difference in overall health-care use in the 12-month follow-up period (72 [41%] of 174 participants in the opioid group reported visiting a GP, undergoing imaging, physiotherapy, seeing specialist doctors, or seeking other health care *vs* 78 [45%] of 172 participants in the placebo group; table 3) or use of opioids for people with ongoing pain at weeks 26 or 52 (appendix pp 18–20).

There was no difference between groups in the proportion of participants reporting adverse events (serious and non-serious; table 3; appendix pp 21–27). 13 serious adverse events were reported; one in the opioid group was deemed possibly related to the study treatment (an acute mental disorder). 127 non-serious adverse events were reported in 61 (35%) participants in the opioid group, and 91 non-serious adverse events were reported in 51 (30%) participants in the placebo group. The most common events across both groups were nausea and vomiting (n=33), constipation (n=30), headache (n=10), dizziness (n=9), and somnolence (n=7); all of these were more frequently reported in the opioid group except headache (appendix pp 23–27).

Risk of misuse was not different between groups at weeks 12 and 26, but significantly higher in the opioid group at week 52, with 24 (20%) of 123 participants at risk of misuse according to the Current Opioid Misuse Measure Scale compared with 13 (10%) of 128 people in the placebo group (p=0·049; table 3).

Compliance (taking at least 80% of the prescribed dose when comparing participant-reported medication diary against prescription data)[19] was similar between groups (50 [55%] of 91 in the opioid group, 61 [56%] of 108 in the placebo group; appendix pp 28–29).

78 participants had at least one protocol deviation (44 [25%] of 174 in the opioid group and 34 [20%] of 173 in the placebo group; appendix p 30); the most common deviation was having taken an opioid before randomisation (higher than the allowed dose of up to 15 mg per day of morphine equivalent for up to 5 days) or taking a concomitant opioid during the treatment period.

Success of blinding was assessed at week 6. The majority of participants did not know which group they were randomised to (64 [52%] of 122 in the opioid group and 64 [54%] of 118 in the placebo group); 29 (24%) of 122 participants correctly guessed they were in the opioid group and 37 (31%) of 118 participants correctly guessed they were in the placebo group. There was a small difference between participants who were in the

opioid group but thought they were receiving a placebo (29 [24%] of 122) and participants who were in the placebo group but thought they were receiving an opioid (17 [14%] of 118; appendix pp 28–29). No economic evaluation was done because no difference was found between treatment groups for the primary outcome.

Discussion

This study found there was no benefit of an opioid compared with placebo in people receiving guideline care for acute non-specific low back pain or neck pain. No significant difference was found in pain severity at the primary timepoint (6 weeks); however, we could not exclude a small benefit favouring placebo. The difference in pain scores between the groups increased over time until week 52, at which time there was a small but significant difference favouring placebo. For secondary outcomes, there was either no difference or small effects favouring placebo. There was no difference in the proportions of participants reporting an adverse event between groups; however, there were more reports of nausea, constipation, and dizziness in the opioid group than the placebo group. Participants in the opioid group had a greater risk of opioid misuse at week 52 than those in the placebo group. This finding is based on the Current Opioid Misuse Measure, which assesses key risk factors such as signs and symptoms of intoxication, emotional volatility, addiction, and problematic medication behaviour. Our results suggest that even a short course of opioids can increase the risk of long-term misuse. Population-based data from Australia suggest that 2·6% of adults prescribed opioids were still using opioids 12 months later.[20]

This is the first blinded, placebo-controlled, multicentre trial of an opioid for acute non-specific spinal pain to measure treatment effects including short-term harms (adverse events) and long-term harms (opioid misuse risk). The trial was prospectively registered, and the trial design, conduct, analysis, and reporting have been transparent[15,19] and independent. A limitation is that approximately 25% of data were missing at the primary timepoint, which reduced the power of the trial and could introduce bias if the data were not missing at random. This limitation was managed by analysing all participants with at least one post-baseline measurement using a repeated-measure model, thus reducing the proportion of excluded participants to 10% of all randomised participants. Sensitivity analyses using multiple imputations and tipping point analyses supported the robustness of the main findings and showed that the findings were unlikely to have been affected by the missing data. This rate of missing data is common in trials of opioids versus placebo. In two systematic reviews,[21,22] 20–21% of trials for general musculoskeletal pain (207 trials) and chronic back pain (20 trials) had more than 20% missing data.

	Opioid (n=174)	Placebo (n=172)	Fisher exact test p-value
Safety			
Serious adverse events	9 events; 7 (4%)	4 events; 4 (2%)	0·54
Related	1 event; 1 (1%)	0 events; 0	1·00
Unrelated	6 events; 4 (2%)	3 events; 3 (2%)	1·00
Outside treatment window	2 events; 2 (1%)	1 event; 1 (1%)	1·00
Adverse events	127 events; 61 (35%)	91 events; 51 (30%)	0·30
Health-care use	208 events; 72 (41%)	225 events; 78 (45%)	0·52
General practitioner	46 events; 33 (19%)	58 events; 39 (23%)	0·42
Imaging	31 events; 19 (11%)	24 events; 19 (11%)	1·00
Other health care	47 events; 24 (14%)	46 events; 28 (16%)	0·54
Physiotherapy	71 events; 42 (24%)	86 events; 46 (27%)	0·62
Specialist doctor	13 events; 10 (6%)	11 events; 8 (5%)	0·80
Use of concomitant medications for back and neck pain	381 events; 98 (56%)	385 events; 100 (58%)	0·74
Simple analgesia	91 events; 44 (25%)	77 events; 44 (26%)	1·00
NSAID	128 events; 65 (37%)	153 events; 73 (42%)	0·37
Combination opioid	48 events; 29 (17%)	36 events; 20 (12%)	0·21
Strong opioid	25 events; 16 (9%)	29 events; 18 (11%)	0·72
Weak opioid	3 events; 3 (2%)	3 events; 2 (1%)	1·00
Other	86 events; 35 (20%)	87 events; 37 (22%)	0·79
Use of concomitant medications for other reasons			
Simple analgesia	1 event; 1 (1%)	1 event; 1 (1%)	1·00
NSAID	1 event; 1 (1%)	1 event; 1 (1%)	1·00
Combination opioid	1 event; 1 (1%)	0 events; 0	1·00
Strong opioid	1 event; 1 (1%)	0 events; 0	1·00
Other	9 events; 7 (4%)	4 events; 4 (2%)	0·54
At risk of misuse (scoring 9 or more on current opioid misuse measure scale)			
Week 12	28/124 (23%)	22/129 (17%)	0·34
Week 26	24/121 (20%)	14/126 (11%)	0·077
Week 52	24/123 (20%)	13/128 (10%)	0·049
Total hours off paid work*			
n	140	147	..
Mean (SD)	24·1 (70·95)	12·3 (35·22)	0·073†
Median (IQR)	0·0 (0·0–8·0)	0·0 (0·0–16·0)	..
Range	0–460	0–374	..

Except for risk of misuse, percentages are calculated using all randomised participants who received their allocated intervention as the denominator. Denominators in the risk of misuse data are only participants with available data for this outcome. NSAID=non-steroidal anti-inflammatory drug. *For total hours off paid work, n is the number of all participants with available information on missed work including those who did not miss any work. †p value obtained using a *t* test. NA=not applicable.

Table 3: **Safety and other outcomes**

Another limitation is the compliance to the medication regimen. Only 199 (58%) of all 346 participants reported their compliance and of those, just more than half across were compliant (taking ≥80% of prescribed medicines). Importantly, compliance did not differ between groups, is consistent with other drug trials in back pain, and might reflect real-world practice.[23] A further limitation is that we did not collect data on exactly what guideline care was offered to participants in both groups. However, we did collect data on key types of health-care utilisation and concomitant medications (table 3) and did not detect

any difference between treatment groups. Deviations from the treatment protocol were monitored and are reported (appendix p 30).

Our findings show that even judicious, short-term use of an opioid conferred no benefits in pain reduction and led to a small increase in pain at the medium-term and long-term compared with placebo. The opioid group had worse quality-of-life mental health scores than the placebo group. The placebo group did better in some other outcomes, although differences were not significant. Although no difference was found in overall time to recovery, more people in the placebo group recovered in the first 14 days compared with those in the opioid group. Importantly, taking opioids had a risk of long-term misuse. The absence of effect of the opioid medicine is unlikely to be due to the oxycodone–naloxone combination. Less than 3% of the naloxone that is orally ingested reaches systemic circulation and does not have an effect on the analgesic effects of oxycodone, which has a bioavailability of 60–70%.[24] The use of oxycodone over other opioid choices reflects clinical practice in Australia, where oxycodone is the most common medicine prescribed for acute back pain.[7]

Of 346 participants, the OPAL study sample included 170 (49%) female participants, and had a mean age of 44·7 years (SD 15·8), which is representative of the population with low back and neck pain.[25] Although we did not collect racial, ethnic, or cultural data, we sampled from both metropolitan and regional geographical areas in and around Sydney, including areas with low socioeconomic status, and high cultural and linguistic diversity (Arabic, Chinese, Vietnamese, Greek, and Australian Aboriginal).

These findings differ from previous reviews on other pain conditions that have found a small effect of opioid analgesics compared with placebo for chronic low back pain[22] and other acute musculoskeletal pain.[21] However, they support findings of previous reviews showing that opioids did not add any extra pain-relieving effect to paracetamol for acute musculoskeletal injuries,[26] and were not superior to non-steroidal anti-inflammatories (NSAIDs).[21] Three previous trials compared opioids with placebo for spinal pain, two of which differ from our findings (they found a moderate effect for opioids, but were at high risk of bias),[27,28] and one of which supports our findings (no effect, low risk of bias, but the regimen included NSAIDs).[29]

Previous studies have reported substantial harms from long-term opioid use.[30] We report a small but significant risk of harm at 1 year even after short-term use. This finding is counter to guidelines, which recommend that opioids can be used judiciously for acute back pain, given that we found that there are no benefits but there is risk of harm. Our findings do, however, support the changes in guideline recommendations for low back pain management, which have seen a shift in focus from pharmacological to non-pharmacological treatments, such as physical and psychological therapies.[31] That is, the first line management of acute low back pain and neck pain should rely on reassurance and advice to stay active, and simple analgesics such as NSAIDs if necessary.[32]

Short-term, judicious use of an opioid analgesic plus guideline care did not confer any benefits for people with acute low back pain or neck pain when compared with placebo plus guideline care and had a small but significant harmful effect on risk of opioid misuse in the long-term. There is no evidence that opioids should be prescribed for people with acute non-specific low back pain or neck pain.

Contributors

C-WCL, CGM, AJM, JL, ROD, LB, and BWK conceived the trial and secured funding. C-WCL was responsible for the trial oversight. CMPJ, LB, SS, and C-WCL verified the data in this study. CMPJ prepared the data for analysis. LB and SS conducted the statistical analysis. CMPJ wrote the first draft of the manuscript with input from C-WCL. CMPJ, ROD, BWK, JL, AJM, CGM, LB, SS, and C-WCL agreed on a masked interpretation of the results, and then provided critical feedback and edits to the manuscript. All authors reviewed the manuscript before submission. For additional roles and responsibilities please see the appendix (pp 2–3). All authors had full access to all the data in this study and accept responsibility to submit for publication.

Declaration of interests

C-WCL and CGM are supported by National Health and Medical Research Council fellowships (APP1193939, awarded to C-WCL; and APP1194283, awarded to CGM). All other authors declare no competing interests.

Data sharing

De-identified sections of the dataset will be available from the corresponding author upon reasonable request from the time of publication.

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