

Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial



Christopher M Williams, Christopher G Maher, Jane Latimer, Andrew J McLachlan, Mark J Hancock, Richard O Day, Chung-Wei Christine Lin

Summary

Background Regular paracetamol is the recommended first-line analgesic for acute low-back pain; however, no high-quality evidence supports this recommendation. We aimed to assess the efficacy of paracetamol taken regularly or as-needed to improve time to recovery from pain, compared with placebo, in patients with low-back pain.

Methods We did a multicentre, double-dummy, randomised, placebo controlled trial across 235 primary care centres in Sydney, Australia, from Nov 11, 2009, to March 5, 2013. We randomly allocated patients with acute low-back pain in a 1:1:1 ratio to receive up to 4 weeks of regular doses of paracetamol (three times per day; equivalent to 3990 mg paracetamol per day), as-needed doses of paracetamol (taken when needed for pain relief; maximum 4000 mg paracetamol per day), or placebo. Randomisation was done according to a centralised randomisation schedule prepared by a researcher who was not involved in patient recruitment or data collection. Patients and staff at all sites were masked to treatment allocation. All participants received best-evidence advice and were followed up for 3 months. The primary outcome was time until recovery from low-back pain, with recovery defined as a pain score of 0 or 1 (on a 0–10 pain scale) sustained for 7 consecutive days. All data were analysed by intention to treat. This study is registered with the Australian and New Zealand Clinical Trial Registry, number ACTN 12609000966291.

Findings 550 participants were assigned to the regular group (550 analysed), 549 were assigned to the as-needed group (546 analysed), and 553 were assigned to the placebo group (547 analysed). Median time to recovery was 17 days (95% CI 14–19) in the regular group, 17 days (15–20) in the as-needed group, and 16 days (14–20) in the placebo group (regular *vs* placebo hazard ratio 0.99, 95% CI 0.87–1.14; as-needed *vs* placebo 1.05, 0.92–1.19; regular *vs* as-needed 1.05, 0.92–1.20). We recorded no difference between treatment groups for time to recovery (adjusted $p=0.79$). Adherence to regular tablets (median tablets consumed per participant per day of maximum 6; 4.0 [IQR 1.6–5.7] in the regular group, 3.9 [1.5–5.6] in the as-needed group, and 4.0 [1.5–5.7] in the placebo group), and number of participants reporting adverse events (99 [18.5%] in the regular group, 99 [18.7%] in the as-needed group, and 98 [18.5%] in the placebo group) were similar between groups.

Interpretation Our findings suggest that regular or as-needed dosing with paracetamol does not affect recovery time compared with placebo in low-back pain, and question the universal endorsement of paracetamol in this patient group.

Funding National Health and Medical Research Council of Australia and GlaxoSmithKline Australia.

Introduction

Low-back pain is the leading cause of disability worldwide.¹ Guidelines for acute low-back pain universally recommend paracetamol as the first-line analgesic.^{2,3} Although the effect of paracetamol for low-back pain is similar to that of other analgesics used for low-back pain,^{4,5} no direct evidence supports this universal recommendation. In a systematic review⁶ we noted no evidence to support the use of paracetamol for low-back pain. All seven of the included trials had substantial methodological flaws, and only one trial included more than 25 participants per group. No trial has compared paracetamol with placebo or compared as-needed dosing with the regular recommended dosing. In view of these uncertainties, the Paracetamol for Low-Back Pain Study (PACE) aimed to investigate the efficacy of paracetamol taken regularly or as-needed to improve time to recovery from pain, compared with placebo for patients with acute low-back pain. PACE also aimed to establish whether regular or as-needed paracetamol improved short-term pain

(1–12 weeks), disability, function, global rating of symptom change, sleep, or quality of life compared with placebo.

Methods

Trial design and participants

PACE was a multicentre, double-dummy, randomised, placebo controlled trial. The study protocol⁷ and analysis plan⁸ have been published. In brief, 235 primary care clinicians (181 general practitioners, 50 pharmacists, and four physiotherapists) across Sydney, Australia, screened consecutive patients who sought care for low-back pain directly or in response to a community advertisement. Inclusion criteria were a new episode of acute low-back pain (defined as pain between the 12th rib and buttock crease that was shorter than 6 weeks' duration and preceded by 1 month of no pain) with or without leg pain, and at least moderate-intensity pain (measured by an adaptation of item 7 of the Short Form [36] Health Survey). Exclusion criteria were suspected serious spinal pathology (eg, spinal cancer, infection, fracture); current

Published Online

July 24, 2014

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S0140-6736(14)60805-9)

[S0140-6736\(14\)60805-9](http://dx.doi.org/10.1016/S0140-6736(14)60805-9)

See Online/Comment

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S0140-6736(14)60978-8)

[S0140-6736\(14\)60978-8](http://dx.doi.org/10.1016/S0140-6736(14)60978-8)

The George Institute for Global Health, Sydney Medical School, University of Sydney, Camperdown, NSW, Australia (C M Williams PhD, Prof C G Maher PhD, Prof J Latimer, C-W C Lin PhD); Faculty of Pharmacy and Centre for Education and Research in Ageing, University of Sydney, Sydney, NSW, Australia

(Prof A J McLachlan PhD); Faculty of Human Sciences, Macquarie University, Sydney, NSW, Australia

(M J Hancock PhD); Clinical Pharmacology, University of New South Wales and St Vincent's Hospital, Darlinghurst, NSW, Australia (Prof R O Day MD); and Hunter Medical Research Institute and School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia (C M Williams)

Correspondence to:

Dr Christopher M Williams, Hunter Medical Research Institute, Longworth Avenue, Wallsend, NSW 2287, Australia cwilliams@georgeinstitute.org.au

use of full, regular recommended doses of an analgesic; spinal surgery in the preceding 6 months; contraindication to paracetamol; use of psychotropic drugs for a disorder judged to prevent reliable recording of study information; or pregnant or planning pregnancy.

Ethics approval was granted by the University of Sydney Human Research Ethics Committee. All participants provided written informed consent.

Randomisation and masking

Concealed random allocation to one of the three treatment groups (regular paracetamol, as-needed paracetamol, or placebo) was done in a 1:1:1 ratio. The treating clinician provided eligible patients with guideline recommended advice³ to remain active and avoid bed rest, and reassurance of the favourable prognosis of acute low-back pain. The patient was then supplied with a sealed box of study medicines and referred to the study. These medicines were prepared independently with a computer-generated randomisation schedule; a researcher not taking part in patient recruitment or data collection created a centralised randomisation schedule using the random number function in EXCEL, and a company that was independent of the study prepared the treatment packs using this schedule. Study medicine boxes were identifiable only by a unique identification number. Research staff not involved in preparation of medicine boxes collected baseline information by telephone and instructed patients to open the box and begin treatment. After confirmation of eligibility and opening of the box, patients were deemed to have been randomised to the trial. Clinicians, participants, and staff collecting outcome data, assessing outcomes, and analysing data were masked to group allocation.

Procedures

With the double-dummy design, participants were asked to take two types of tablets for up to 4 weeks: two tablets from the regular box every 6–8 h (six tablets per day), and one or two tablets from the as-needed box when needed for pain relief (4–6 h apart, to a maximum of eight tablets per day). Participants in the regular group had 665 mg modified-release paracetamol tablets in the regular box and placebo tablets in the as-needed box. Participants in the as-needed group received placebo tablets in the regular box and 500 mg paracetamol immediate-release tablets in the as-needed box. Participants in the placebo group had placebo tablets in both boxes. Placebo tablets were identical in appearance to the active tablets but did not contain paracetamol. Participants were asked to continue the study medicine until they recovered or for 4 weeks, whichever occurred first.

Clinicians were asked to schedule a review at 1 week to reinforce the study treatments (irrespective of recruitment method [ie, direct or advertisement]). If needed, rescue medications were available for participants with continuing severe pain. Rescue medication was 2 days'

supply of naproxen 250 mg (two tablets initially, then one tablet every 6–8 h as needed). We chose naproxen on the basis of investigator consensus about effectiveness and safety⁹ and because of its longer half-life, needing less frequent dosing than other analgesics.

Follow-up data, obtained at 1, 2, 4, and 12 weeks, were recorded by participants into a booklet and transcribed to a case report form during a telephone interview with research staff, or transcribed directly by the participant to an online database. Participants recorded pain scores into a daily pain and drug diary until recovery or 4 weeks. Participants who had recovered by week 4 were contacted every 2 weeks until recovery or the end of week 12 to obtain pain scores. Participants were asked to return their diary after the intervention period or with booklets containing secondary outcomes at the end of week 12.

Outcomes

The primary outcome was time until recovery from pain (in days).⁸ We chose this outcome on the basis of previous findings of fast recovery in a cohort receiving regular paracetamol.⁴ As such, we postulated that regular paracetamol would improve recovery by decreasing pain intensity and allowing people with acute low-back pain to remain active and resume normal movement as soon as possible.

Recovery was defined as the first day of 0 or 1 pain intensity, measured on a 0–10 pain scale, maintained for 7 consecutive days (sustained recovery). We selected this definition on the basis of consensus among study investigators that 7 days of being pain free would be more meaningful to patients than just 1 day. To test the robustness of our findings we also defined recovery as first recovery (the first day of 0 or 1 pain intensity on the 0–10 pain scale).

Secondary outcomes were pain intensity, disability, function, global rating of symptom change, sleep quality, and quality of life. Process measures consisted of adherence to drug (daily and at 4 weeks); concomitant treatment use and work absenteeism (at 4 and 12 weeks); adverse events (at 1, 2, 4, and 12 weeks); and treatment satisfaction and patient masking (at 12 weeks). Socioeconomic characteristics, previous and current history of low-back pain, psychosocial characteristics, and expectancy and credibility of treatment were obtained at baseline.

Pain intensity was recorded as average pain intensity for the past 24 h on a numerical pain rating scale from 0 to 10, scored from 0 (no pain) to 10 (worst possible pain).¹⁰ Disability was assessed with the Roland Morris 24 scale,¹⁰ scored from 0 (no disability) to 24 (high disability). Feelings of depression were scored from 0 (not at all) to 10 (extremely). Function was assessed with the Patient Specific Functional Scale,¹⁰ with the average of three items scored from 0 (unable to perform) to 10 (able to perform at preinjury level). Global rating of symptom change was scored

from -5 (vastly worse) to +5 (completely recovered).¹⁰ Sleep quality was based on item 6 of the Pittsburgh Sleep Quality Index (scored as very good, fairly good, fairly bad, or very bad),¹¹ obtained at baseline and at 1, 2, 4, and 12 weeks, with poor sleep quality defined as answering “fairly bad” or “very bad”. Quality of life was assessed with the Physical and Mental components of Short Form 12 (version 2),¹² obtained at baseline and at 4 and 12 weeks, with population mean of 50 and standard deviation of 10.

Self-reported adherence was the proportion of the recommended number of tablets that the participant reported they consumed, assessed at week 4 follow-up point (28 days) and reported on a 0–100 visual analogue scale; this measure was adapted from the Brief Adherence Rating Scale. Risk of persistence was scored from 0 (no risk) to 10 (very large risk). Credibility and expectation were assessed with the Credibility Expectancy Questionnaire,¹³ scored from 3 (low credibility or expectancy) to 27 (high credibility or expectancy). We defined serious adverse events as any event resulting in death or hospital admission, including pregnancy. We defined adverse events as the occurrence or diagnosis of any new medical disorder or exacerbation of any old medical disorder since most recent contact with researchers, and assessed this measure by questioning

participants at weeks 1, 2, 4, and 12. Satisfaction with treatment was assessed by direct questioning at week 12 (“overall, how satisfied were you with the study treatment?”), with satisfaction defined as a rating greater than 3 on a scale from 0 (not at all satisfied) to 6 (extremely satisfied). We assessed masking by direct questioning at week 12 with the question “do you believe the medication in box 1 (regular dosing) was real paracetamol, box 2 (as-needed dosing) was real paracetamol, or that neither were real paracetamol?”. Use of other drugs or health services for low-back pain was assessed by direct questioning at the week 4 and week 12 follow-up points. Provision of rescue medication (naproxen) was assessed by direct questioning at the week 1, week 2, and week 4 follow-up points.

Statistical analyses

With the assumption of a median recovery time of 14 days in the regular group⁴ and 17 days in the comparison groups, a sample of 1650 patients would provide 80% power to detect a difference of 3 days in median time to recovery, with a two-sided α of 0.05 and allowing for 10% non-adherence.

All data were analysed by intention to treat. Effects of treatment on the primary outcome were estimated by a Cox proportional-hazard model, with adjustment made

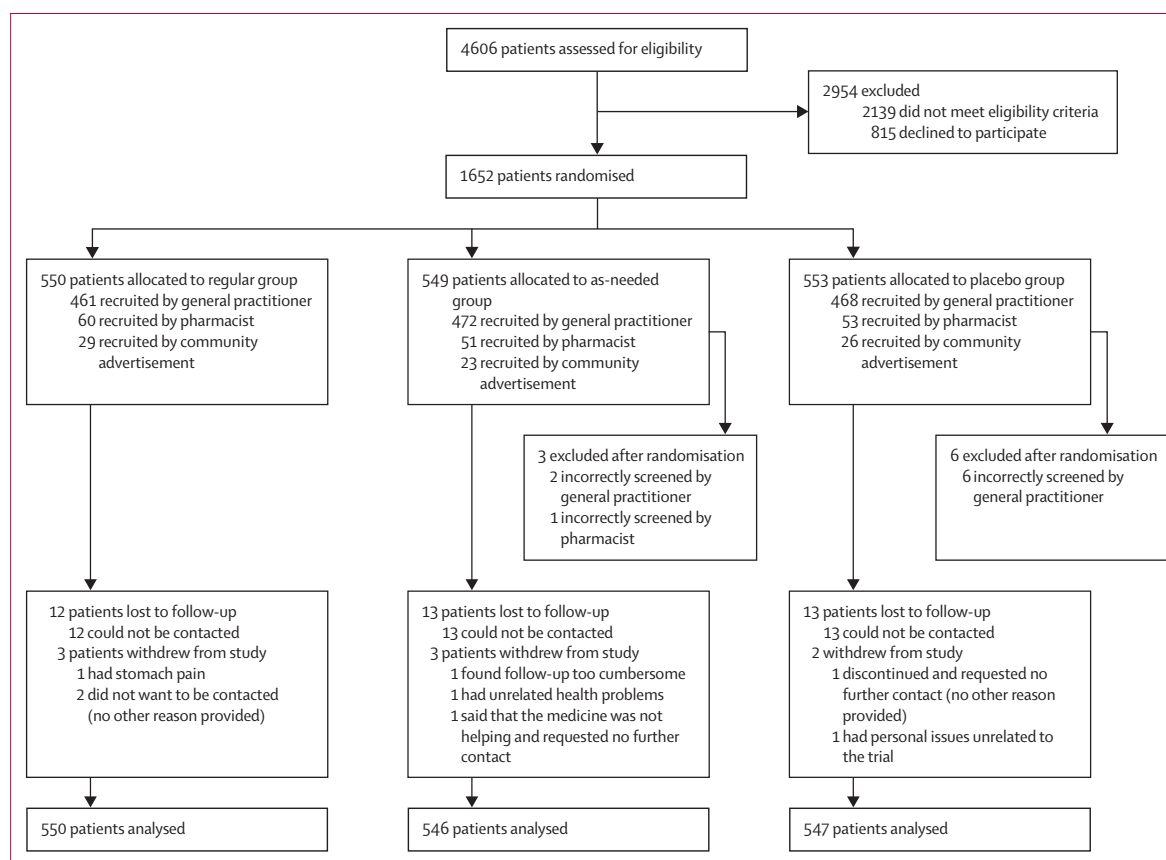


Figure 1: Consort diagram

	Regular group (N=550)	As-needed group (N=546)	Placebo group (N=547)
Patient characteristics			
Age (years)	44.1 (14.8); N=550	45.4 (16.7); N=545	45.4 (15.9); N=546
Women	264/550 (48%)	256/546 (47%)	246/547 (45%)
Private health insurance	276/550 (50%)	243/545 (45%)	250/543 (46%)
Currently employed	424/550 (77%)	403/546 (74%)	388/541 (72%)
Household income per week (per year)			
Negative or no income	19/540 (4%)	11/531 (2%)	22/530 (4%)
AUS\$1–\$649 (\$1–\$33 799)	133/540 (25%)	167/531 (31%)	168/530 (32%)
\$650–\$1699 (\$33 800–\$88 399)	243/540 (45%)	243/531 (46%)	226/530 (43%)
\$1700–\$3999 (\$88 400–\$207 999)	119/540 (22%)	92/531 (17%)	96/530 (18%)
≥\$4000 (≥\$208 000)	26/540 (5%)	18/531 (3%)	18/530 (3%)
Use of drugs for another disorder	201/550 (37%)	227/543 (42%)	202/543 (37%)
Episode characteristics			
Days since onset of pain	10.1 (10.1); N=550	9.7 (10.0); N=545	9.7 (9.8); N=546
Number of previous episodes	6.3 (13.7); N=547	7.2 (14.9); N=543	7.2 (16.9); N=544
Presence of pain extending beyond the knee	108/547 (20%)	113/546 (21%)	99/543 (18%)
Number of days reduced usual activity	3.7 (6.3); N=548	3.6 (5.8); N=543	3.4 (5.3); N=546
Disability	12.5 (5.4); N=550	12.7 (5.3); N=547	12.9 (5.3); N=546
Feelings of depression in the past week	3.2 (2.9); N=547	3.1 (2.9); N=545	3.1 (2.9); N=546
Perceived risk of persistent pain	4.6 (2.8); N=548	4.6 (2.8); N=544	4.4 (2.8); N=546
Back pain episode compensable	31/546 (6%)	44/543 (8%)	43/545 (8%)
Pain intensity	6.3 (1.9); N=550	6.3 (2.0); N=545	6.2 (1.8); N=545
Global rating of change	0.0 (2.1); N=548	−0.1 (2.2); N=545	−0.1 (2.1); N=545
Poor sleep quality	273/549 (50%)	272/545 (50%)	242/546 (44%)
Function	3.5 (1.7); N=547	3.6 (1.9); N=544	3.7 (1.9); N=544
Quality of life—physical	42.7 (9.8); N=548	42.3 (10.0); N=544	42.1 (10.6); N=546
Quality of life—mental	44.3 (8.0); N=548	44.7 (8.0); N=544	44.5 (7.9); N=546
Credibility score	19.0 (4.9); N=547	18.5 (5.3); N=542	19.3 (5.0); N=544
Expectation score	21.2 (5.7); N=547	21.1 (5.5); N=542	21.7 (5.6); N=544
Data are mean (SD) or n/N (%). N refers to the number of participants providing data. Days since onset of pain refers to the number of days since the onset of the current episode of low-back pain. Number of days of reduced activity refers to number of days the present episode forced a reduction in usual activity for more than half a day. Back pain episode compensable refers to patients claiming compensation for the present episode. AUS\$1=US\$0.94 (as of June, 2014).			
Table 1: Baseline characteristics			

for baseline pain intensity because it is an important prognostic factor.¹⁴ To minimise multiple statistical testing we used a global Wald test to assess the overall null hypothesis. If a significant difference was recorded ($p < 0.05$), pairwise comparisons were done.¹⁵ Hazard ratios (HRs) and median survival times with 95% CIs were calculated for each group.

Longitudinal mixed models were used to estimate treatment effects on continuous secondary outcomes. A log-binomial regression was used for the categorical outcome (sleep quality), with robust Poisson regression as backup in case of convergence issues.¹⁶ The main tests compared the overall outcome score between groups based on baseline and four follow-up assessments for that outcome. Statistical significance in these models was defined as p values less than 0.01.

Sensitivity analyses for the primary outcome used Cox regression models to assess the effects of recovery definition, imputation of missing data, and additional

baseline characteristics (ie, pain intensity, number of days since onset of pain, and number of previous episodes). For secondary outcomes, the effects of these characteristics were also explored. The frequency of adverse events (classified by International Classification of Diseases version 10 coding) was compared between groups with the Fisher exact test.

All primary data were double entered and checked for consistency. Secondary data were checked after data entry. Two statisticians who were masked to allocation independently did statistical analyses with SAS software (version 9.3). Discrepancies were resolved before unmasking. This study is registered with the Australian and New Zealand Clinical Trials Registry, number ACTN12609000966291.

Role of the funding source

PACE was an investigator-initiated trial funded by the National Health and Medical Research Council of

Australia. GlaxoSmithKline Australia provided subsequent supplementary funding and paracetamol and matched placebo tablets. The funders of the study had no other role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

From Nov 11, 2009, to Dec 13, 2012, 4606 patients were screened and 1652 patients were randomly assigned to treatment groups (figure 1). The mean age was 45 years (SD 16) and 876 (53%) patients were men. Nine patients were excluded by a masked researcher after randomisation because new information provided to

	Regular group (N=550)	As-needed group (N=546)	Placebo group (N=547)
Self-reported daily consumption			
Regular tablets per day			
Week 1	5.4 (3.7–6.0); N=491	5.4 (3.4–6.0); N=478	5.4 (3.4–6.0); N=474
Week 2	4.3 (0.3–6.0); N=455	4.1 (0.0–6.0); N=456	4.0 (0.0–6.0); N=450
Week 3	4.0 (0.0–6.0); N=342	3.1 (0.0–6.0); N=343	2.9 (0.0–6.0); N=330
Week 4	1.6 (0.0–6.0); N=308	0.6 (0.0–6.0); N=313	1.2 (0.0–5.7); N=296
Overall	4.0 (1.6–5.7); N=532	3.9 (1.5–5.6); N=528	4.0 (1.5–5.7); N=529
As-needed tablets per day			
Week 1	1.9 (1.0–4.3); N=490	1.9 (1.0–4.0); N=473	1.9 (1.0–4.0); N=472
Week 2	0.0 (0.0–1.4); N=453	0.0 (0.0–1.0); N=454	0.0 (0.0–1.0); N=448
Week 3	0.0 (0.0–1.0); N=340	0.0 (0.0–0.9); N=343	0.0 (0.0–1.0); N=328
Week 4	0.0 (0.0–0.6); N=306	0.0 (0.0–0.3); N=312	0.0 (0.0–0.7); N=296
Overall	0.9 (0.4–2.7); N=532	1.0 (0.4–2.9); N=528	1.0 (0.5–2.7); N=529
Self-reported adherence questionnaire			
Participants consuming more than 70% of the recommended dose	230/451 (51%)	229/446 (51%)	196/414 (47%)
Concomitant treatments			
Participants receiving rescue medication (naproxen)			
Total	2/518 (<1%)	4/513 (1%)	6/517 (1%)
Week 1	0/518	2/513 (<1%)	3/517 (1%)
Week 2	2/518 (<1%)	2/513 (<1%)	3/516 (1%)
Participants using other drugs			
Total	107/525 (20%)	116/513 (23%)	119/525 (23%)
During intervention period (weeks 1–4)	59/515 (11%)	82/505 (16%)	71/508 (14%)
After intervention period (weeks 5–12)	67/504 (13%)	71/504 (14%)	67/511 (13%)
Participants using other health services			
Total	164/525 (31%)	160/515 (31%)	158/525 (30%)
During intervention period (weeks 1–4)	133/515 (26%)	123/506 (24%)	127/510 (25%)
After intervention period (weeks 5–12)	79/506 (16%)	78/507 (15%)	69/511 (14%)
Adverse events			
Participants reporting a serious adverse event	5/550 (1%)	4/546 (1%)	5/547 (1%)
Participants reporting an adverse event	99/534 (19%)	99/529 (19%)	98/531 (18%)
Hours absent from work			
Week 1 (day 0–day 7)	0.0 (0.0–8.0); N=454	0.0 (0.0–7.0); N=449	0.0 (0.0–8.0); N=416
All other weeks	0.0 (0.0–0.0); N=454	0.0 (0.0–0.0); N=449	0.0 (0.0–0.0); N=416
Treatment satisfaction			
Satisfied with treatment	365/478 (76%)	342/472 (72%)	335/458 (73%)
Assessment of patient masking			
Neither pack contained real paracetamol	113/498 (23%)	137/494 (28%)	156/505 (31%)
Regular pack contained real paracetamol	261/498 (52%)	224/494 (45%)	237/505 (47%)
As-needed pack contained real paracetamol	124/498 (25%)	133/494 (27%)	112/505 (22%)
Data are median (IQR) or n/N (%). N refers to the number of participants providing data. Self-reported daily consumption refers to the number of tablets the participant reported that they consumed per day until recovery or the end of the treatment period (28 days) as recorded in the daily medication diary.			

Table 2: Trial process measures

researchers meant that these patients did not initially meet the eligibility criteria (figure 1). Of the 1643 participants, 550 were allocated to the regular group, 546 to the as-needed group, and 547 to the placebo group. The primary outcome could be determined for 534 (97%) of the regular group, 530 (97%) of the as-needed group, and 532 (97%) of the placebo group. The completeness of survival data, measured by the completeness index,¹⁷ was 94.4%.

Table 1 shows baseline characteristics. Participants had a mean pain intensity of 6.3 (SD 1.9). Across all three groups the mean number of days since onset of pain was 9.9 (SD 10). The credibility of the study treatment and participants' treatment expectations were high and similar across groups (credibility 18.9 [SD 5.1] and treatment expectation 21.3 [5.6] of 27). Participants recruited directly by community advertisement had a mean pain intensity of 5.3 (SD 1.6) and the mean number of days since onset was 15.7 (10.7).

Treatment adherence was similar across groups (table 2). The median number of regular tablets taken daily (until sustained recovery, or 4 weeks) was 4.0 (IQR 1.5–5.7) of the recommended 6.0 (equivalent to a median daily dose of 2660 mg paracetamol for participants in the regular group). All groups reported increased adherence in the first 2 weeks of the intervention, with median doses equivalent to 3500 mg/day in week 1 and 2800 mg/day in week 2 for the regular group (table 2). The median number of as-needed tablets across groups was 1.9 tablets (IQR 1.0–4.0) daily in week 1 (1000 mg/day paracetamol) and 1.0 tablets (0.4–2.7) daily overall (500 mg/day paracetamol). Counts of returned medicines (appendix) and results from the Brief Adherence Rating Scale (table 2) lent support to these findings. 230 patients in

the regular group, 196 patients in the as-needed group, and 229 patients in the placebo group consumed 70% or more of the recommended course of treatment (table 2).

By 12 weeks, 466 (85%) participants in the regular group, 452 (83%) in the as-needed group, and 461 (84%) in the placebo group reached sustained recovery (figure 2). The global significance test suggested no difference in time to recovery between groups, controlling for baseline pain intensity (adjusted $p=0.79$). Median days to recovery were 17 (95% CI 14–19) in the regular group, 17 (15–20) in the as-needed group, and 16 (14–20) in the placebo group (regular vs placebo, HR 0.99, 95% CI 0.87–1.14; as-needed vs placebo, 1.05, 0.92–1.19; regular vs as-needed, 1.05, 0.92–1.20). Table 3 details the change in secondary outcomes scores at each follow-up point for all treatment groups. Longitudinal mixed models of secondary outcomes showed no difference between groups for any secondary outcome during follow-up (appendix).

Most patients (1042 of 1408; 74%) were satisfied with treatment (table 2). The use of rescue medication (naproxen) was low and similar across groups. During the intervention period there was small-to-moderate use of other drugs (table 2), and other health services after removal of GP visits (212/1528 [14%]). The number and type of drugs and health services used were similar across groups (tables 4, 5). 296 (19%) of 1594 participants had an adverse event, with no difference across the three groups (table 2). Five (1%) participants in the regular group, four (1%) in the as-needed group, and five (1%) in the placebo group had serious adverse events unrelated to the study treatment (table 2, appendix).

Time to recovery did not significantly differ between groups ($p=0.55$) when the first recovery definition was used, lending support to the robustness of the primary analysis (appendix). We noted no difference between groups with imputation methods for best-case and worst-case recovery (missing daily pain scores imputed as a recovered value, $p=0.72$; missing daily pain scores imputed as a non-recovered value, $p=0.79$) or after adjustment for baseline characteristics (pain, number of days since onset of pain, and number of previous episodes, $p=0.90$; data not shown). Adjustment of these characteristics did not change the findings for secondary outcomes.

After consideration of the results we did a post-hoc analysis to assess the effect of paracetamol in the early phase of treatment. We constructed linear mixed models that included the daily pain scores up to day 14 to estimate effects of treatment overall and for each day. These analyses showed no treatment effect (appendix).

Discussion

We have shown that neither regular nor as-needed dosing of paracetamol improved recovery compared with placebo. Consistent with the primary results, paracetamol also had no effect on pain, disability, function, global

See Online for appendix

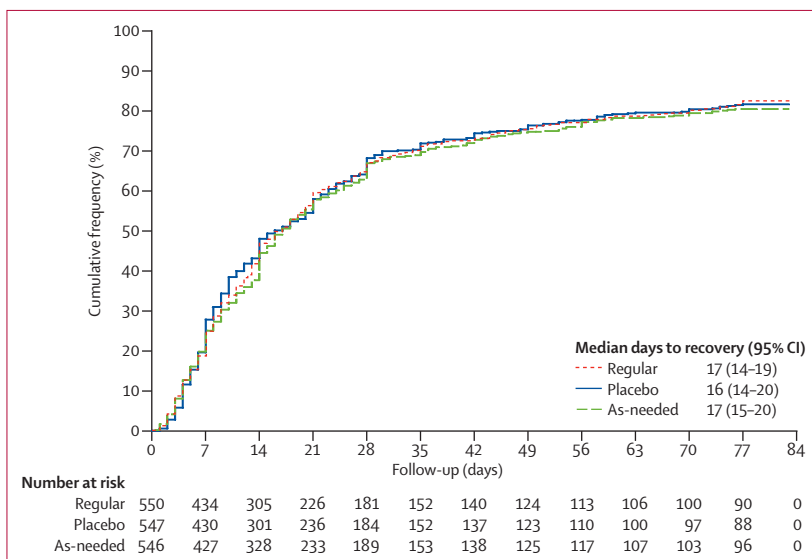


Figure 2: Kaplan-Meier curves for sustained recovery by treatment group, adjusted for baseline pain score Global $p=0.79$.

	Regular group (N=550)	As-needed group (N=546)	Placebo group (N=547)
Pain intensity			
Week 1			
N	517	499	504
Mean (SD)	3.7 (2.6)	3.8 (2.7)	3.6 (2.6)
Median (IQR)	3.0 (2.0-6.0)	4.0 (2.0-6.0)	3.0 (1.0-5.0)
Week 2			
N	509	498	497
Mean (SD)	2.6 (2.6)	2.6 (2.5)	2.5 (2.5)
Median (IQR)	2.0 (0.0-4.0)	2.0 (0.0-4.0)	2.0 (0.0-4.0)
Week 4			
N	509	507	499
Mean (SD)	1.7 (2.3)	1.8 (2.4)	1.7 (2.3)
Median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-3.0)	1.0 (0.0-3.0)
Week 12			
N	506	514	505
Mean (SD)	1.2 (2.2)	1.3 (2.2)	1.3 (2.3)
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Disability score			
Week 1			
N	513	498	500
Mean (SD)	7.7 (6.5)	8.0 (6.5)	8.3 (6.5)
Median (IQR)	6.0 (2.0-13.0)	7.0 (3.0-12.5)	7.0 (3.0-13.0)
Week 2			
N	507	496	497
Mean (SD)	5.2 (6.1)	5.4 (5.9)	5.3 (6.1)
Median (IQR)	3.0 (0.0-9.0)	3.0 (0.0-9.0)	3.0 (0.0-9.0)
Week 4			
N	504	506	497
Mean (SD)	3.2 (5.2)	3.5 (5.3)	3.3 (5.1)
Median (IQR)	0.0 (0.0-4.0)	1.0 (0.0-5.0)	0.0 (0.0-5.0)
Week 12			
N	504	514	503
Mean (SD)	2.4 (4.7)	2.6 (4.9)	2.4 (4.5)
Median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-3.0)	0.0 (0.0-3.0)
Global change			
Week 1			
N	514	497	503
Mean (SD)	2.1 (2.0)	2.0 (2.2)	2.1 (2.2)
Median (IQR)	2.0 (1.0-4.0)	2.0 (0.0-4.0)	3.0 (1.0-4.0)
Week 2			
N	507	498	496
Mean (SD)	2.8 (2.1)	2.7 (2.1)	2.8 (2.2)
Median (IQR)	3.0 (2.0-4.0)	3.0 (1.0-4.0)	3.0 (2.0-5.0)
Week 4			
N	507	506	498
Mean (SD)	3.4 (2.1)	3.4 (2.1)	3.5 (2.1)
Median (IQR)	4.0 (3.0-5.0)	4.0 (2.0-5.0)	4.0 (3.0-5.0)
Week 12			
N	505	514	503
Mean (SD)	3.8 (2.0)	3.7 (2.1)	3.8 (2.0)
Median (IQR)	5.0 (4.0-5.0)	5.0 (3.0-5.0)	5.0 (4.0-5.0)
(Continues in next column)			

	Regular group (N=550)	As-needed group (N=546)	Placebo group (N=547)
(Continued from previous column)			
Function			
Week 1			
N	513	498	499
Mean (SD)	6.2 (2.6)	6.1 (2.6)	6.2 (2.5)
Median (IQR)	6.0 (4.0-8.3)	6.0 (4.0-8.0)	6.0 (4.3-8.3)
Week 2			
N	507	496	496
Mean (SD)	7.3 (2.6)	7.2 (2.5)	7.4 (2.5)
Median (IQR)	8.0 (5.7-9.7)	7.7 (5.3-9.7)	8.0 (5.7-10.0)
Week 4			
N	502	504	497
Mean (SD)	8.2 (2.5)	8.1 (2.4)	8.2 (2.4)
Median (IQR)	9.3 (7.0-10.0)	9.3 (7.0-10.0)	9.3 (7.0-10.0)
Week 12			
N	502	512	503
Mean (SD)	8.7 (2.3)	8.7 (2.1)	8.7 (2.2)
Median (IQR)	10.0 (8.7-10.0)	10.0 (8.0-10.0)	10.0 (8.7-10.0)
Poor sleep quality			
Week 1	143/514 (27.8%)	129/501 (25.7%)	127/496 (25.6%)
Week 2	85/508 (16.7%)	88/495 (17.8%)	85/497 (17.1%)
Week 4	59/507 (11.6%)	57/500 (11.4%)	52/503 (10.3%)
Week 12	54/506 (10.7%)	55/503 (10.9%)	44/514 (8.6%)
SF12 Physical score			
Week 4			
N	381	386	377
Mean (SD)	50.3 (9.3)	49.7 (10.4)	50.8 (9.1)
Median (IQR)	52.9 (44.3-57.2)	53.1 (43.2-57.5)	53.1 (45.4-57.8)
Week 12			
N	252	264	243
Mean (SD)	54.9 (8.6)	55.3 (7.9)	54.7 (8.8)
Median (IQR)	57.8 (52.4-60.5)	57.8 (53.6-60.5)	57.8 (51.5-60.5)
SF12 Mental score			
Week 4			
N	381	386	377
Mean (SD)	43.7 (6.2)	43.9 (7.0)	44.4 (6.1)
Median (IQR)	45.0 (40.4-48.0)	45.1 (40.1-48.3)	45.4 (41.3-48.3)
Week 12			
N	252	264	243
Mean (SD)	45.6 (5.3)	45.6 (5.1)	44.7 (5.5)
Median (IQR)	45.6 (42.8-49.0)	46.3 (43.3-48.5)	45.4 (42.7-48.2)
Data are mean (SD), median (IQR), or n/N (%); N refers to the number of participants providing data.			
Table 3: Secondary outcomes during study follow-up			

symptom change, sleep, or quality of life. Adverse events between treatment groups did not differ.

PACE was a large, high-quality, multicentre trial. The trial setting matches the recommendations in guidelines

	Regular group (N=550)	As-needed group (N=546)	Placebo group (N=547)
Up to week 4			
N	515	505	508
Paracetamol*	10 (1.9%)	22 (4.4%)	19 (3.7%)
Paracetamol with opioid*	9 (1.7%)	11 (2.2%)	10 (2.0%)
Anticonvulsant	2 (0.4%)	1 (0.2%)	1 (0.2%)
Muscle relaxant	1 (0.2%)	4 (0.2%)	0
NSAID	30 (5.8%)	39 (7.7%)	23 (4.5%)
NSAID with opioid	5 (1.0%)	3 (0.6%)	2 (0.4%)
Opioid	7 (1.4%)	4 (0.8%)	4 (0.8%)
Other	2 (0.4%)	6 (1.2%)	2 (0.4%)
Psychoactive	0	1 (0.2%)	1 (0.2%)
Rescue medication (naproxen)	3 (0.6%)	4 (0.8%)	6 (1.2%)
Topical	2 (0.4%)	1 (0.2%)	1 (0.2%)
Unspecified	2 (0.4%)	2 (0.4%)	0
Number of patients using concomitant drugs	59 (11.5%)	82 (16.2%)	71 (14.0%)
Weeks 5–12			
N	504	504	511
Paracetamol	21 (4.2%)	25 (5.0%)	18 (3.5%)
Paracetamol with opioid	8 (1.6%)	13 (2.6%)	9 (1.8%)
Anticonvulsant	1 (0.2%)	3 (0.6%)	0
Muscle relaxant	2 (0.4%)	0	0
NSAID	25 (5.0%)	21 (4.2%)	24 (4.7%)
NSAID with opioid	0	1 (0.2%)	1 (0.2%)
Opioid	4 (0.8%)	3 (0.6%)	2 (0.4%)
Other	4 (0.8%)	1 (0.2%)	6 (1.2%)
Psychoactive	0	5 (1.0%)	0
Rescue medication (naproxen)	1 (0.2%)	0	3 (0.6%)
Topical	1 (0.2%)	0	3 (0.6%)
Number of patients using concomitant drugs	67 (13.3%)	71 (14.1%)	67 (13.1%)

Data are number of participants who reported taking the drugs. NSAID with opioid refers to any NSAID–opioid combination medicine. Paracetamol with opioid refers to any paracetamol–opioid combination. Rescue medicine refers to the study rescue medication (naproxen) provided by a study general practitioner. Topical refers to any ointment or cream applied to skin, including NSAIDs. Unspecified refers to medicine not described. Other refers to antihypertensive drugs, cold and flu remedies, alternative medicines (eg, glucosamine or chondroitin), herbal medicine (unspecified), antibiotics, sedatives, calcium channel blockers, or lipid-modifying drugs. NSAID=non-steroidal anti-inflammatory drug. *Paracetamol not supplied as part of the study—non-concurrent use with study medicines.

Table 4: Concomitant drugs used in weeks 1–4 and weeks 5–12

that low-back pain should mainly be managed in primary care.^{2,3} Participant characteristics at baseline were consistent with those of patients from other cohort studies of acute low-back pain in primary care.^{18,19} Several features reduced the risk of bias including central

	Regular group (N=550)	As needed group (N=546)	Placebo group (N=547)
Up to week 4			
N	515	505	508
General practitioner*	69 (13%)	57 (11%)	45 (9%)
Medical specialist	7 (1%)	6 (1%)	6 (1%)
Chiropractor	14 (3%)	8 (2%)	11 (2%)
Physiotherapy	45 (9%)	56 (11%)	54 (11%)
Osteopath	4 (1%)	5 (1%)	5 (1%)
Emergency	3 (1%)	0	1 (0%)
Massage therapy	9 (2%)	11 (2%)	8 (2%)
Other allied health	3 (1%)	3 (1%)	2 (<1%)
Spinal injection	5 (1%)	3 (1%)	1 (<1%)
Acupuncture	4 (1%)	2 (<1%)	7 (1%)
Other complimentary therapies	4 (1%)	4 (1%)	8 (2%)
CT scan	2 (<1%)	8 (2%)	1 (<1%)
X-ray	3 (1%)	2 (<1%)	3 (1%)
Other imaging	2 (<1%)	1 (<1%)	2 (<1%)
Blood test	0	2 (<1%)	0
Number of patients using concomitant health services	133 (26%)	123 (24%)	127 (25%)
Weeks 5–12			
N	506	507	511
General practitioner*	18 (4%)	24 (5%)	26 (5%)
Medical specialist	4 (1%)	3 (1%)	5 (1%)
Chiropractor	14 (3%)	4 (1%)	8 (2%)
Physiotherapy	30 (6%)	35 (7%)	24 (5%)
Osteopath	3 (1%)	2 (<1%)	1 (<1%)
Emergency	3 (1%)	3 (1%)	1 (<1%)
Massage therapy	4 (1%)	4 (1%)	7 (1%)
Other allied health professional	2 (<1%)	0	0
Spinal injection	5 (1%)	3 (1%)	5 (1%)
Acupuncture	3 (1%)	4 (1%)	5 (1%)
Other complimentary therapies	3 (1%)	7 (1%)	3 (1%)
MRI	3 (1%)	3 (1%)	4 (1%)
CT scan	1 (<1%)	2 (<1%)	1 (<1%)
X-ray	1 (<1%)	3 (1%)	1 (<1%)
Other imaging	1 (<1%)	0	0
Number of patients using concomitant health services	79 (16%)	78 (15%)	69 (13%)

Data are the number of participants who reported they accessed the health services. *Includes subsequent visit to recruiting general practitioner. Emergency refers to participants who presented to emergency department but were not admitted. Other allied health professional includes exercise physiologist, dietician, psychologist, podiatrist, and occupational therapist. Other complimentary therapies refers to remaining therapies described in isolation or not part of a service description (eg, tai chi, back brace, pilates, gym, naturopathy, manipulation, vibration platform, Bowen therapy, yoga, or Chinese medicine). Other imaging refers to bone scan or ultrasound.

Table 5: Concomitant health services used in weeks 1–4 and weeks 5–12

randomisation, allocation concealment, masking, and very low attrition. The risk of bias was reduced further by pre-publication of a statistical analysis plan.

A potential limitation of PACE is that participants typically did not take the full recommended dose of paracetamol. Previous trials of low-back pain have used paracetamol doses ranging from 1000 mg/day to 4000 mg/day.⁶ In PACE we adopted the Australian recommended maximum dose of 4000 mg/day,²⁰ but the overall median intake was equivalent to 2660 mg/day. The accumulated response from regular dosing, equivalent to 4000 mg/day, might have been more effective. However, in our post-hoc analysis we did not note any signal of effect on pain intensity during the first weeks of the trial when the median dose (3500 mg/day) was close to the recommended maximum.

Adherence in PACE was similar to paracetamol adherence in other pain states for which paracetamol is recommended as first-line care. In studies of osteoarthritis, Pahor and colleagues²¹ reported that only 26% of patients took the recommended dose of 4000 mg/day, and Temple and colleagues²² reported adherence at 1 month to be about 3000 mg/day. PACE participants were very well supported to adhere with the recommended dose, receiving explicit advice about dosing from the clinician and research staff, which was then reinforced at follow-up. The fact that many participants were still not able to comply might result from impractical dosing requirements of paracetamol or suggest that more intensive strategies are needed for improved adherence.²³

Another potential limitation is that some participants used other treatments during the intervention period, as opposed to the recommended rescue medication, despite advice to not take additional treatments. Although this issue has not been extensively assessed, other trial findings have shown that these additional treatments do not provide benefits above guideline recommended advice and simple analgesics.^{4,5,24} Importantly, we noted no difference in the use of other medicines or health services between groups, and so these other treatments are unlikely to have masked an effect of paracetamol.

Although guidelines endorse paracetamol for acute low-back pain, this recommendation is based on scarce evidence. In the only trial of low-back pain (n=46) that compared paracetamol (3000 mg/day) with no treatment, recovery rates did not differ.²⁵ More often, paracetamol has been compared with non-steroidal anti-inflammatory drugs (NSAIDs). Investigators of a Cochrane review⁵ concluded that the effect of NSAIDs was equal to that of paracetamol (three trials, total n=309) and only marginally better than placebo (8 points on a 0–100 pain scale; four trials, total n=745); however, paracetamol has a better safety profile than NSAIDs. Our findings, based on a much larger sample, suggest that simple analgesics such as paracetamol might not be important in the management of acute low-back pain (panel).

Although we showed no effect of paracetamol on recovery time, participants recovered at a faster rate than that typically reported in other cohorts with acute back pain receiving miscellaneous or usual treatments.¹⁹ In PACE, median recovery was 16–17 days, and by 12 weeks nearly 85% of participants had recovered. Similar recovery was also noted in a study⁴ investigating first-line treatments for acute low-back pain. A possible explanation of these more favourable outcomes is that in both studies patients were provided with good-quality advice and reassurance, a feature that is often absent from usual care.²⁶ While we cannot disregard the possibility of a placebo effect in PACE leading to improved recovery, the provision of advice and reassurance of the favourable prognosis might be the more important factor in management of acute low-back pain than drug therapy. Research should focus on whether the recommended components of advice and reassurance are beneficial.

Our findings suggest that the efficacy of paracetamol should be carefully considered, with respect to the safe and effective use of medicines for low-back pain. Although our findings call into question the use of paracetamol to improve outcomes for acute low-back pain, these results should be replicated before paracetamol is completely dismissed in the management of low-back pain. Importantly, the safety profile of paracetamol is favourable compared with other analgesics recommended for low-back pain (eg, NSAIDs).²⁰ Because these other medicines have not been shown to provide additional

Panel: Research in context

Systematic review

We previously did a systematic review of clinical trials of paracetamol for acute low-back pain,⁴ in which we could find no randomised controlled trials that compared paracetamol with placebo and none that compared as-needed paracetamol with regular paracetamol. In Dec 20, 2013, we searched PubMed and PEDro for studies published since Aug 1, 2007. For relevant trials we used the text search terms “acute low-back pain”, and “paracetamol” or “acetaminophen” and a publication date filter. We did not identify any relevant trials.

Interpretation

Our findings provide the first evidence for the effectiveness of paracetamol for acute low-back pain. Neither regular nor as-needed paracetamol improved recovery time or pain intensity, disability, function, global change in symptoms, sleep, or quality of life at any stage during a 3-month follow up. In previous studies, paracetamol was usually compared with non-steroidal anti-inflammatory drugs. Investigators of a Cochrane Review²⁰ concluded these medicines to be equally effective (three trials, total n=309) and that non-steroidal anti-inflammatory drugs are only marginally better than placebo (8 points on a 0–100 pain scale; 4 trials, total n=745). The results of our study, based on a much larger sample, suggest that simple analgesics such as paracetamol might not be of primary importance in the management of acute low-back pain, and the universal recommendation in clinical practice guidelines to provide paracetamol as a first-line treatment should be reconsidered. In view of the quick timeframe in which participants in our trial improved across all the outcomes measured, compared with other cohorts, advice and reassurance (as provided in our trial) might be a more important aspect of medical care than pharmacological strategies for acute episodes of low-back pain.

benefit beyond that of paracetamol,²⁰ and are only marginally better than is placebo,⁵ it is not clear which drug should be preferred for management of low-back pain. Our results convey the need to reconsider the universal endorsement of paracetamol in clinical practice guidelines as first-line care for low-back pain, and suggest that advice and reassurance, rather than analgesics, should be the focus of first-line care.

At present, no management strategies for acute low-back pain have shown effectiveness to improve outcomes substantially beyond its natural prognosis. Because low-back pain is the leading cause of disability worldwide,¹ improved focus on development of new, effective treatments is warranted. In PACE, even during the first 14 days, paracetamol had no effect on outcomes. One pharmacological research direction would be to understand why paracetamol is effective in some acute pain states (eg, tooth extraction²⁷ and postoperative pain²⁸) but not for low-back pain.

PACE provides high-quality evidence that, in addition to advice and reassurance, neither regular nor as-needed paracetamol significantly speed recovery from acute low-back pain. Although participants improved quickly in PACE, paracetamol had no effect on pain, disability, function, global symptom change, sleep quality, or quality of life.

Contributors

CMW participated in the conception and design of the study, recruitment and training of study sites, acquisition of data, statistical analysis and interpretation of data, drafting of the report, critical revision of the report for important intellectual content, and some process analyses. CGM participated in the conception and design of the study, interpretation of data, drafting of the report, critical revision of the report for important intellectual content, obtaining funding, administrative and technical support, and supervision. JL participated in the conception and design of the study, interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative and technical support, and supervision. AJM participated in the conception and design of the study, medicine audits, interpretation of data, critical revision of the report for important intellectual content, statistical analysis, obtaining funding, administrative and technical support, and supervision. MJH participated in the conception and design of the study, acquisition of data, interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative and technical support, and supervision. ROD participated in the conception and design of the study, interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative and technical support, and supervision. C-WCL participated in the conception and design of the study, acquisition of data, interpretation of data, critical revision of the report for important intellectual content, administrative and technical support, and supervision. All authors approved the final submitted version.

Declaration of interests

AJM has received funding for a postgraduate research scholarship from GlaxoSmithKline. CGM has received funding to review teaching materials prepared by GlaxoSmithKline. The other authors declare no competing interests.

Acknowledgments

Two independent statisticians did primary, secondary, and process analyses (Qiang Li and Severine Bompoin). This study was an investigator-initiated study funded by a project grant from National Health and Medical Research Council of Australia. GlaxoSmithKline Australia provided subsequent supplementary funding and the

paracetamol and matched placebo. We thank the participants of this research, the clinicians involved in participant recruitment, and the research support staff involved in site monitoring, data collection, data management, and data analysis. CGM and JL are supported by Australian Research Council Future Fellowships FT-100100603 and FT-0991861, respectively. C-WCL is supported by a Career Development Fellowship from the National Health and Medical Research Council, Australia (APP1061400).

References

- Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2163–96.
- Chou R, Qaseem A, Snow V, et al, and the Clinical Efficacy Assessment Subcommittee of the American College of Physicians, and the American College of Physicians, and the American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; **147**: 478–91.
- Koes BW, van Tulder M, Lin C-WC, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J* 2010; **19**: 2075–94.
- Hancock MJ, Maher CG, Latimer J, et al. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. *Lancet* 2007; **370**: 1638–43.
- Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2008; **1**: CD000396.
- Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. *Eur Spine J* 2008; **17**: 1423–30.
- Williams CM, Latimer J, Maher CG, et al. PACE—the first placebo controlled trial of paracetamol for acute low back pain: design of a randomised controlled trial. *BMC Musculoskelet Disord* 2010; **11**: 1691–96.
- Williams CM, Maher CG, Latimer J, et al. PACE—the first placebo controlled trial of paracetamol for acute low back pain: statistical analysis plan. *Trials* 2013; **14**: 248.
- Ong CKS, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007; **5**: 19–34.
- Pengel LHM, Refshauge KM, Maher CG. Responsiveness of pain, disability, and physical impairment outcomes in patients with low back pain. *Spine* 2004; **29**: 879–83.
- Buyse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193–213.
- Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004; **42**: 851–59.
- Smeets RJEM, Beelen S, Goossens MEJB, Schouten EGW, Knottnerus JA, Vlaeyen JWS. Treatment expectancy and credibility are associated with the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. *Clin J Pain* 2008; **24**: 305–15.
- Hayden JA, Dunn KM, van der Windt DA, Shaw WS. What is the prognosis of back pain? *Best Pract Res Clin Rheumatol* 2010; **24**: 167–79.
- Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. *Control Clin Trials* 2000; **21**: 527–39.
- Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159**: 702–06.
- Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet* 2002; **359**: 1309–10.
- Henschke N, Maher CG, Refshauge KM, et al. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ* 2008; **337**: a171.
- Menezes Costa LDC, Maher CG, Hancock MJ, McAuley JH, Herbert RD, Costa LOP. Prognosis in people with back pain. *Can Med Assoc J* 2012; **184**: 613–24.

- 20 Buckley N, Calabretto H, Del Mar C, et al. Australian Medicines Handbook 2013, 13th edn. Adelaide: Australian Medicines Handbook Pty Ltd, 2013.
- 21 Pahor M, Guralnik JM, Wan JY, et al. Lower body osteoarticular pain and dose of analgesic medications in older disabled women: the Women's Health and Aging Study. *Am J Public Health* 1999; **89**: 930–34.
- 22 Temple AR, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6–12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther* 2006; **28**: 222–35.
- 23 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353**: 487–97.
- 24 Koes BW, van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. *BMJ* 2006; **332**: 1430–34.
- 25 Milgrom C, Finestone A, Lev B, Wiener M, Floman Y. Overexertional lumbar and thoracic back pain among recruits: a prospective study of risk factors and treatment regimens. *J Spinal Disord* 1993; **6**: 187–93.
- 26 Williams CM, Maher CG, Hancock MJ, et al. Low back pain and best practice care: a survey of general practice physicians. *Arch Intern Med* 2010; **170**: 271–77.
- 27 Weil K, Hooper L, Afzal Z, et al. Paracetamol for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev* 2007; **3**: CD004487.
- 28 Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008; **4**: CD004602.