Research Paper

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Paracetamol is ineffective for acute low back pain even for patients who comply with treatment: complier average causal effect analysis of a randomized controlled trial

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Abstract

In 2014, the Paracetamol for Acute Low Back Pain (PACE) trial demonstrated that paracetamol had no effect compared with placebo in acute low back pain (LBP). However, noncompliance was a potential limitation of this trial. The aim of this study was to investigate the efficacy of paracetamol in acute LBP among compliers. Using individual participant data from the PACE trial (ACTN12609000966291), complier average causal effect (CACE), intention-to-treat, and per protocol estimates were calculated for pain intensity (primary), disability, global rating of symptom change, and function (all secondary) after 2 weeks of follow-up. Compliance was defined as intake of an average of at least 4 of the prescribed 6 tablets of regular paracetamol per day (2660 mg in total) during the first 2 weeks after enrolment. Exploratory analyses using alternative time points and definitions of compliance were conducted. Mean between-group differences in pain intensity on a 0 to 10 scale using the primary time point and definition of compliance were not clinically relevant (propensity-weighted CACE 0.07 [−0.37 to 0.50] $P = 0.76$; joint modelling CACE 0.23 [−0.16 to 0.62] $P = 0.24$; intention-to-treat 0.11 [−0.20 to 0.42] $P = 0.49$; per protocol 0.29 [−0.07 to 0.65] $P = 0.12$); results for secondary outcomes and for exploratory analyses were similar. Paracetamol is ineffective for acute LBP even for patients who comply with treatment. This reinforces the notion that management of acute LBP should focus on providing patients advice and reassurance without the addition of paracetamol.

Keywords: Low back pain, Paracetamol, Acetaminophen, Compliance, Adherence, CACE Analysis

1. Introduction

The Paracetamol for Acute Low Back Pain (PACE) trial was the first placebo-controlled randomized controlled trial (RCT) investigating the efficacy of paracetamol (acetaminophen) for acute low back pain (LBP).[29–31] In this RCT, 1652 people seeking care for LBP were randomized to take paracetamol regularly, paracetamol as needed for pain, or placebo using a blinded double-dummy design. The unexpected result that paracetamol had no effect compared with placebo on pain intensity, time until recovery, disability, and function in acute LBP received worldwide attention in the medical literature and the lay-press. Nonadherence to study medication was identified as a potential limitation in the original publication of the PACE results as well as in a number of commentaries discussing the impact of the trial[4,16,17,31]; in a descriptive analysis of nonadherence in PACE, 70% of patients were found to be nonadherent over the 4-week treatment period, and overall adherence to guideline-recommended care for acute LBP was described as "poor."[4] In RCTs, noncompliance has always been an issue and may even influence their results.[21] However, the question as to whether there is benefit of an intervention in participants who adequately adhere to treatment is difficult to answer using conventional techniques used in the analysis of RCTs (ie, intention-to-treat [ITT] analysis and per protocol analysis).

Complier average causal effect (CACE) analysis involves comparing participants who were randomized to the intervention and complied, to participants from the control group who would have complied to the intervention had they been randomized to the intervention (so-called "would be compliers"). As participants in the control group are never offered the active treatment in reality, there are no observed data in the control group for adherence to active treatment. Complier average causal effect analysis is therefore essentially a missing data problem. Complier average causal effect analyses have been used to assess the efficacy among compliers of intervention programs in substance abuse, behavioral interventions, and a multifactorial intervention in physiotherapy.[1,2,8–11,18,24,26] In the field of LBP, CACE analysis has been used to assess the influence of noncompliance on effectiveness of a cognitive behavioral intervention.[15]

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This analysis aims to investigate the efficacy of paracetamol in acute LBP among participants who complied with regular paracetamol treatment in the PACE trial using a CACE analysis, to address the uncertainty that compliance may have influenced drug efficacy.[1,26] In addition, we conducted ITT analysis and per protocol analysis to compare with the CACE analysis.

2. Methods

2.1. Ethics

The University of Sydney Human Research Ethics Committee granted ethical approval of the PACE trial protocol. Written informed consent was provided by all participants. The PACE trial was registered with the Australian and New Zealand Clinical Trial Registry, number ACTN12609000966291.

2.2. Participants and procedures

The PACE trial was a multicenter, double-dummy, randomized, placebo-controlled trial that was conducted from November 2009 to March 2013. The study protocol, analysis plan, and main outcomes have been published.[29–31] In summary, 4606 people seeking care for acute nonspecific low-back pain or responding to a community advertisement were screened by 235 primary care clinicians across Sydney, Australia. The trial included 1652 participants with a new episode of moderate or severe-intensity LBP with or without leg pain. Participants were randomly allocated (in a 1:1:1 ratio) to receive 2 tablets of 665-mg modified-release paracetamol tablets 3 times a day regularly (n = 550), or 2 tablets of 500-mg immediate-release paracetamol tablets up to 4 times a day as-needed for pain (n = 549), or placebo (n = 553). Participants, clinicians, and researchers were blinded to allocation of treatment during the trial. Participants were instructed to use study medication until they had experienced 7 consecutive days with pain scores of 0 or 1 of 10 (measured on a numerical pain rating scale), or for a maximum of 4 weeks, whichever occurred first. Participants were asked to return to their clinician for review after 1 week, at which time the use of study medication was reviewed. Rescue medication (naproxen 250 mg) was available for participants with continuing ongoing pain as required.

Participants recorded pain scores and number of tablets taken in a daily pain and drug diary until recovery or for a maximum of 4 weeks. Follow-up data were collected at 1, 2, 4, and 12 weeks after randomization. Data were either entered directly by the participant into an online database or recorded by participants in a booklet and transcribed to a case report form during a telephone interview with research staff. Returned tablets were counted by research staff to confirm self-reported compliance. In this CACE analysis, data from the as-needed treatment group were not used because the "need" to take medication would have been different for each individual participant, preventing the use of 1 universal definition of compliance in this treatment group.

2.3. Outcome measures

For this CACE analysis, pain intensity measured on a numerical rating scale from 0 (no pain) to 10 (worst possible pain) was the primary outcome; analyses were also performed for disability (Roland–Morris Disability Questionnaire, scored from 0 [no disability] to 24 [high disability]), global rating of symptom change (scored from −5 [vastly worse] to +5 [completely recovered]), and function (Patient-Specific Function Scale, with the average of 3 items scored from 0 [unable to perform] to 10 [able to perform at preinjury level]), and these outcomes represent 2 of the 3 core outcome domains for nonspecific LBP.[7] Although measurements were conducted in the PACE trial for the third core outcome domain (health-related quality of life), this outcome was omitted from the CACE analysis because of missing data (the Short Form 12 [SF12]), which we expected would compromise the CACE estimation. Time until recovery, the primary outcome of the original PACE analysis, was omitted because methods for survival CACE analysis have not yet been developed.

2.4. Definitions of compliance to the study intervention and time points

Compliance was defined as taking an average of at least 4 tablets per day (approximately 66% of the prescribed dosage or 2660 mg per day) of modified-release paracetamol until recovery or for a maximum of 2 weeks for the primary outcome of the CACE analysis (pain intensity at 2 weeks of follow-up).

Two alternative cutoff points for compliance were defined a priori to assess whether the treatment effect differed according to the level of compliance: taking an average of 5 tablets per day (83% of the prescribed dosage or 3325 mg per day) and taking 6 tablets per day (100% of the prescribed dosage or 3990 mg per day). The 2-week questionnaire was chosen as the primary time point as this was closest to the median recovery time[31]; exploratory analyses were performed at 1- and 4-week follow-up for pain intensity only. For the exploratory analysis of pain intensity at 4 weeks, the definition of compliance was expanded to "until recovery or for a maximum of 4 weeks."

2.5. Statistical analysis

Using individual participant data from the PACE trial, baseline participant and back pain episode characteristics were compared between observed compliers and observed noncompliers in the regular paracetamol treatment group, using standardized differences (St.Diffs). For binary variables, the St.Diff was calculated as the difference in proportions divided by the SD, that is, (p1−p2)/sqrt {(p1 [1−p1] + p2 [1 − p2])/2}. For categorical variables with more than 2 levels, we used a method proposed by Yang and Dalton based on a multivariate Mahalanobis distance method which generalizes the St.Diff metric.[32] St.Diffs larger than 0.1 were considered to be relevant and were reported in the "Results" section.

We calculated ITT, CACE, and per protocol (PP) estimates for the 4 outcomes of interest (pain intensity, disability, global rating of symptom change, and function). Intention-to-treat analyses were performed consistent with the original analysis of the PACE trial, comparing outcomes between all participants randomized to the regular paracetamol group and all patients randomized to the placebo group using linear mixed models adjusted for all baseline characteristics.[30,31] Based on our definition of compliance, we created a dichotomous variable indicating observed compliance status. We used this dichotomous variable for the PP analysis, where we compared outcomes of observed compliers from the regular paracetamol group with outcomes of observed compliers in the placebo group using linear mixed models adjusted for all baseline characteristics. Outcomes of the PP analysis are not included in the main results of this article, but are added to the supplementary information (available at http://links.lww.com/PAIN/A866). The reason for this is that we were interested in comparing results of the CACE analysis to results of a PP analysis, which may provide biased estimates of efficacy

for compliers, as the reasons for noncompliance could be different for the regular paracetamol group than for the placebo group. For example, noncompliance in the regular paracetamol group could be related to side effects despite efficacy, whereas noncompliance in the placebo group may be due to lack of efficacy.[13] In the Supplementary Information, the difference between PP and CACE analyses is discussed in more detail (available at http://links.lww.com/PAIN/A866).

As the underlying assumptions for CACE analysis are untestable, we obtained CACE estimates using both a propensity-weighted estimation approach and a joint modeling estimation approach, which serve as each other's sensitivity analysis.[26] More information about the underlying assumptions for these CACE estimation techniques can be found in the Supplementary Information (available at http://links.lww.com/PAIN/A866). For the propensity-weighted CACE estimation, compliance to regular paracetamol was predicted on baseline covariates using logistic regression with a dichotomous variable indicating the observed compliance status. The prediction model was developed using only data from the regular paracetamol group. This model was then used to calculate the likelihood of compliance (propensity score) in the placebo group. To prevent missing propensity scores due to missing baseline data, missing baseline variables were imputed once using fully conditional specification (ie, imputation on a variable-by-variable basis in an iterative fashion, with an imputation model specified for each incomplete baseline variable[27]). The imputed data set was used to predict the propensity score. Once derived, the propensity scores were added back to the original nonimputed baseline data set, and each participant was weighted as follows: in the regular paracetamol treatment arm, compliers received a weight of 1 and noncompliers a weight of 0; in the placebo treatment arm, the weight was calculated as the odds of the propensity score p (odds = p/[1 − p]). We investigated if any residual imbalances existed after weighting by calculating St.Diffs between baseline variables between compliers in the regular paracetamol group and weighted placebo group participants (see Supplementary Information, available at http://links.lww.com/PAIN/A866). Finally, we performed an analysis comparing compliers in the regular paracetamol group to odds-weighted patients in the placebo group. Propensity-weighted CACE analyses were adjusted for all baseline characteristics to correct for residual imbalances. To assess a potential "dose–response" effect, we performed a prespecified subgroup analysis according to quintiles of likelihood of compliance (using the propensity scores created for the propensity-weighted CACE analysis). For this subgroup analysis, the primary cutoff point for compliance (taking an average of at least 4 tablets of modified-release paracetamol per day) and primary time point (2 weeks of follow-up) were used; for each quintile group, a mean difference and corresponding confidence interval was calculated.

For the CACE analysis using joint modeling, 2 models were simultaneously estimated: a model for compliance and a model for the outcome (pain intensity). Estimates were adjusted for all baseline characteristics. This estimation approach resulted in a comparison between observed compliers in the regular paracetamol group to inferred compliers (would be compliers) in the placebo group.

Results of all the analyses (ITT, CACE propensity and CACE joint modeling, and PP) are presented as mean differences between paracetamol and placebo groups with 95% confidence intervals and corresponding *P*-values. Intention-to-treat, PP, and propensity-weighted CACE analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC), joint modeling CACE estimation was performed in Mplus version 7.[19]

3. Results

3.1. Characteristics of compliers to regular paracetamol

The baseline characteristics of participants in the regular paracetamol group are presented in **Table 1**; participants were split into compliers and noncompliers based on our main definition of compliance (an average of at least 4 tablets of 665 mg regular paracetamol per day during the first 2 weeks). **Table 1** also shows St.Diffs between observed compliers and noncompliers. At the primary time point of the CACE analysis (2 weeks), 394 of 550 participants in the paracetamol group (72%) were classified as compliers.

When comparing compliers and noncompliers, compliers tended to be somewhat older (44.9 vs 42.4 years, St.Diff 0.17); were more likely to be male (54% vs 46%, St.Diff 0.15); were more likely to have private health insurance (52% vs 46%, St.Diff 0.12); had a different distribution of household income (St.Diff 0.23); were less likely to have pain extending beyond the knee (17% vs 26%, St.Diff 0.22); had a longer period of reduced usual activity (4.1 vs 3.2 days, St.Diff 0.13); scored higher for feelings of depression (3.4 vs 2.8, St.Diff 0.18); reported a higher perceived risk of persistent pain (4.8 vs 4.1 of 10, St.Diff 0.22); more often reported poor sleep quality (51% vs 46%, St.Diff 0.10); scored lower on function (3.4 vs 3.7, St.Diff 0.15); and scored lower for physical quality of life (42.4 vs 43.3, St.Diff 0.11).

3.2. Estimates of the complier average causal effect models

Table 2 presents ITT and CACE estimates for pain intensity, disability, global rating of symptom change, and function in the PACE trial at week 2 with compliance defined as an average intake of at least 4 tablets per day during the first 2 weeks.

For the primary outcome measure, none of the analyses indicated a difference in pain intensity (ITT: mean difference 0.11 [−0.20 to 0.42] $P = 0.49$; joint modeling CACE: mean difference 0.23 [−0.16 to 0.62] $P = 0.24$; propensity-weighted CACE: mean difference 0.07 [−0.37 to 0.50] $P = 0.76$). Similar results were obtained for the secondary outcomes disability, global rating of symptom change, and function. Confidence intervals of estimates for pain intensity, global rating of symptom change, and function were all between −1 and 1 and therefore excluded clinically meaningful differences; the confidence interval of the estimate of disability exceeded 1 in both the propensity-weighted CACE estimation and the joint modelling CACE estimation; however, this difference is still smaller than the minimal clinically important difference of 30% change from baseline (in PACE, approximately 4 points).[14]

3.3. Exploratory analyses

Figure 1 shows results of the exploratory ITT and CACE analyses using primary and alternative cutoff points for compliance (an average of at least 5 tablets per day and 6 tablets per day) and primary and alternative time points (1 and 4 weeks). Mean differences in pain intensity between regular paracetamol and placebo were calculated for 3 definitions of compliance at 3 time points using 3 analysis techniques, yielding a total of 21 estimates.

Minimal differences in pain intensity were only found for 2 of the 21 analyses: the joint modeling CACE estimate after 2 weeks with compliance defined as an average of at least 5 paracetamol tablets per day (mean difference 0.45 [0.02-0.88], $P = 0.039$) and for the propensity-weighted CACE estimate after 2 weeks with compliance defined as 6 paracetamol tablets per day (mean

Table 1

Baseline characteristics for observed compliers and noncompliers in the regular paracetamol group, including standardized mean differences between observed compliers and observed noncompliers.

	Regular paracetamol (N = 550)		Standardized differences
	Observed compliers (N = 394)	Observed noncompliers (N = 142)	
Patient characteristics			
Age (y)	44.9 (14.9), N = 394	42.4 (14.5), N = 142	**0.171**
Women	182/393 (46%)	75/140 (54%)	**0.146**
Private health insurance	203/394 (52%)	65/142 (46%)	**0.115**
Currently employed	305/394 (77%)	107/142 (75%)	0.048
Household income per week (per year)			**0.342**
Negative or no income	13/384 (3%)	6/142 (4%)	
AUD 1-649 (1-33799)	89/384 (23%)	42/142 (30%)	
AUD 650-1699 (33800-88399)	174/384 (45%)	59/142 (42%)	
AUD 1700-3999 (88400-207999)	86/384 (22.4%)	32/142 (23%)	
≥AUD 4000 (≥208000)	22/384 (6%)	3/142 (2%)	
Use of drugs for another disorder	148/394 (38%)	49/142 (35%)	0.064
LBP episode characteristics			
Days since onset of pain	10.2 (10.3), N = 394	9.8 (9.6), N = 142	0.037
No. of previous episodes	6.4 (12.8), N = 392	6.5 (16.4), N = 141	0.009
Presence of pain extending beyond the knee	68/392 (17%)	37/141 (26%)	**0.217**
No. of days reduced usual activity	4.1 (7.0), N = 393	3.2 (4.9), N = 141	**0.134**
Disability (RMDQ)	12.7 (5.5), N = 390	12.9 (5.9), N = 139	0.027
Feelings of depression in last week	3.4 (2.9), N = 392	2.8 (3.0), N = 141	**0.175**
Perceived risk of persistent pain	4.8 (2.7), N = 392	4.1 (2.9), N = 142	**0.224**
Back pain episode compensable	20/392 (5%)	10/140 (7%)	0.085
Pain intensity (NRS)	6.3 (1.9), N = 394	6.2 (2.0), N = 142	0.039
Global rating of symptom change	0.0 (2.1), N = 393	0.1 (2.0), N = 141	0.054
Poor sleep quality	200/393 (51%)	65/142 (46%)	**0.103**
Function (nominated activity)	3.4 (1.7), N = 392	3.7 (1.9), N = 141	**0.151**
Quality of life—physical (SF-12)	42.4 (9.0), N = 384	43.3 (9.4), N = 140	**0.112**
Quality of life—mental (SF-12)	44.3 (7.7), N = 384	43.7 (7.8), N = 140	0.071
Credibility score (CEQ)	19.1 (4.9), N = 390	18.8 (4.8), N = 140	0.064
Expectation score (CEQ)	19.8 (5.4), N = 389	19.4 (5.3), N = 141	0.080

Data are mean (SD) or n/N (%); boldface entries under standardized differences indicate St.Diffs > 0.1.
AUD, Australian Dollar; CEQ, Credibility/Expectancy Questionnaire; LBP, low back pain; NRS, numerical rating scale; RMDQ, Roland–Morris Disability Questionnaire; St.Diffs, standardized differences; SF-12; 12-item short form survey.

difference 0.41 [0.00-0.82] $P = 0.049$); however, no correction was made for multiple testing. Furthermore, the confidence intervals for these estimates do not include clinically meaningful differences. For all other time points, no differences in pain intensity were found.

Results of the ITT analysis for pain intensity at 2 weeks for quintiles of compliance (defined as an average of at least 4 tablets per day over 2 weeks) are depicted in **Figure 2**. No difference in pain intensity was found between regular paracetamol and placebo for any of the compliance subgroups. There appears to be no clear dose–response relationship between compliance and effect of paracetamol.

4. Discussion

In this secondary analysis of the PACE trial, we found that paracetamol had no clinically meaningful effect when compared with placebo on pain intensity, disability, global rating of symptom change, and function in people with acute LBP who complied with regular paracetamol.

Table 2

Outcomes of PACE trial (pain intensity, disability, global rating of symptom change, and function) at week 2 with compliance defined as an average intake of ≥4 tablets per day for the regular paracetamol group vs placebo group.

Outcome	ITT	Propensity-weighted CACE	Joint modeling CACE
Pain intensity (NRS) (scale range 0-10)	0.11 (−0.20 to 0.42), $P = 0.49$	0.068 (−0.37 to 0.50), $P = 0.76$	0.23 (−0.16 to 0.62), $P = 0.24$
Disability (RMDQ) (scale range 0-24)	0.11 (−0.60 to 0.82), $P = 0.76$	0.054 (−0.93 to 1.04), $P = 0.91$	0.37 (−0.55 to 1.30), $P = 0.43$
Global rating of symptom change (scale range −5 to +5)	0.0019 (−0.26 to 0.27), $P = 0.99$	0.059 (−0.33 to 0.44), $P = 0.76$	−0.083 (−0.42 to 0.25), $P = 0.62$
Function (Patient-Specific Function Scale) (scale range 0-10)	−0.069 (−0.38 to 0.24), $P = 0.67$	0.0043 (−0.45 to 0.45), $P = 0.99$	−0.28 (−0.67 to 0.11), $P = 0.16$

All values represent mean difference (lower limit of 95% CI, upper limit of 95% CI) *P* value; mean differences calculated by subtracting placebo group mean from regular paracetamol group mean. All analyses were adjusted for sex and baseline age, private health insurance, employment status, household income, use of drugs for another disorder, days since onset of pain, number of previous episodes, presence of pain extending beyond the knee, number of days reduced usual activity, disability (RMDQ), feelings of depression, perceived risk of persistent pain, back pain episode compensability, pain intensity, global rating of symptom change, sleep quality, function, quality of life (mental and physical components of the 12-item short form survey [SF-12]), and credibility and expectation scores (CEQ). Values rounded to 2 significant figures.
CACE, complier average causal effect; CEQ, Credibility/Expectancy Questionnaire; ITT, intention-to-treat; NRS, numerical rating scale; RMDQ, Roland–Morris Disability Questionnaire.

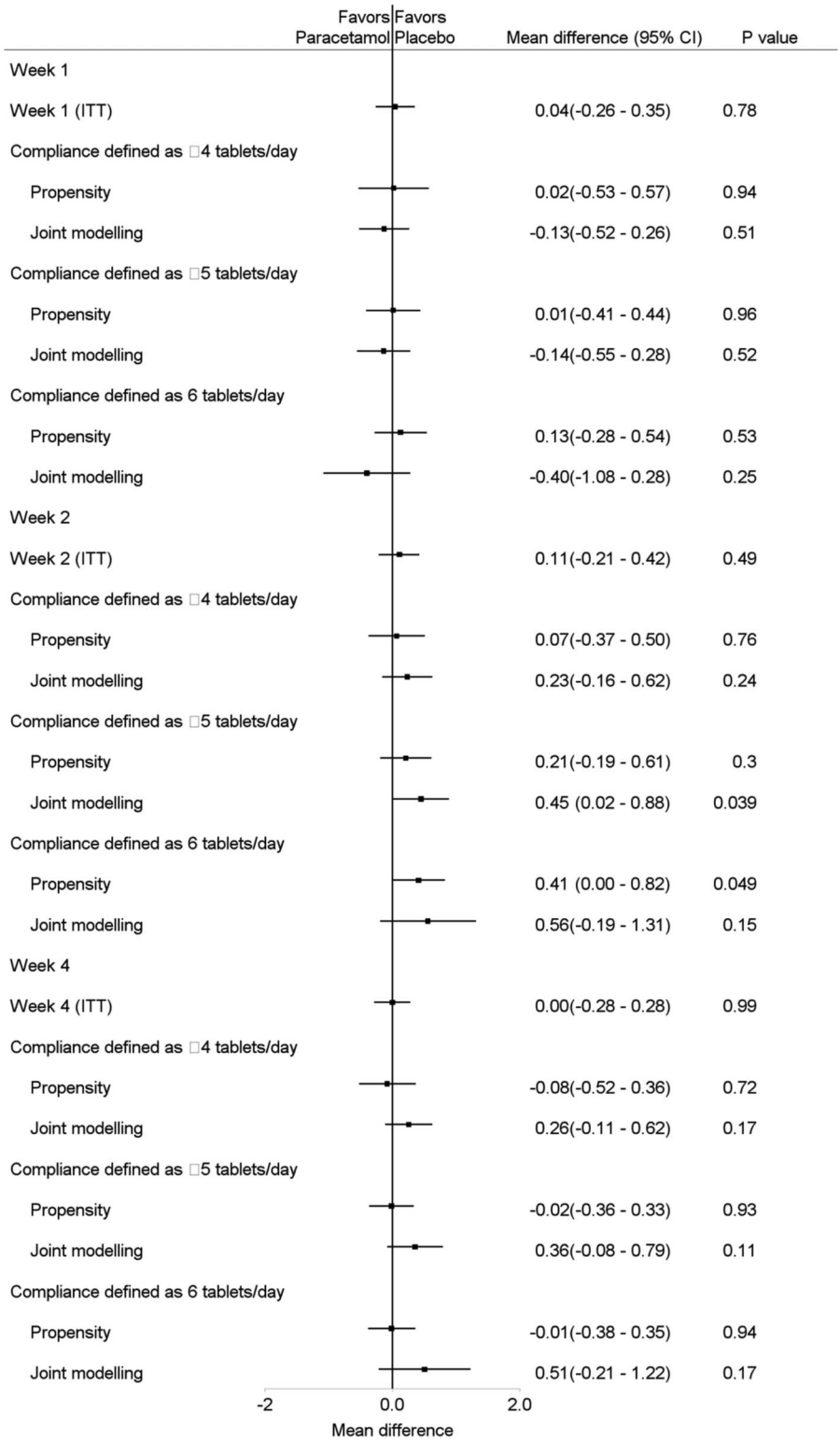

Figure 1. Exploratory ITT and CACE analyses for pain intensity including both primary and alternative cutoff points for compliance (an average of at least 5 tablets per day and 6 tablets per day, calculated over the periods of interest) as well as primary and alternative time points (1 and 4 weeks). Values rounded to 2 significant figures. CACE, complier average causal effect; CI, confidence interval; ITT, intention to treat. Boxes represent 'an average of at least', eg, "Compliance defined as an average of at least 4 tablets/day".

The CACE analysis technique produces robust estimates of efficacy amongst compliers; furthermore, we applied 2 distinct methods to estimate CACEs, which serve as each other's sensitivity analysis.[26] The credibility of our findings is supported by the fact that no large differences exist between these 2 estimation techniques.[26] Data used in this analysis were collected in a large and well-conducted RCT.[23,31]

The CACE analysis technique has 2 main weaknesses. First, no universally accepted definition of compliance to paracetamol for LBP exists. Using our main definition of compliance, 72% of

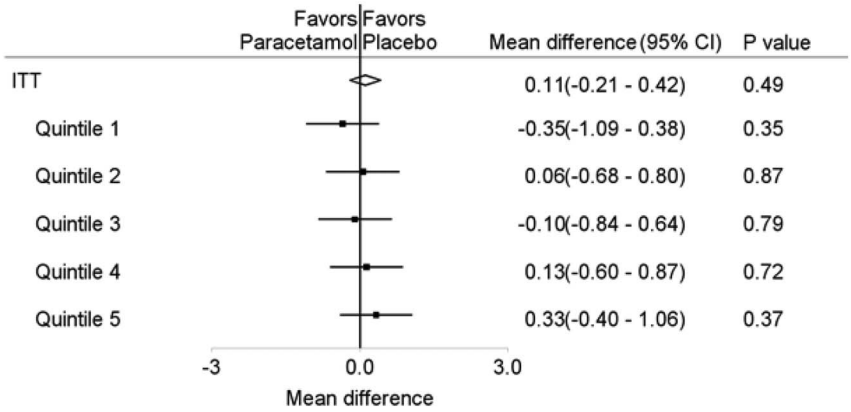

Figure 2. Exploratory ITT analysis for pain intensity at 2 weeks for quintiles of likelihood of compliance (with compliance defined as taking an average of at least 4 tablets of modified-release paracetamol per day during 2 weeks of follow-up). Quintile groups are presented in order of increasing likelihood of being compliant, with quintile 1 representing the group that was least likely to be compliant and quintile 5 representing the group that was most likely to be compliant. CI, confidence interval; ITT, intention to treat.

participants in the regular paracetamol group were classified as compliers. We explored stricter definitions of compliance and found results consistent with the primary analysis; however, as the percentage of compliers was lower using these definitions, CACE estimates using these definitions are less robust. Second, CACE estimates were based on patient-reported compliance filled out in paper drug diaries, which may not have perfectly represented actual consumption of tablets. However, counts of returned medicines and results from the brief adherence rating scale were consistent with patient-reported compliance.[31]

The findings of this secondary analysis should be placed in context of the original analysis of the PACE trial, which is still the only RCT that has assessed the efficacy of paracetamol for acute LBP and is considered to be the best available evidence.[23] As mentioned in the introduction, noncompliance to study medication was considered a potential limitation of the PACE results.[4,16,17,31] The results of this analysis suggest this is not the case and thus support the conclusion from the original analysis of the PACE trial that paracetamol is ineffective for acute LBP when compared with placebo. It is important to note that CACE analysis is a technique that accounts for a very specific participant group, namely those who comply with treatment. Although this analysis technique may be useful in trials where noncompliance is an issue, results of the ITT analysis remain the most relevant to clinical practice.

After a lack of efficacy of paracetamol for acute LBP was demonstrated by the PACE trial, paracetamol was no longer recommended as first choice analgesic in 4 of 8 recently published national clinical practice guidelines.[3,6,22,28] However, other recent guidelines still endorse the prescription of paracetamol for acute LBP.[5,12,20,25] One possible justification was that paracetamol may be effective in those who comply with the dosing regimen. Our CACE analyses have demonstrated that the efficacy of paracetamol is unlikely to change even in patients with total compliance to the regular regimen, reinforcing that management of acute LBP should focus on providing patients advice and reassurance without the addition of paracetamol.

In conclusion, paracetamol is not more effective than placebo for acute LBP in compliers of the treatment regimen. Complier average causal effect analyses using different cut points showed that paracetamol had no effect on pain intensity and secondary outcomes when compared with placebo for participants that complied to regular paracetamol in the PACE trial. These results support the original findings of the PACE trial.

Conflict of interest statement

The University of Sydney School of Pharmacy receives funding from GlaxoSmithKline for a postgraduate research scholarship supervised by A.J. Mclachlan. C.G. Maher has received funding to review teaching materials prepared by GlaxoSmithKline. C.-W. Christine Lin, A.J. Mclachlan, C.M. Williams, and C.G. Maher were investigators of the PACE trial. C.-W. Christine Lin, C.G. Maher, A.J. Mclachlan, B.W. Koes, and L. Billot received in-kind support from Pfizer Australia for an investigator-initiated trial of pregabalin vs placebo in sciatica, but retained full autonomy of the trial. The remaining authors have no conflicts of interest to declare.

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Author contributions: C.-W. Christine Lin, A.J. Mclachlan, C.M. Williams, and C.G. Maher made substantial intellectual contributions to the development of the original study protocol, data

collection, statistical analysis and drafting the original results of the PACE trial. M. Schreijenberg, C.-W. Christine Lin, A.J. Mclachlan, C.M. Williams, S.J. Kamper, B.W. Koes, C.G. Maher, and L. Billot all made substantial intellectual contributions to the development of the CACE analysis protocol. M. Schreijenberg and L. Billot had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M. Schreijenberg drafted the manuscript, which was revised by C.-W. Christine Lin, A.J. Mclachlan, C.M. Williams, S.J. Kamper, B.W. Koes, C.G. Maher, and L. Billot. All authors have read and approved the final manuscript.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A866.

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