Is there an association between reporting adverse events and outcomes of patients with acute low back pain?

Marco Schreijenberg, Martijn W. Heymans, Alessandro Chiarotto, Wendy T.M. Enthoven, Chung-Wei Christine Lin, Andrew J. McLachlan, Christopher G. Maher, Bart W. Koes

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ABSTRACT

Introduction

In people with acute low back pain (LBP), there may be an association between reporting adverse events (AEs) of treatment and outcomes of LBP. This study aimed to 1) investigate the association between baseline characteristics of participants and reporting AEs and 2) the association between reporting treatment related AEs and outcome in people with acute LBP.

Methods

Data from the PACE-trial, evaluating paracetamol versus placebo in acute LBP, was used in this analysis as an observational cohort. The association between baseline characteristics and reporting AEs by participants was investigated using a logistic regression model. The association between reporting AEs and outcomes of LBP was investigated using mixed effects models for LBP intensity, physical functioning and health-related quality of life (hrQoL) and Cox proportional hazards models for time until recovery.

Results

Reporting any AE was strongly associated with the use of medicines for a health problem other than LBP (odds ratio (95% CI) 1.42 (1.07-1.88)). Reporting any AE was not associated with less favorable outcomes for LBP intensity, physical functioning, hrQoL or time until recovery (respective coefficients 0.00 (-0.07-0.07), 0.02 (-0.05-0.10), -0.44 (-1.08-0.20), -0.54 (-1.37-0.29) and HR 1.09 (0.94-1.26)). Due to the very low number of serious AES (death or hospitalization) there was insufficient information to investigate the association between reporting these AEs and baseline characteristics or the association with outcomes of LBP.

Conclusions

In the PACE trial, reporting adverse events after using paracetamol or placebo was associated with the use of medicines for other health problems, but not with (unfavorable) outcomes of LBP.

INTRODUCTION

Paracetamol has represented the first-choice pain medication for patients with acute low back pain (LBP) (1). Although it has been more recently demonstrated that paracetamol is not more effective than placebo in acute LBP (2), paracetamol is still recommended in 4 out of 8 recently updated national clinical practice guidelines for the management of LBP (3-11). Paracetamol is one of the most widely used analgesics and is perceived as a relatively safe medicine by consumers and clinicians (12-14). However, paracetamol overdose is a major cause of acute liver failure globally (15). furthermore, observational studies have found paracetamol ingestion to be associated with an increased risk of cardiovascular, gastro-intestinal and kidney-related AEs in some patient groups (13).

Treatment outcomes in people with acute LBP are influenced by patient expectations and beliefs (16). Haanstra and colleagues demonstrated that expectations related to the effectiveness of treatment were associated with pain intensity after 4 weeks of follow-up and recovery from LBP (17). Similarly, there may be an association between reporting AEs and the outcomes of LBP. The impact of AEs on outcomes can be best studied in large observational cohort studies; however, in the available cohort studies of people with recent onset low back pain, AEs were not rigorously investigated (18). A suitable alternative available data source is to investigate the impact of AEs in patients with acute LBP in a large randomized controlled trial (RCT). With 1652 participants, the PACE trial, which investigated the efficacy of paracetamol, is one of the largest RCTs in people with acute LBP (2).

The aim of this study is to identify baseline socio-demographic and clinical characteristics associated with reporting AEs in trial participants with acute LBP; and second, to investigate the association between reporting AEs and outcomes of acute LBP.

METHODS

Participants and design:

The PACE trial was a multicenter, double-dummy, randomized, placebo-controlled trial that was conducted from November 2009 until March 2013 in Sydney, Australia. The study protocol (19), analysis plan (20) and main results (2) have been published elsewhere. In short, the PACE trial recruited 1643 participants with a new episode of at least moderate LBP (measured by an adaptation of item 7 of the Short Form 36 Health Survey (21)) which were randomly allocated (in a 1:1:1 ratio) to receive 2 x 665 mg modified-release paracetamol tablets administered 3 times a day regularly (n = 550), or 1 to 2 tablets of 500 mg immediate-release paracetamol tablets taken up to 4 times a day as-needed for pain (n = 549), or identical placebo (n = 553) until recovery from LBP or for a maximum of four weeks. Participants recorded pain intensity scores and number

of tablets taken in a daily pain and drug diary. Follow-up data were collected at 1, 2, 4 and 12 weeks after randomization. No treatment effects were observed between study groups (2); therefore for the current study, the complete study population was used and analyzed as an observational cohort study such that allocation to treatment was not included in the analysis.

Ethics

The PACE trial had approval from University of Sydney Human Research Ethics Committee and was prospectively registered with the Australian and New Zealand Clinical Trial Registry (ACTN12609000966291).

Measures

In the PACE trial, AEs were recorded after 1, 2, 4 and 12 weeks of follow-up; for each AE, start date, end date, details and ICD-10 code (obtained using the International Classification of Diseases and Related Health Problems, 10th edition (22)) were recorded (2). AEs were defined as the occurrence or diagnosis of any new medical disorder or exacerbation of any old medical disorder since the most recent contact with the researchers (2). Serious adverse events (SAEs) were defined as any event resulting in death or hospital admission, including pregnancy (2).

To investigate the association between baseline characteristics and reporting AEs, the baseline characteristics as presented in the PACE trial-publications were used (2, 19). These included dichotomous, categorical and continuous variables: sex, age, employment status, income, use of medication for other health conditions, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days of reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations, and physical and mental health-related quality of life (HRQoL) (2, 19).

For the analysis regarding the association between reporting AEs and outcomes of LBP, the core outcome domains for LBP (i.e. pain intensity, physical function and HRQoL (23)) and time until recovery from LBP (the primary outcome of PACE) were used. These outcomes were measured as follows:

- LBP-intensity recorded as average pain intensity the last 24 hours using an 11-point NRS (score range 0–10; higher score means more pain) (24). LBP-intensity was measured at baseline and daily until 12 weeks follow-up or until recovery from LBP.
- Physical functioning measured with the Roland Morris Disability Questionnaire (RMDQ; score range 0–24; higher score indicating poorer back-related physical functioning) (25). Physical functioning was measured at baseline and at 1, 2, 4 and 12 weeks follow-up.

- HRQoL measured with the physical and mental aggregate scores of the Short Form 12 (SF-12, with a population mean of 50 and standard deviation of 10; higher score indicating better HRQoL) (21). HRQoL was measured at baseline and at 4 and 12 weeks follow-up.
- Time until recovery from LBP as assessed with the daily low back pain severity scores. Recovery was defined as the first day of 0 or 1 pain intensity on a 0-10 pain scale, maintained for seven consecutive days.

Statistical analysis

Software used for the statistical analysis was R version 3.5.3 (26). For the descriptive statistics of AEs, frequency tables were created including the number of AEs reported per participant, the minimum, maximum, mean and median were calculated.

To investigate the association between baseline characteristics and reporting of AEs ('yes/no'), initially a full logistic regression model was created with the reporting of any AE as dependent variable and with all baseline covariates and treatment allocation as covariates. Subsequently, a backward stepwise model selection procedure based on Akaike's Information Criterion (AIC) was performed using the stepAIC function from the MASS package in R (27). For covariates in the final model, Odds Ratios (ORs) and their corresponding 95% confidence intervals (CIs) and p-values were calculated.

To explore the association between reporting AEs ('yes/no') and repeated measurements for outcomes of LBP, uncorrected mixed effects models (including covariates for time and the reporting of AEs) and corrected mixed effects models (including covariates for time, the reporting of AEs, treatment allocation and all baseline covariates) were constructed with outcomes of LBP as dependent variables and AEs as a covariate. For pain intensity and physical functioning, Poisson mixed effects models were constructed as pain data was zero-inflated and non-normally distributed in the PACE trial (Supplementary Figure 1). Poisson models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data (28, 29). The GLMMadaptive R package was used to create the Poisson mixed effects models (30). For HRQoL, linear mixed effects models were constructed as the aggregate scores for mental and physical HRQoL were normally distributed. The lme4 R package was used to create the Poisson mixed effects models (31). Regression coefficients with 95% CIs for the association of reporting any adverse event on average pain intensity, physical functioning and mental and physical HRQoL were calculated. For the time until recovery analysis, Cox proportional hazards models were constructed; for this outcome, hazard ratios (HRs) with 95% CIs for recovery for participants reporting AEs were calculated; furthermore, median recovery times and survival differences were calculated. The Survival R package was used to create the Cox proportional hazards models (32).

RESULTS

Descriptive statistics for AEs in the PACE trial are presented in Table 1. In total, 1594 out of 1643 participants provided information about AEs, of which 296 participants (19%) reported at least one AE. The number of AEs reported per participant ranged from a minimum of 0 to a maximum of 3; the median was 0. There were no differences in number of participants reporting AEs and SAEs between treatment groups. Only 1% of all 1643 participants reported a SAE (14 events in total; 5 in the regular paracetamol group, 4 in the paracetamol as-needed group and 5 in the placebo-group).

Table 1: Descriptive statistics for adverse events in the PACE trial.

	Regular Paracetamol group (n = 550)	Paracetamol As-needed group (n = 546)	Placebo group (n = 547)	Total (n = 1643)
Any adverse event	99/534 (19%)	99/529 (19%)	98/531 (18%)	296/1594 (19%)
Serious adverse event	5/550 (1%)	4/546 (1%)	5/547 (1%)	14/1643 (1%)

Data are n/N (%)

Reporting any AE by PACE trial participants was associated with baseline age, days since onset of pain, feelings of depression and use of medicines for other health conditions (Table 2). The use of medicines for health conditions other than LBP had the strongest association with reporting any AE; participants who used drugs for other health problems had an adjusted OR for reporting any AE of 1.42 (95% CI 1.07-1.88) when compared to participants not taking medicines for other conditions.

Table 2: Association between the reporting of adverse events (dependent variable) and baseline characteristics (covariates) in the PACE trial.

Covariate	Regression coefficient	Odds Ratio (exp(Coefficient)	Lower limit 95% CI of OR	Upper limit 95% CI of OR	P-value
Intercept	-2.81	0.06	0.04	0.09	<0.01
Age	0.01	1.01	1.01	1.02	<0.01
Days since onset of pain	0.03	1.03	1.01	1.04	<0.01
Feelings of depression in last week	0.06	1.07	1.02	1.11	<0.01
Use of drugs for another disorder	0.35	1.42	1.07	1.88	0.01

All covariates measured at baseline. Values rounded to 2 decimals.

Coefficients for the association between reporting any AE and outcomes of LBP in PACE are presented in Table 3 and a graphical representation of the uncorrected association between reporting any AE and outcomes of LBP during follow-up is shown in Figure 1.

Table 3: Coefficients for the association of outcomes of LBP (dependent variables) and the reporting of adverse events (covariates) in the PACE trial.

	Pain intensity (NRS, scale range 0-10)	Physical functioning	HRQoL-mental (SF-12)	HRQoL-physical (SF-12)	Time until recovery
Regression coefficient for reporting any adverse event - uncorrected	0.08 (0.00, 0.16) p = 0.04	0.13 (0.04, 0.22) p = 0.01	-0.89 (-1.56,-0.23) p = 0.01	-2.13 (-3.08,-1.18) p = 0.00	HR 0.92 (0.81, 1.06) p = 0.25
Regression coefficient for reporting any adverse event - corrected	0.00 (-0.07, 0.07) p = 0.93	0.02 (-0.05, 0.10) p = 0.57	-0.44 (-1.08, 0.20) p = 0.17	-0.54 (-1.37, 0.29) p = 0.20	HR 1.09 (0.94, 1.26) p = 0.24

All numbers rounded to 2 decimal places. 'Corrected' models were corrected for treatment group, gender, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; NRS: Numerical Rating Scale; OR: Odds Ratio; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-12: Short Form 12.

As an example, the uncorrected coefficient for reporting any AE versus reporting no AEs (0.08, 95% CI 0.00 – 0.16) is interpreted as the change in the log average pain intensity for participants reporting any AE when compared to participants that reported no AEs, when all other predictors remain constant. The associations between reporting any AE and pain intensity, physical functioning and HRQoL were not apparent in the corrected mixed effects models.

Reporting any AE was not associated with time until recovery from back pain in both the uncorrected and the corrected Cox proportional hazards analysis (Table 3). Information for both recovery from back pain and AEs was available for 1588 out of 1643 participants (for this analysis, data were missing for 55 participants (3%)). After 12 weeks of follow-up, 1398 out of 1588 participants recovered from LBP. Uncorrected median time until recovery from LBP was 12 days (95% CI 11-14 days) in the participants that did not report any adverse events and 16 days (95% CI 14-18 days) in the participants that reported adverse events; this survival difference is not considered substantial (p = 0.3).

DISCUSSION

In people with acute LBP that participated in the PACE trial, reporting any AE was associated with older age, more days since onset of pain, increased feelings of depression and use of medicines for another health condition; there was no association between

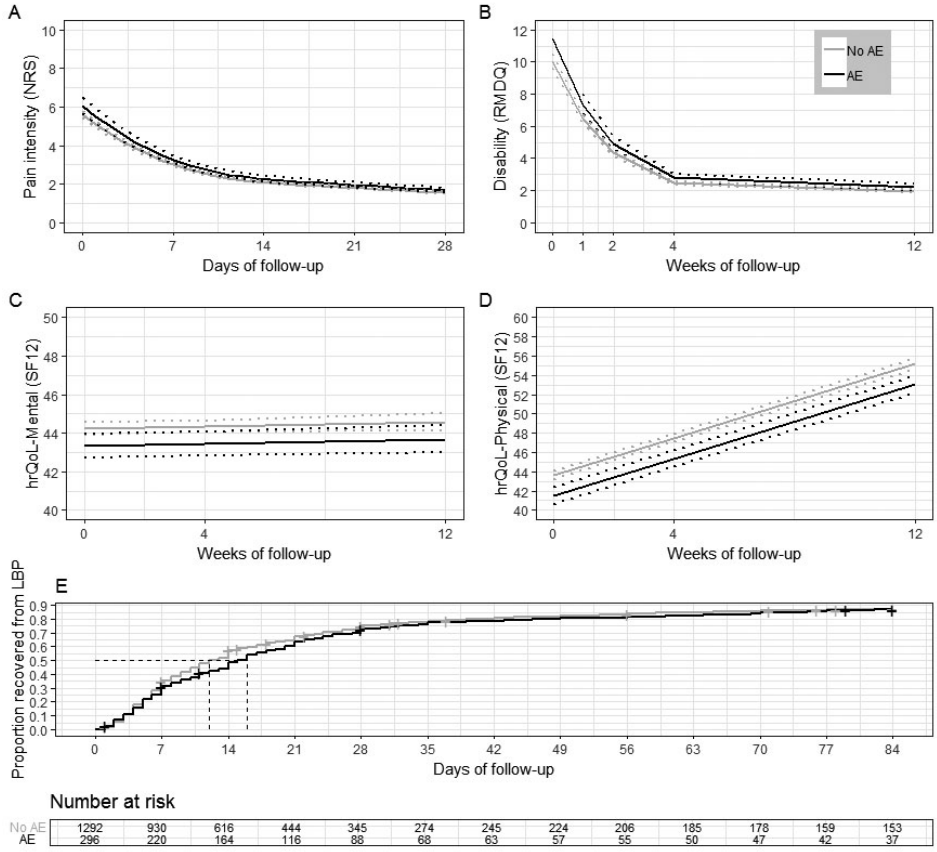

Figure 1: Effects of reporting any adverse event on core outcomes of LBP (Pain intensity (A), Physical functioning (B) and HRQoL (C and D) and Time until first recovery from LBP (E). Graphs obtained from uncorrected regression models containing only the reporting of adverse events and time as covariates. Y-axis was truncated for plots B, C, D, and E in order to improve visibility of results. The blue line indicates the participant group that did not report any adverse events, the red line indicates the participant group that reported adverse events. HRQoL: health-related Quality of Life; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; SF12: Short Form 12

treatment group and reporting AEs. Reporting any AE was not associated with (less favorable) outcomes for LBP intensity, physical functioning, HRQoL or time until recovery in participants of PACE.

The strength of this study is the use of a very large dataset of people with acute LBP where data on AEs were reliably captured over the treatment course and up to 8 weeks following the end of the treatment period. Given the fact that paracetamol has a half-life between 1 and 4 hours, it is unlikely that paracetamol-related AEs have occurred after this follow-up period. This study has a number of limitations: first, although the sample size of 1643 patients may be large for an RCT in LBP, it is relatively small compared to the large

observational cohort studies that AEs are ideally investigated in. Second, information bias may have arisen in the registration of AEs, as AEs were a patient-reported secondary endpoint in the PACE trial. Third, although in this study we assessed the association between AEs and baseline characteristics, and AEs and outcomes, we did not assess if the reported AEs were related to the study medicines. The findings that reporting an AE was associated with use of medicines for another health condition would suggest that not all AEs would be related to the study treatment.

Two recent systematic reviews discuss the safety of paracetamol for low back pain (12, 33); both included the PACE trial in their meta-analyses. These systematic reviews focused primarily on the risk of experiencing AEs for patients taking paracetamol when compared to patients taking placebo. No differences were found in number of patients reporting AEs or SAEs or withdrawing from the study because of AEs, which is in line with our findings in the present study (12, 33). Machado and colleagues reported that participants taking paracetamol were 3.8 times more likely than participants taking placebo to have abnormal liver function tests results, although the clinical relevance of this is unclear (12) In the PACE trial, liver function testing was not performed; the reported risk ratio for abnormal liver function tests could therefore not be investigated in the current analysis. Hepatic failure was reported in 1 participant from the placebo group of the PACE trial (2). Apart from the hepatic AEs reported in systematic reviews of RCTs in back pain, a systematic review of observational studies also found an association between paracetamol use and cardiovascular, gastro-intestinal and renal AEs (13). The current study attempts to place the risk of reporting AEs as found in these recent systematic reviews in the context of clinical practice by presenting associations between reporting AEs and the outcomes of LBP.

The best evidence that is currently available suggests that paracetamol is not more effective than placebo for LBP (3, 12, 33); therefore, paracetamol should no longer be recommended to patients for the management of acute LBP in primary care. However, this study suggests that if patients with acute LBP do take paracetamol and consequently experience AEs, overall this is not associated with less favorable outcomes of LBP either. Patients with acute LBP who are older, have had back pain for a longer period before seeking care, had feelings of depression in the last week or use medicines for other health conditions may be more likely to report AEs of paracetamol; these characteristics could represent a more vulnerable patient group of older people with more comorbidities and polypharmacy.

Future studies into the AEs associated with taking paracetamol for LBP could investigate the associations between objective AEs and SAEs (e.g. as confirmed with liver function tests) and the baseline characteristics and outcomes of patients with LBP in order to identify patient groups that have an increased risk of experiencing SAEs.

CONCLUSIONS

In people with acute LBP that participated in the PACE trial, reporting any AE was associated with older age, more days since onset of pain, increased feelings of depression and use of medicines for health conditions; there was no association between treatment group and reporting AEs. Reporting any AE after using paracetamol or placebo was not associated with worse results in the core outcomes for LBP or in time until recovery from LBP.

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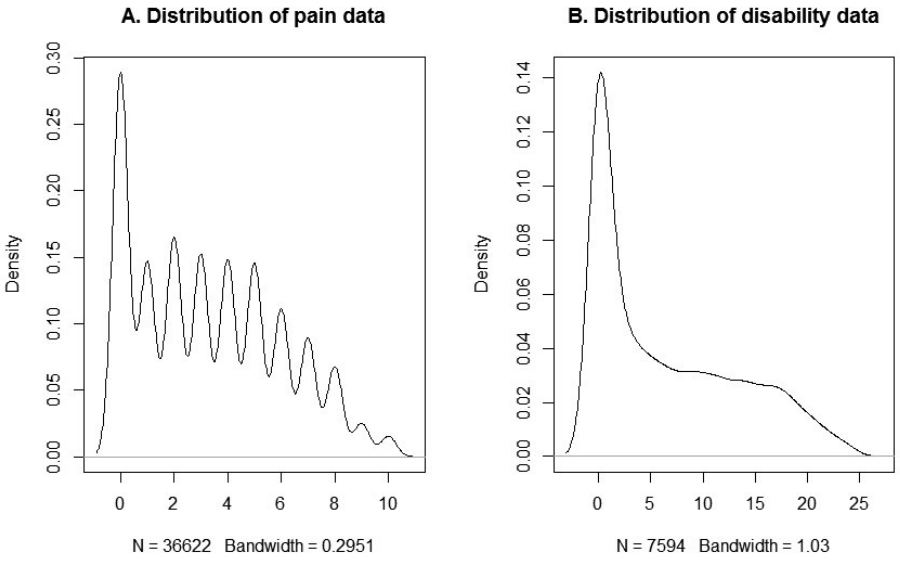

Supplementary Figure 1: Distribution of pain data (A) and Physical function data (B) in the PACE trial.