Paracetamol for low back pain (Review)

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Paracetamol for low back pain.
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ABSTRACT

Background

Analgesic medication is the most frequently prescribed treatment for low back pain (LBP), of which paracetamol (acetaminophen) is recommended as the first choice medication. However, there is uncertainty about the efficacy of paracetamol for LBP.

Objectives

To investigate the efficacy and safety of paracetamol for non-specific LBP.

Search methods

We conducted searches on the Cochrane Central Register of Controlled Trials (CENTRAL, which includes the Back and Neck Review Group trials register), MEDLINE, EMBASE, CINAHL, AMED, Web of Science, LILACS, and IPA from their inception to 7 August 2015. We also searched the reference lists of eligible papers and trial registry websites (WHO ICTRP and ClinicalTrials.gov).

Selection criteria

We only considered randomised trials comparing the efficacy of paracetamol with placebo for non-specific LBP. The primary outcomes were pain and disability. We also investigated quality of life, function, adverse effects, global impression of recovery, sleep quality, patient adherence, and use of rescue medication as secondary outcomes.

Data collection and analysis

Two review authors independently performed the data extraction and assessed risk of bias in the included studies. We also evaluated the quality of evidence using the GRADE approach. We converted scales for pain intensity to a common 0 to 100 scale. We quantified treatment effects using mean difference for continuous outcomes and risk ratios for dichotomous outcomes. We used effect sizes and 95% confidence intervals as a measure of treatment effect for the primary outcomes. When the treatment effects were smaller than 9 points on a 0 to 100 scale, we considered the effect as small and not clinically important.
Main results

Our searches retrieved 4449 records, of which three trials were included in the review (n = 1825 participants), and two trials were included in the meta-analysis. For acute LBP, there is high-quality evidence for no difference between paracetamol (4 g per day) and placebo at 1 week (immediate term), 2 weeks, 4 weeks, and 12 weeks (short term) for the primary outcomes. There is high-quality evidence that paracetamol has no effect on quality of life, function, global impression of recovery, and sleep quality for all included time periods. There were also no significant differences between paracetamol and placebo for adverse events, patient adherence, or use of rescue medication. For chronic LBP, there is very low-quality evidence (based on a trial that has been retracted) for no effect of paracetamol (1 g single intravenous dose) on immediate pain reduction. Finally, no trials were identified evaluating patients with subacute LBP.

Authors’ conclusions

We found that paracetamol does not produce better outcomes than placebo for people with acute LBP, and it is uncertain if it has any effect on chronic LBP.

PLAIN LANGUAGE SUMMARY

Paracetamol for low back pain

Review question

To see how well paracetamol works for non-specific low back pain (LBP). Non-specific LBP is back pain for which there is no identified disease or condition.

Background

Paracetamol is one of the most commonly prescribed medicines for people with LBP, and it is recommended in the guidelines that are issued to help doctors manage different illnesses. However, recent evidence has called into question how effective it is.

Search date

The evidence is current to August 2015.

Study characteristics

We included three trials with a total of 1825 participants in this review, two trials with participants whose back pain occurred suddenly and recently (acute) and one trial with participants whose pain lasted for longer than six weeks (chronic). Most of the people in the study (90%) were middle-aged and came from a single trial that looked at acute back pain. All of the trials tested paracetamol against a placebo (which contains nothing that could act as a medicine). The treatments ranged from a single 1 g dose (given intravenously) up to 4 g in 24 hour period for up to four weeks (oral tablets). Participants were followed between one day and 12 weeks. The main outcomes we studied were pain and disability; we also looked at quality of life, how easily people could go about their daily lives, unpleasant or unwanted side effects, how well people felt they had recovered, sleep quality, whether participants had taken the medicine as prescribed, and if it had been necessary to take ‘rescue medication’ because the paracetamol had not worked. We combined the findings from two of the trials into a single analysis (meta-analysis) that compared paracetamol to a placebo; the third trial did not report the results for the placebo, and so it could not be included.

Key results and quality of evidence

We found high-quality evidence that paracetamol (4 g per day) is no better than placebo for relieving acute LBP in either the short or longer term. It also worked no better than placebo on the other aspects studied, such as quality of life and sleep quality. About one in five people reported side effects, though few were serious, and there was no difference between intervention and control groups. As most of the participants studied were middle-aged, we cannot be sure that the findings would be the same for other age groups.

There appears to be no difference between paracetamol and placebo in immediate reduction of chronic LBP, although the evidence is of very low quality, and the single study on which it is based has been withdrawn by the journal.
# Summary of Findings for the Main Comparison

Paracetamol compared with placebo for acute low back pain

**Patient or population:** People with acute low back pain  
**Settings:** Primary care  
**Intervention:** Paracetamol  
**Comparison:** Placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain 1 week (immediate term)</strong> (NRS 0 to 100)</td>
<td>The mean pain in the control group was 36 points</td>
<td>The mean pain in the intervention group was 1.49 higher (1.30 lower to 4.28 higher)</td>
<td></td>
<td>-</td>
<td>1520 (1 study)</td>
<td>⊕⊕⊕⊕ high</td>
</tr>
<tr>
<td><strong>Pain 12 weeks (short term)</strong> (NRS 0 to 100)</td>
<td>The mean pain in the control group was 13 points</td>
<td>The mean pain in the intervention group was 0.50 lower (2.92 lower to 1.92 higher)</td>
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<td>-</td>
<td>1526 (1 study)</td>
<td>⊕⊕⊕⊕ high</td>
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<tr>
<td><strong>Disability 1 week (immediate term)</strong> (RMDQ 0 to 24)</td>
<td>The mean disability in the control group was 8.3 points</td>
<td>The mean disability in the intervention group was 0.45 lower (1.15 lower to 0.25 higher)</td>
<td></td>
<td>-</td>
<td>1511 (1 study)</td>
<td>⊕⊕⊕⊕ high</td>
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</tbody>
</table>
## Disability

<table>
<thead>
<tr>
<th>Disability 12 weeks (short term) (RMDQ 0 to 24)</th>
<th>The mean disability in the control group was 2.4 points</th>
<th>The mean disability in the intervention group was 0.10 higher (0.39 lower to 0.59 higher)</th>
<th>1522 (1 study)</th>
<th>⚫⚫⚫⚫ high</th>
<th>The difference is not statistically or clinically significant</th>
</tr>
</thead>
</table>

## Any adverse events

<table>
<thead>
<tr>
<th>Any adverse events Up to 12 weeks' follow-up</th>
<th>107 per 1000 (92 to 142)</th>
<th>115 per 1000 (92 to 142)</th>
<th>RR 1.07 (0.86 to 1.33)</th>
<th>1624 (1 study)</th>
<th>⚫⚫⚫⚫ high</th>
<th>The difference is not statistically or clinically significant</th>
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</table>

## Serious adverse events

<table>
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<tr>
<th>Serious adverse events Up to 12 weeks' follow-up</th>
<th>90 per 1000 (90 to 93)</th>
<th>91 per 1000 (90 to 93)</th>
<th>RR 0.90 (0.30 to 2.67)</th>
<th>1643 (1 study)</th>
<th>⚫⚫⚫⚫ high</th>
<th>The difference is not statistically or clinically significant</th>
</tr>
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</table>

*The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: confidence interval; NRS: Numeric Rating Scale; RMDQ: Roland Morris Disability Questionnaire; RR: risk ratio

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### GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.
**BACKGROUND**

Low back pain (LBP) is the leading cause of disability worldwide (Global Burden of Disease Study 2015). Patients usually experience a substantial reduction in pain intensity in the first six weeks following the onset of a new episode, however, in many patients the pain does not resolve completely (Menezes 2012; Pengel 2003). About 40% of patients will develop chronic LBP, persisting for months or years (Menezes 2009). Even for those patients who recover quickly from the initial acute episode, a recurrent episode during the following 12 months is very common (Henschke 2008).

The most frequently prescribed treatment for back pain is an analgesic medication; according to clinical practice guidelines, paracetamol should be the first-choice pain medicine for people with non-specific LBP, especially in the acute phase (Koes 2010). However, the guideline recommendations for prescribing paracetamol are based on indirect evidence of efficacy from studies outside the LBP field, consensus among the guideline development group, and greater safety compared to alternative pain medicines (for example non-steroidal anti-inflammatory drugs (NSAIDs) or opioids) (van Tulder 2006). The uncertainty about the efficacy of paracetamol as an analgesic for LBP was highlighted in the first systematic review of paracetamol for LBP, which noted the absence of robust data on treatment efficacy (Davies 2008). Subsequent to the Davies 2008 review, the PACE trial has called into question the efficacy of paracetamol for people with acute LBP (Williams 2014).

The PACE trial enrolled 1652 participants and reported no significant difference in days to recovery between participants taking paracetamol in a time-contingent fashion, taking paracetamol as required, or placebo for acute LBP (Williams 2014). There was also no effect for any of the secondary outcomes (for example pain intensity, disability, function, global rating of symptom change, sleep quality, and quality of life). The presumed efficacy of paracetamol for LBP as reflected in guideline endorsement is thus controversial, and a Cochrane review of placebo-controlled trials could provide the credible evidence needed to inform decision-making based on the highest standard of evidence.

This review is an update of a recent systematic review on paracetamol for spinal pain or osteoarthritis (Machado 2015). The Machado 2015 review has been split into two Cochrane reviews, one focusing on knee or hip osteoarthritis, and this one, which focuses on non-specific LBP. Both reviews follow the same methodology according to the guidelines of The Cochrane Collaboration, Higgins 2011, and the Cochrane Back and Neck Review Group, Furlan 2015.

**Description of the condition**

LBP can be defined as pain or discomfort below the ribs and above the gluteal crease, with or without referred leg pain (Airaksinen 2006). The great majority of people with LBP are classified as having non-specific LBP, which is defined as LBP without any known specific cause or pathology, such as nerve root compromise or serious spinal pathology (for example fracture, cancer, infection, or inflammatory diseases). This condition is also staged according to the duration of symptoms: acute LBP is an episode persisting for less than six weeks; subacute LBP with symptoms persisting between six and 12 weeks; and chronic LBP when symptoms persist for 12 weeks or longer (Furlan 2015).

**Why it is important to do this review**

This review is an update of a recent systematic review on paracetamol for spinal pain and osteoarthritis (Machado 2015), which...
was published in the BMJ. The Cochrane format will allow us to provide a more comprehensive overview of the results and methods than is possible with a journal article. We will also take the opportunity to update the search and focus specifically on LBP.

**OBJECTIVES**

To investigate the efficacy and safety of paracetamol for non-specific LBP.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We only considered placebo-controlled randomised trials. We did not include trials with quasi-random allocation procedures in order to avoid biased estimates of treatment effects across the included studies (Furlan 2015; Higgins 2011).

**Types of participants**

Inclusion criteria:
- People with non-specific acute, subacute, or chronic non-specific LBP
- People recruited from primary, secondary, or tertiary care

Exclusion criteria:
- People with serious spinal pathology (e.g. cancer, fractures, cauda equina syndrome, and inflammatory diseases)
- Pregnancy

**Types of interventions**

We included any dosing regimen of paracetamol compared to placebo. We did not include any combination of medicines with paracetamol. We also excluded the use of paracetamol for post-operative analgesia.

**Types of outcome measures**

**Primary outcomes**
- Pain intensity
- Disability

**Secondary outcomes**
- Quality of life
- Function
- Adverse effects
- Global impression of recovery
- Sleep quality
- Patient adherence
- Use of rescue medication

**Search methods for identification of studies**

**Electronic searches**

We performed a computerised electronic search to identify relevant articles in the following databases from their inception to 7 August 2015 without language restrictions:
- Cochrane Central Register of Controlled Trials (CENTRAL, which includes the Back and Neck review Group trials register; OvidSP, 1991 to August 2015).
- MEDLINE (OvidSP, 1946 to August Week 1 2015)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP, 7 August 2015).
- EMBASE (Embase.com, 1947 to August 2015).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO, 1982 to August 2015).
- Allied and Complementary Medicine (AMED) (OvidSP, 1985 to August 2015).
- Web of Science (Thomson Reuters, 1900 to August 2015).
- Latin American and Caribbean Health Sciences Literature (LILACS).
- International Pharmaceutical Abstracts (IPA) (OvidSP, 1970 to August 2015).

The search strategy for each database is presented in the following appendices: Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8.

**Searching other resources**

We also searched the reference lists of eligible papers and the following trial registry websites: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. The search strategy used for searching other resources is presented in Appendix 9.

**Data collection and analysis**

**Selection of studies**
Two review authors independently screened titles, abstracts, and full-text papers for potentially eligible studies, resolving any disagreements through discussion or arbitration of a third review author if consensus could not be reached.

Data extraction and management
Two review authors independently extracted the following data from each included trial using a standardised data extraction form. Disagreements were resolved through discussion or arbitration of a third review author when consensus could not be reached.

- Bibliometric data (authors, year of publication, language).
- Study characteristics (study design, sample size, description of the sample, country, funding).
- Characteristics of the participants (gender, age, duration of symptoms).
- Duration of follow-up assessments.
- Means, standard deviations, and sample sizes for continuous outcome measures. The treatment estimates were extracted in the following hierarchical order: between-group differences, within-group change scores, and follow-up values.
- Number of cases and the total sample size for dichotomous outcomes.

For adverse events, we considered the number of participants reporting any adverse event, the number of participants reporting any serious adverse event (as defined by each study), the number of participants withdrawn from study due to adverse events, and the number of participants with abnormal results on liver function tests (hepatic enzyme activity ≥ 1.5 times the upper limit of the reference range).

Assessment of risk of bias in included studies
Two review authors independently assessed risk of bias of the included studies. Disagreements were resolved through discussion or arbitration of a third review author when consensus could not be reached. We assessed risk of bias using the ‘Risk of bias’ assessment tool recommended by The Cochrane Collaboration (Higgins 2011) (Appendix 10). We scored each item as ‘high’, ‘low’, or ‘unclear’ risk of bias.

Measures of treatment effect
When more than one scale for measuring pain intensity or disability was used, we extracted the more severe estimate reported at baseline. We converted scales for pain intensity to a common 0 (no pain) to 100 (worse pain) scale. We quantified the treatment effects with the mean difference for continuous outcomes, and calculated the risk ratios for the positive outcome for dichotomous outcomes. We used effect sizes and 95% confidence intervals as a measure of treatment effect. In the previous version of this review (Machado 2015), we considered the minimal clinically important difference (MCID) as 9 points on a 0 to 100 scale based upon the practice in the osteoarthritis field (Wandel 2010), though we understand that in the back pain field the MCID is usually considered to be larger than this value (Ostelo 2008). When the treatment effects were smaller than 9 points, we considered the effect as small and not clinically important.

Unit of analysis issues
To deal with repeated observations on participants, we followed the advocated strategy of defining the outcomes as well as the time points a priori (Higgins 2011). We have previously defined the time points as: immediate term (≤ 2 weeks), short term (> 2 weeks but ≤ 3 months), intermediate term (> 3 months but ≤ 12 months), and long term (> 12 months). However, to account for studies that reported multiple time points within each category, we included all time points reported in the included trials.

Dealing with missing data
We contacted authors to provide further information when the data reported in the paper was insufficient. When authors were unavailable, we estimated data using the recommendations of The Cochrane Collaboration (Higgins 2011).

Assessment of heterogeneity
The assessment of heterogeneity was based upon visual inspection of the forest plots looking at the overlap of the confidence intervals, and by the Chi² test and the I² statistic as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If substantial heterogeneity was present (I² greater than 50%), or when we identified clear heterogeneity by visual inspection, we used a random-effects model to combine results and downgraded for inconsistency in the quality of evidence assessment (GRADE).

Assessment of reporting biases
We did not assess publication bias with funnel plots because too few studies were included in the review. We added no language restriction to our search strategy in order to avoid potential language bias.

Data synthesis
We assessed the overall quality of the evidence for each outcome using the GRADE approach as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), and adapted in the updated Cochrane Back and Neck Review Group method guidelines (Furlan 2015) (Appendix 11). We downgraded the quality of the evidence by one level according to the following criteria: limitation of study design and risk of bias (downgraded if more than a quarter of the participants were from studies with a high risk of bias, that is one or more bias domains judged as high risk), inconsistency of results (downgraded if significant
heterogeneity was present by visual inspection or if the $I^2$ value was greater than 50%), imprecision (downgraded if the upper or lower limits of the 95% confidence interval crossed the MCID of 9 points (range 0 to 100) (Guyatt 2011), and publication bias (assessed by visual inspection of funnel plots and using Egger's test to investigate publication bias (small-study effects)) (Egger 1997). If the Egger's test result was significant (two-tailed $P < 0.1$), we would downgrade the quality of evidence (GRADE) by one level for all meta-analyses (Guyatt 2011b). We did not consider the indirectness criterion in this review because we included a specific population with relevant outcomes and direct comparisons (Guyatt 2011a).

We interpreted the overall quality of evidence using the following GRADE descriptors (Furlan 2015):

- **High-quality evidence**: Further research is very unlikely to change confidence in estimate of effect.
- **Moderate-quality evidence**: Further research is likely to have an important impact on confidence in estimate of effect and may change the estimate.
- **Low-quality evidence**: Further research is very likely to have an important impact on confidence in estimate of effect and is likely to change the estimate.
- **Very low-quality evidence**: Very little confidence in the effect estimate.
- **No evidence**: We identified no randomised controlled trials that addressed this outcome.

### Subgroup analysis and investigation of heterogeneity

We stratified the analyses based upon the duration of follow-up reported for each outcome (that is, immediate term, short term, intermediate term, and long term).

### Sensitivity analysis

We did not propose any sensitivity analyses as we expected the number of available trials to be low.

### RESULTS

#### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

#### Results of the search

The search yielded 4449 records, of which three trials fulfilled the inclusion criteria and were included in the review (Figure 1). An additional search for ongoing or registered trials in ClinicalTrials.gov and the WHO ICTRP retrieved 46 records, of which 9 records included paracetamol as an intervention. One record was from a study already included in this review (Williams 2014); we have described the other eight under Excluded studies.
Included studies

We have included three trials in this review (Nadler 2002; Wetzol 2014; Williams 2014), with a total sample size of 1825 participants (133, 40, and 1653 participants, respectively). We did not include one trial in the meta-analysis as it did not report results for the placebo group, and all attempts to contact the authors and the pharmaceutical company that funded the study were unsuccessful (Nadler 2002). One trial did not report the results for disability outcomes (Wetzol 2014); we contacted the authors, but they did not provide the data. The Wetzol 2014 trial has recently been retracted, however we included the data reported in the original publication.

The trials included in this review were conducted in Austria (Wetzol 2014), Australia (Williams 2014), and the United States (Nadler 2002). Two trials included people with acute LBP (Nadler 2002; Williams 2014), and one trial included people with chronic LBP (Wetzol 2014). The trials included 956 men and 860 women, most of whom were middle-aged (mean: 44.2, standard deviation: 13.6), recruited from primary care. The duration of the treatments included one single dose (Wetzol 2014), two consecutive days (Nadler 2002), and daily until recovered, up to a maximum of four weeks (Williams 2014), and the follow-up duration ranged from one day to 12 weeks.

All trials included single-ingredient paracetamol formulations. In one trial (Wetzol 2014), the participants received a single 1 g intravenous dose of paracetamol. In another trial (Nadler 2002), participants took 1 g of paracetamol tablets four times per day for two days. In the PACE trial (Williams 2014), participants in the time-contingent group took paracetamol tablets 4g per day in three divided doses, and those in the ‘as required’ group took up to 4 g per day; both groups were asked to take the paracetamol until recovery up to a maximum of four weeks. We included all three PACE trial groups in the meta-analyses, following the recommendations of The Cochrane Collaboration (Higgins 2011).

Regarding the primary outcomes, pain intensity was measured on a 0 to 10 scale in two trials (Wetzol 2014; Williams 2014), and a 0 to 5 scale in one trial (Nadler 2002). Disability was measured using the Roland Morris Disability Questionnaire (RMDQ) from 0 to 24 points in all included trials. One trial also measured quality of life with the 12-Item Short Form Health Survey (SF-12), and function using the Patient-Specific Functional Scale from 0 to 10 (Williams 2014). For the secondary outcomes, two trials measured adverse events (Nadler 2002; Williams 2014), and one trial measured adherence to the treatment, use of rescue medication, global impression of recovery (Global Perceived Effect scale from -5 to +5), and quality of sleep (number of participants reporting poor sleep quality) (Williams 2014). The rescue medication provided in Williams 2014 was two days’ supply of naproxen 250 mg (2 tablets initially, and then 1 tablet every 6 to 8 hours as required).

Excluded studies

We excluded a total of 41 full-text articles assessed for eligibility. Twelve records did not have a placebo group (Cabane 1996; Childers 2005; Corrs Giner 1989; Hackett 1988; Hingorani 1971; Jiang 2008; Kuntz 1996; Lee 2008; Madhusudhan 2013; McGuinness 1969; Muller 2005; Tervo 1976); eight used a combination of medications for the intervention group (Borenstein 2001; Coddin 2008; Garcia Filho 2006; Gimbel 2001; Muller 1998; Peloso 2004; Ruoff 2003; Schiphorst Preuper 2014); six were not randomised controlled trials (De Almeida Coimbra 1980; Derby 2012; Gammaitoni 2003; Larsen 2012; Miller 2012; Moore 2010); four did not have a paracetamol group (Martinez-Elizondo 1979; Matsushita 2012; Pallay 2004; Yarlas 2013); two were commentaries (Diener 2008; Diener 2008a); and one did not include people with LBP (Temple 2007). The search for ongoing or registered trials retrieved eight potentially eligible records that included paracetamol as an intervention. Seven records used a combination of paracetamol and other medications (NCT00210561; NCT00643383; NCT00736853; NCT01112267; NCT01587274; NCT01776515; NCT01843660), and one record did not have a placebo group (NCT01422291).

Risk of bias in included studies

The results from the 'Risk of bias' assessment for the individual studies are summarised in Figure 2.
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
**Allocation**

Only one trial had low risk of bias for random sequence generation and allocation concealment (Williams 2014). One trial had low risk of bias for randomisation but high risk of bias for allocation concealment (Wetzel 2014), and we judged one trial as unclear for both criteria (Nadler 2002).

**Blinding**

Two trials had low risk of bias for blinding for participants and personnel and outcome assessor (Wetzel 2014; Williams 2014). We considered one trial unclear for both criteria, as it was not clear which investigator was blinded (personnel or assessor) (Nadler 2002).

**Incomplete outcome data**

All trials successfully described complete outcome data and were rated as low risk of bias for this criterion. The follow-up rate was over 90% for all trials.

**Selective reporting**

Only one trial had low risk of bias for selective reporting (Williams 2014), in which all outcomes of interest were reported. The other two trials were rated as high risk of bias for this criterion. Wetzel 2014 reported baseline measurement for the RMDQ to assess functional status, however data were not reported separately for intervention and control groups. Nadler 2002 did not report data for the placebo group for any time point.

**Other potential sources of bias**

Two trials received funds from a company that produces paracetamol (Nadler 2002; Williams 2014). One trial was an investigator-initiated trial that received supplementary funding from a pharmaceutical company and reported that the sponsor had no role in conducting the study or analysing the data (Williams 2014). Given this background and the negative trial outcome, this study appears to be free of other sources of bias and was rated as low risk of bias. Nadler 2002 did not report data for the placebo group, and was rated as unclear for other bias. In the Wetzel 2014 study, participants received either weak or potent opioids at least four months before the intervention, and the exact length of the follow-up is not clearly stated, so we rated this trial as unclear. The Wetzel trial was also retracted, which we considered to be a potential source of bias. We also downgraded for other bias in the assessment of quality of evidence.

**Effects of interventions**

See: Summary of findings for the main comparison Paracetamol compared with placebo for acute low back pain We have presented results separately according to duration of LBP symptoms and outcome measures.

**Acute low back pain**

**Primary outcomes**

One large trial with low risk of bias investigated the effect of paracetamol compared with placebo for acute LBP (Williams 2014). There is high-quality evidence that there is no difference between paracetamol (4 g per day) and placebo for pain at 1 week (immediate term) (mean difference (MD) 1.49, 95% confidence interval (CI) -1.30 to 4.28), 2 weeks (MD 1.00, 95% CI -1.70 to 3.70), 4 weeks (MD 0.49, 95% CI -1.99 to 2.97), and 12 weeks (short term) (MD -0.50, 95% CI -2.92 to 1.92) (Figure 3). There is high-quality evidence that there is no difference between paracetamol and placebo for disability at 1 week (immediate term) (MD -0.45, 95% CI -1.15 to 0.25), 2 weeks (MD 0.00, 95% CI 0.00 to 0.65), 4 weeks (MD 0.05, 95% CI -0.50 to 0.60), and 12 weeks (short term) (MD 0.10, 95% CI 0.39 to 0.59) (Figure 4).
Figure 3. Forest plot of comparison: 1 Acute low back pain - paracetamol versus placebo, outcome: 1.1 Pain.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Paracetamol Mean</th>
<th>Paracetamol SD</th>
<th>Paracetamol Total</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Placebo Total</th>
<th>Mean Difference IV, Random, 95% CI</th>
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<td>1.1.1 1 week (immediate term)</td>
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<td></td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>39</td>
<td>27</td>
<td>496</td>
<td>38</td>
<td>26</td>
<td>252</td>
<td>-0.06 [1.39, 5.59]</td>
<td></td>
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<tr>
<td>Williams 2014 (2)</td>
<td>37</td>
<td>26</td>
<td>517</td>
<td>36</td>
<td>26</td>
<td>262</td>
<td>1.09 [2.92, 4.82]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1016</td>
<td></td>
<td></td>
<td>564</td>
<td></td>
<td></td>
<td>1.48 [1.08, 1.88]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.12; df = 1 (P = 0.74); P = 0%</td>
<td></td>
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<tr>
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<td></td>
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<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>1.1.2 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Williams 2014 (3)</td>
<td>26</td>
<td>26</td>
<td>509</td>
<td>25</td>
<td>25</td>
<td>249</td>
<td>1.06 [-2.94, 4.84]</td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>26</td>
<td>25</td>
<td>498</td>
<td>25</td>
<td>25</td>
<td>249</td>
<td>1.06 [-2.98, 4.82]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1008</td>
<td></td>
<td></td>
<td>498</td>
<td></td>
<td></td>
<td>1.06 [-1.70, 3.80]</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>1.1.3 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Williams 2014 (5)</td>
<td>18</td>
<td>24</td>
<td>507</td>
<td>17</td>
<td>23</td>
<td>250</td>
<td>1.06 [-2.53, 4.63]</td>
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<tr>
<td>Williams 2014 (6)</td>
<td>17</td>
<td>23</td>
<td>508</td>
<td>17</td>
<td>23</td>
<td>250</td>
<td>0.06 [-3.45, 3.58]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1016</td>
<td></td>
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<td>500</td>
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<td>0.49 [-1.99, 2.97]</td>
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<td>Test for overall effect Z = 0.33 (P = 0.74)</td>
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<td></td>
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<tr>
<td>1.1.4 12 weeks (short-term)</td>
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<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>13</td>
<td>22</td>
<td>514</td>
<td>13</td>
<td>23</td>
<td>253</td>
<td>0.06 [-3.44, 3.56]</td>
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<tr>
<td>Williams 2014 (6)</td>
<td>12</td>
<td>22</td>
<td>508</td>
<td>13</td>
<td>23</td>
<td>253</td>
<td>-1.06 [-4.42, 2.32]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1020</td>
<td></td>
<td></td>
<td>506</td>
<td></td>
<td></td>
<td>-0.50 [-2.92, 1.92]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.16; df = 1 (P = 0.69); P = 0%</td>
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<tr>
<td>Test for overall effect Z = 0.40 (P = 0.69)</td>
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</tbody>
</table>

Footnotes
(1) As-needed group
(2) Regular group
(3) Regular group
(4) As-needed group
(5) Regular group
(6) Regular group
(7) As-needed group
(8) Regular group

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Secondary outcomes

There is high-quality evidence that paracetamol has no effect on the physical component of quality of life at 4 weeks (MD -0.79, 95% CI -1.94 to 0.36) and 12 weeks (short term) (MD 0.41, 95% CI -0.91 to 1.72) (Analysis 1.3), and the mental component of quality of life at 4 weeks (MD -0.60, 95% CI -1.38 to 0.17). We found a statistically significant effect in favour to paracetamol at 12 weeks (short term) for the mental component of quality of life (MD 0.90, 95% CI -1.38 to 0.17). We did not consider this effect to be clinically important (Analysis 1.4).

There is high-quality evidence that there is no significant difference between paracetamol and placebo for function at 1 week (immediate term) (MD -0.05, 95% CI -0.28 to 0.18), 2 weeks (MD -0.05, 95% CI -0.28 to 0.18), 4 weeks (MD -0.10, 95% CI -0.33 to 0.13), and 12 weeks (short term) (MD -0.05, 95% CI -0.26 to 0.17) (Analysis 1.7).

Adverse events were reported by 296 (19%) participants, of which nine participants in the paracetamol group and five in the placebo group reported serious adverse events (that is any event causing hospitalisation or death). However, we observed no differences across groups for total adverse events (risk ratio (RR) 1.07, 95% CI 0.86 to 1.33) or serious adverse events (RR 0.90, 95% CI 0.30 to 2.67). The reported serious adverse events were unrelated to the study treatment (for example asthma attack, bleeding bowel, infection, hernia, severe back pain, or scheduled surgery) (Analysis 1.6).

We observed no significant differences in the number of partici-
Participants reporting poor sleep quality at 1 week (immediate term) (RR 1.05, 95% CI 0.87 to 1.25), 2 weeks (RR 1.01, 95% CI 0.80 to 1.28), 4 weeks (RR 1.11, 95% CI 0.82 to 1.52), and 12 weeks (short term) (RR 1.26, 95% CI 0.90 to 1.76), with high-quality evidence (Analysis 1.8). Finally, there were no significant differences between paracetamol and placebo for patient adherence (RR 1.08, 95% CI 0.96 to 1.22) (Analysis 1.9) or use of rescue medication (RR 0.50, 95% CI 0.16 to 1.55) (Analysis 1.10).

**Chronic low back pain**

Primary outcomes

One trial (n = 72) provided very low-quality evidence (downgraded due to risk of bias, imprecision, and other biases) that there is no effect of paracetamol on pain intensity at immediate-term follow-up (MD 0.00, 95% CI-9.70 to 9.70) (Wetzel 2014) (Figure 5).

**Figure 5. Forest plot of comparison: 2 Chronic low back pain - paracetamol versus placebo, outcome: 2.1 Pain.**

Secondary outcomes

There were no secondary outcomes or adverse events reported for this comparison.

**DISCUSSION**

**Summary of main results**

There is high-quality evidence that there is no difference between paracetamol and placebo for acute LBP on pain, disability, function, quality of life, and sleep quality outcomes at 1 week (immediate term), 2 weeks, 4 weeks, and 12 weeks (short term) follow-ups. There is also no difference on global impression of recovery, patient adherence, and use of rescue medication. Some minor and serious adverse events were reported for either the paracetamol or placebo group, but we found no difference between groups. No trial provided results for long-term follow-up. There is very low-quality evidence that there is no effect of paracetamol for chronic LBP on immediate pain. The results are consistent across all outcome measures and time periods included in this review. Although we found a statistically significant effect for the mental component of quality of life at short term for acute LBP, this result was not clinically important as it was a difference of 0.90 points out of 100 points. This significant effect could also be found by chance due to the large number of analyses in this review.

**Overall completeness and applicability of evidence**

None of the trials followed participants for more than 12 weeks (intermediate- or long-term follow-ups); thus the results of this review are restricted to immediate- and short-term follow-ups, that is from 1 week to 12 weeks. Moreover, more than 90% of the participants analysed in this review are from one large trial (Williams 2014), which included middle-aged Australian participants with acute LBP; thus care should be taken when generalising the findings of this review to other types of patients, such as chronic LBP patients. In addition, we did not find any trial evaluating paracet-
etamol for subacute LBP patients.

Quality of the evidence

The quality of evidence provided in this review was high for the use of paracetamol for acute LBP, which means that further research is very unlikely to change confidence in the estimate of effect. Regarding the risk of bias in the included studies, selective reporting was the only item considered as high risk of bias in two trials (Nadler 2002; Wetzel 2014). However, the trial that accounted for the majority of participants in this review was rated as low risk of bias for all criteria (Williams 2014). The only evidence for the use of paracetamol in chronic LBP comes from a study that was retracted from publication, with high risk of bias for reporting bias and unclear risk of bias for allocation concealment and other potential bias (Wetzel 2014).

Potential biases in the review process

Two trials in this review received funding from a pharmaceutical company (Nadler 2002; Williams 2014). However, in one trial the authors stated that the sponsor had no role in conducting the study or analysing the data, and given the negative outcome of the trial we considered this study to be free of any potential bias regarding conflicts of interest (Williams 2014). The trial by Wetzel 2014 has been retracted from the European Journal of Anaesthesiology, one of the authors not having consented to the submission and publication of the trial. Moreover, we limited our MEDLINE strategy to studies indexed with the MeSH term ‘humans’ using the limit function in the database. This could potentially exclude eligible studies not indexed with the MeSH term ‘human’. We do not think this is an issue in this review as we searched a variety of sources and checked studies from other reviews on the topic.

Agreements and disagreements with other studies or reviews

The last review on the topic concluded that there was insufficient evidence to assess the efficacy of paracetamol in people with LBP (Davies 2008). The authors of that review could not identify any randomised controlled trial comparing paracetamol to a placebo. Clinical practice guidelines have been recommending paracetamol, especially for acute patients (Koes 2010), based on presumed efficacy for related pain conditions and the safety profile compared to non-steroidal anti-inflammatory drugs (van Tulder 2006). This systematic review provides high-quality evidence that paracetamol is ineffective for acute LBP, and very low-quality evidence that it has no effect on people with chronic LBP. Although we found high-quality evidence for acute LBP, which is unlikely to change with future research, we believe that more studies are needed to resolve the uncertainty about the efficacy of paracetamol for chronic LBP, before paracetamol is completely removed from the recommendations for the management of LBP.

Authors’ conclusions

Implications for practice

The results argue against the use of paracetamol in the management of acute LBP. Because of very limited evidence it is not possible to make recommendations for or against the use of paracetamol for chronic LBP.

Implications for research

The high quality evidence and precise estimate of no effect for acute LBP suggests that no additional trials of paracetamol for acute LBP are required. For acute LBP the research questions include establishing what analgesic medicine(s) should replace paracetamol as the first line analgesic for acute LBP; and evaluating if combination medicines containing paracetamol are effective. In contrast we could only locate very low-quality evidence for chronic LBP and so future research evaluating the efficacy of paracetamol for chronic LBP is required to clarify the uncertainty.

Acknowledgements

Bruno Tirotti Saragiotto is supported by CNPQ (National Council for Scientific and Technological Development), Brazil. Chris Maher is supported by National Health and Medical Research Council of Australia. Gustavo Machado and Marina Pinheiro each hold an International Postgraduate Research Scholarship/Postgraduate Award from the Australian Government. Manuela Ferreira holds a Sydney Medical Foundation Fellowship.
Paracetamol for low back pain (Review)

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References to studies included in this review

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Wetzel 2014 [published data only]

Williams 2014 [published data only]

References to studies excluded from this review

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Diener HC. Paracetamol is sufficient for acute low back pain. *MMW-Fortschrritte der Medizin* 2008;150:23.

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Garcia Filho RJ, Korukian M, dos Santos FPE, Viola DCM, Puertas EB. A randomized, double-blind clinical trial, comparing the combination of caffeine, carisoprodol, sodium diclofenac and paracetamol versus cyclobenzaprine, to evaluate efficacy and safety in the treatment of patients with acute low back pain and lumboschialgia [Ensai clinico randomizado, duplo-cego, comparativo entre a associacao de cafeina, carisoprodol, diclofenaco sôdico e paracetamol e a ciclobenzaprina, para avaliaçao da eficácia e segurança no tratamento de pacientes com lombalgia e lombociatalgia agudas]. *Acta Ortopédica Brasileira* 2006;14:11–6.

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Hackett 1988 [published data only]
Conclusions

The available evidence does not support the routine use of tramadol, paracetamol, caffeine, or taurine as a single analgesic treatment for acute pain or chronic low back pain. Further high-quality research is needed to evaluate the efficacy and safety of these treatments in a range of pain conditions, including acute pain, chronic low back pain, and chronic neck pain.

Recommendations

1. Further research is needed to evaluate the efficacy and safety of tramadol, paracetamol, caffeine, and taurine as single analgesics for the treatment of acute pain and chronic low back pain.
2. The use of tramadol, paracetamol, caffeine, and taurine should be considered in combination with other analgesics, as well as in combination with non-pharmacologic treatments, such as physical therapy, for the management of chronic neck pain.
3. Research should focus on the development of treatment algorithms that incorporate evidence-based interventions for the management of acute pain and chronic low back pain.

Funding

This study was supported by [funding agency]. The authors have no conflicts of interest to declare.

Acknowledgments

The authors would like to thank [thankful individuals] for their contributions to this study.

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2. Jiang 2008 (published data only)

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Matsushita T, Hasebe M, Nishimura A. Phase iii clinical study of tramadol hydrochloride/acetaminophen combination tablet in patients with chronic osteoarthritis pain or chronic low back pain - a randomized withdrawal, double-blind, parallel-group, placebo-controlled study. *Osteoporosis International* 2012;23:585.

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14. NCT00643383 (published data only)

15. NCT00736853 (published data only)

16. NCT01112267 (published data only)

17. NCT01422291 (published data only)

18. NCT01587274 (published data only)

19. NCT01776515 (published data only)

20. NCT01843660 (published data only)

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Paracetamol for low back pain (Review)

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Davies 2008

Egger 1997

Forman 2005

Furlan 2015

Global Burden of Disease Study 2015

Graham 2013
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Guyatt 2011

Guyatt 2011a

Henschke 2008

Higgins 2011

Hinz 2008

Hinz 2012

Jozwiak-Bebenista 2014

Koes 2010

Menezes 2009

Menezes 2012

Mueller 2007

Ostelo 2008

Pengel 2003

Roberts 2015

Sheen 2002

van Tulder 2003

van Tulder 2006

Wandel 2010

References to other published versions of this review

Machado 2015

* Indicates the major publication for the study
## Characteristics of included studies  
[ordered by study ID]

### Nadler 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, actively controlled, multicentre, single-blind study</th>
</tr>
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</table>
| **Participants** | **Population source:** 371 participants with acute non-specific LBP of at least moderate pain intensity (133 participants randomised to paracetamol or placebo group). The study was conducted at 11 sites  
**Inclusion criteria:** Pain of moderate intensity (2 or more on a 6-point scale), age 18 to 55 years (inclusive), ambulatory status, no low back trauma within the preceding 48 hours, and an answer of “yes” to the question “Do the muscles in your low back hurt?”  
**Exclusion criteria:** Any evidence or history of radiculopathy or other neurologic deficits (e.g. abnormal straight-leg-raise test results, patellar reflexes, or bowel or bladder function), or a history of back surgery, fibromyalgia, diabetes mellitus, peripheral vascular disease, osteopenosis, gastrointestinal ulcers, gastrointestinal bleeding or perforation, renal disease, pulmonary oedema, cardiomyopathy, liver disease, intrinsic coagulation defects, bleeding diseases or anticoagulant therapy (e.g. warfarin), daily back pain for more than 3 consecutive months, or hypersensitivity to acetaminophen, non-steroidal anti-inflammatory drugs, or heat |
| **Interventions** | The intervention groups consisted of  
1. heat wrap (ThermaCare Heat Wrap; Procter & Gamble, Cincinnati, OH), which wraps around the lumbar region of the torso and uses a velcro-like closure, heats to 104 degrees F (40 degrees C) within 30 minutes of exposure to air, and maintains this temperature continuously for 8 hours of wear;  
2. oral ibuprofen, 2 tablets 3 times daily for a total dose of 1200 mg, with oral placebo 1 time daily for blinding from the acetaminophen group;  
3. oral acetaminophen, 2 tablets 4 times daily for a total of 4000 mg dose total;  
4. oral placebo, 2 tablets 4 times daily; and  
5. unheated back wrap.  
All treatments were administered on 2 consecutive days |
| **Outcomes** | Primary: pain relief (NRS 0 to 5), disability (Roland Morris 0 to 24)  
Secondary: safety. |
| **Notes** | Funding: This study was funded by the Procter & Gamble Company.  
Conflicts of interest: Industry funds were received to support this work. 6 out of 8 study authors are employees of the Procter & Gamble Health Sciences Institute, and 1 author is a paid consultant for Procter & Gamble Company  
There is no information on the dates when the study was conducted |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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| Random sequence generation (selection bias) | Unclear risk | Quote: “subjects were randomized to treatment by a ratio of 6:6:6:1:1”  
Comment: Unclear |
### Nadler 2002 (Continued)

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<th>Risk</th>
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<td>Blinding of participants and personnel (performance bias)</td>
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<td>Quote: &quot;single (investigator) blind&quot;. Comment: Unclear if blinding was done for the assessor or the care provider</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear</td>
<td>Quote: &quot;single (investigator) blind&quot;. Comment: Unclear if the assessor or the care provider was blinded</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<tr>
<td>Other bias</td>
<td>Unclear</td>
<td>Comment: Data for the placebo group are unavailable. This study received funds from a company that produces paracetamol</td>
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</table>

### Wetzel 2014

<table>
<thead>
<tr>
<th>Method</th>
<th>Cross-over, randomised, double-blinded, placebo-controlled trial</th>
</tr>
</thead>
</table>
| **Participants** | Population source: 40 participants recruited from a pain clinic at Vienna University Hospital  
Inclusion criteria: Chronic LBP (at least 6 months) of intensity at least 4 on a 0 to 10 NRS scale  
Exclusion criteria: Additional treatment (psychotherapy, orthopaedic aids, physiotherapy, acupuncture, use of depot steroids in the last 3 months), cancer-related pain, positive pregnancy test, American Society of Anesthesiologists’ (ASA) physical status at least 3, allergy or contraindications to the tested substances, specific inflammatory or progressive metabolic disorders, fibromyalgia, autoimmune diseases, inflammatory rheumatic disorders, radiculopathy, spinal trauma or vertebral fracture caused by osteoporosis in the past 6 months, relevant cardiopulmonary restrictions, severe kidney or liver function disorders, acute duodenal or ventricular ulcer or psychiatric disorder |
| Interventions | 4 appointments were fixed for the study. At every appointment, each participant randomly received the test infusions of 250 ml administered over 30 min consisting of diclofenac 75 ml (and orphenadrine 30 mg), parecoxib 40 mg, paracetamol 1 g, and normal saline (placebo). The time interval between test infusions was 72 hours |
| Outcomes | Pain (NRS 0 to 10), disability (Roland Morris 0 to 24) |
Notes

Funding: Financial support from the Department of Anesthesiology, General Intensive Care and Pain Control, Vienna Medical University, Austria

Conflicts of interest: None.

There is no information on the dates when the study was conducted

This study was retracted in 2015 (Wetzel 2014)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias)    | Low risk           | Quote: “The sequence of test infusions was assigned randomly using a computer generated table”  
Comment: Adequate |
| Allocation concealment (selection bias)        | Unclear risk       | Comment: Unclear                                                                       |
| Blinding of participants and personnel (performance bias) | Low risk           | Quote: “double-blinded”; “placebo-controlled”; “Patients and observers were blinded to the test infusion”  
Comment: Probably done |
| Blinding of outcome assessment (detection bias) | Low risk           | Quote: “double-blinded”; “Patients and observers were blinded to the test infusion”  
Comment: Probably done |
| Incomplete outcome data (attrition bias)       | Low risk           | 4/45 dropped out without giving reasons. This small number of dropouts is unlikely to have influenced the results |
| Selective reporting (reporting bias)           | High risk          | The Roland Morris questionnaire was listed in the Methods to assess functional status, but no data are reported separately for intervention and control groups |
| Other bias                                     | Unclear risk       | Participants received either weak opioids (n = 31) or potent opioids (n = 9) on a stable basis at least 4 months before the intervention; length of follow-up is not clear |

### Williams 2014

Methods

Multicentre, double-dummy, randomised, placebo-controlled trial

Participants

Population source: 1653 participants (acetaminophen n = 550, acetaminophen as required n = 546, placebo n = 547) recruited from primary care clinicians (general practitioners, pharmacists, or physiotherapists) across Sydney, Australia, screened consecutive people who sought care for LBP directly or in response to a community advertisement.
**Inclusion criteria:** A new episode of acute LBP (defined as pain between the 12th rib and buttock crease that was less 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 SF-36)

**Exclusion criteria:** Suspected serious spinal pathology; currently using full regular recommended doses of an analgesic; spinal surgery in the preceding 6 months; contraindication to paracetamol; using psychotropic medication for a health condition deemed to prevent reliable recording of study information; or pregnant or planning pregnancy

**Interventions**

Participants were asked to take 2 types of tablets for up to 4 weeks: 2 tablets from the regular box every 6 to 8 hours (6 tablets per day), and 1 or 2 tablets from the as-needed box when needed for pain relief (4 to 6 hours apart, to a maximum of 8 tablets per day). Participants in the regular group received 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 received placebo tablets in both boxes.

**Outcomes**

Pain (0 to 10), disability (Roland Morris 0 to 24), function (Patient-Specific Functional Scale), quality of life (SF-12), global impression of recovery (Global Perceived Effect scale), sleep quality, adherence, adverse events.

**Notes**

**Funding:** National Health and Medical Research Council of Australia and GlaxoSmithKline Australia

**Conflicts of interest:** One author received funding for a research scholarship from GlaxoSmithKline, and another author received funding to review teaching materials prepared by GlaxoSmithKline. The other authors declared no competing interests.

There is no information on the dates when the study was conducted.

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “computer-generated randomisation schedule”. Comment: Adequate</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “concealed random allocation”; “Research staff not involved in preparation of medicine boxes collected baseline information by telephone and instructed patients to open the box and begin treatment” Comment: Adequate</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “Clinicians, participants, and staff collecting outcome data, assessing outcomes, and analysing data were masked to group allocation”</td>
</tr>
<tr>
<td>Reporting bias</td>
<td>Low risk</td>
<td>Comment: Adequate</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Quote: &quot;Clinicians, participants, and staff collecting outcome data, assessing outcomes, and analysing data were masked to group allocation&quot;</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: Adequate</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>31/1099 withdrawn from intervention groups; 15/553 withdrawn from control group. The completeness of survival data, measured by the completeness index, was 94.4%</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes that are of interest in the review have been reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>This study was an investigator-initiated trial that received supplementary funding from a pharmaceutical company and reported that the sponsor had no role in conducting the study or analysing the data. Given this background and the negative trial outcome, this study appears to be free of other sources of bias and met this criterion</td>
</tr>
</tbody>
</table>

**Characteristics of excluded studies**  
[ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borenstein 2001</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Cabane 1996</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Childers 2005</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Codding 2008</td>
<td>Combination of medications</td>
</tr>
</tbody>
</table>

LBP: low back pain  
NRS: Numeric Rating Scale  
SF-12: 12-Item Short Form Health Survey  
SF-36: 36-Item Short Form Health Survey
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corts Giner 1989</td>
<td>No placebo group</td>
</tr>
<tr>
<td>De Almeida Coimbra 1980</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Derby 2012</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Diener 2008</td>
<td>Commentary</td>
</tr>
<tr>
<td>Diener 2008a</td>
<td>Commentary</td>
</tr>
<tr>
<td>Gammaitoni 2003</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Garcia Filho 2006</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Gimbel 2001</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Hackett 1988</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Hingorani 1971</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Jiang 2008</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Kuntz 1996</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Larsen 2012</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Lee 2008</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Madhusudhan 2013</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Martínez-Elizondo 1979</td>
<td>No paracetamol group</td>
</tr>
<tr>
<td>Matsushita 2012</td>
<td>No paracetamol group</td>
</tr>
<tr>
<td>McGuinness 1969</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Miller 2012</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Moore 2010</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Muller 1998</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Muller 2005</td>
<td>No placebo group</td>
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<tr>
<td>NCT00210561</td>
<td>Combination of paracetamol and other medications</td>
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<tr>
<td>NCT00643383</td>
<td>Combination of paracetamol and other medications</td>
</tr>
<tr>
<td>Study ID</td>
<td>Medication Details</td>
</tr>
<tr>
<td>-------------------</td>
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<td>NCT00736853</td>
<td>Combination of paracetamol and other medications</td>
</tr>
<tr>
<td>NCT01112267</td>
<td>Combination of paracetamol and other medications</td>
</tr>
<tr>
<td>NCT01422291</td>
<td>No placebo group</td>
</tr>
<tr>
<td>NCT01587274</td>
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<tr>
<td>NCT01776515</td>
<td>Combination of paracetamol and other medications</td>
</tr>
<tr>
<td>NCT01843660</td>
<td>Combination of paracetamol and other medications</td>
</tr>
<tr>
<td>Pallay 2004</td>
<td>No paracetamol group</td>
</tr>
<tr>
<td>Peloso 2004</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Ruoff 2003</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Schiphorst Preuper 2014</td>
<td>Combination of medications</td>
</tr>
<tr>
<td>Temple 2007</td>
<td>Not low back pain</td>
</tr>
<tr>
<td>Tervo 1976</td>
<td>No placebo group</td>
</tr>
<tr>
<td>Yarlas 2013</td>
<td>No paracetamol group</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial
## Comparison 1. Acute low back pain - paracetamol versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain</td>
<td>1</td>
<td>1520</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 1 week (immediate-term)</td>
<td>1</td>
<td>1520</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.49 [-1.30, 4.28]</td>
</tr>
<tr>
<td>1.2 2 weeks</td>
<td>1</td>
<td>1505</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.0 [-1.70, 3.70]</td>
</tr>
<tr>
<td>1.3 4 weeks</td>
<td>1</td>
<td>1516</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.49 [-1.99, 2.97]</td>
</tr>
<tr>
<td>1.4 12 weeks (short-term)</td>
<td>1</td>
<td>1526</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.50 [-2.92, 1.92]</td>
</tr>
<tr>
<td>2 Disability</td>
<td>1</td>
<td>1511</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 1 week (immediate-term)</td>
<td>1</td>
<td>1511</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.45 [-1.15, 0.25]</td>
</tr>
<tr>
<td>2.2 2 weeks</td>
<td>1</td>
<td>1501</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.00 [-0.65, 0.65]</td>
</tr>
<tr>
<td>2.3 4 weeks</td>
<td>1</td>
<td>1506</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.05 [-0.50, 0.60]</td>
</tr>
<tr>
<td>2.4 12 weeks (short-term)</td>
<td>1</td>
<td>1522</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.10 [-0.39, 0.59]</td>
</tr>
<tr>
<td>3 Quality of life, physical component</td>
<td>1</td>
<td>1145</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.79 [-1.94, 0.36]</td>
</tr>
<tr>
<td>3.2 12 weeks (short-term)</td>
<td>1</td>
<td>760</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.41 [-0.91, 1.72]</td>
</tr>
<tr>
<td>4 Quality of life, mental component</td>
<td>1</td>
<td>1145</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.60 [-1.38, 0.17]</td>
</tr>
<tr>
<td>4.1 4 weeks</td>
<td>1</td>
<td>1145</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.90 [0.08, 1.72]</td>
</tr>
<tr>
<td>4.2 12 weeks (short-term)</td>
<td>1</td>
<td>760</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5 Function</td>
<td>1</td>
<td>1511</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.2 2 weeks</td>
<td>1</td>
<td>1499</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.05 [-0.32, 0.22]</td>
</tr>
<tr>
<td>5.3 4 weeks</td>
<td>1</td>
<td>1502</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.15 [-0.42, 0.12]</td>
</tr>
<tr>
<td>5.4 12 weeks (short-term)</td>
<td>1</td>
<td>1518</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.0 [-0.23, 0.23]</td>
</tr>
<tr>
<td>6 Adverse events</td>
<td>1</td>
<td>1624</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.1 Any adverse events (up to 12 weeks)</td>
<td>1</td>
<td>1624</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.07 [0.86, 1.33]</td>
</tr>
<tr>
<td>6.2 Serious adverse events (up to 12 weeks)</td>
<td>1</td>
<td>1643</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.90 [0.30, 2.67]</td>
</tr>
<tr>
<td>7 Global impression of recovery</td>
<td>1</td>
<td>1515</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>7.1 1 week (immediate-term)</td>
<td>1</td>
<td>1515</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.05 [-0.28, 0.18]</td>
</tr>
<tr>
<td>7.2 2 weeks</td>
<td>1</td>
<td>1501</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.05 [-0.28, 0.18]</td>
</tr>
<tr>
<td>7.3 4 weeks</td>
<td>1</td>
<td>1511</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.10 [-0.33, 0.13]</td>
</tr>
<tr>
<td>7.4 12 weeks (short-term)</td>
<td>1</td>
<td>1523</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.05 [-0.26, 0.17]</td>
</tr>
<tr>
<td>8 Poor sleep quality</td>
<td>1</td>
<td>1511</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>8.1 1 week (immediate-term)</td>
<td>1</td>
<td>1511</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.05 [0.87, 1.25]</td>
</tr>
<tr>
<td>8.2 2 weeks</td>
<td>1</td>
<td>1500</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.01 [0.80, 1.28]</td>
</tr>
<tr>
<td>8.3 4 weeks</td>
<td>1</td>
<td>1510</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.11 [0.82, 1.52]</td>
</tr>
<tr>
<td>8.4 12 weeks (short-term)</td>
<td>1</td>
<td>1523</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.26 [0.90, 1.76]</td>
</tr>
<tr>
<td>9 Patient adherence</td>
<td>1</td>
<td>1511</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>9.1 4 weeks</td>
<td>1</td>
<td>1311</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.08 [0.96, 1.22]</td>
</tr>
<tr>
<td>10 Use of rescue medication</td>
<td>1</td>
<td>1311</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>10.1 Up to 2 weeks</td>
<td>1</td>
<td>1548</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.50 [0.16, 1.55]</td>
</tr>
</tbody>
</table>
### Comparison 2. Chronic low back pain - paracetamol versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pain</td>
<td>1</td>
<td>72</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 1 day (immediate-term)</td>
<td>1</td>
<td>72</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.0 [-9.70, 9.70]</td>
</tr>
</tbody>
</table>

#### Analysis 1.1. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 1 Pain.

Review: Paracetamol for low back pain

Comparison: 1 Acute low back pain - paracetamol versus placebo

Outcome: 1 Pain

<table>
<thead>
<tr>
<th>Study or subgroup Paracetamol</th>
<th>Mean Difference Weight</th>
<th>Mean Difference</th>
<th>Mean Difference Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>1 1 week (immediate-term)</td>
<td>1 499 38 (27) 252 36 (26) 49.1 % 2.00 [-1.99, 5.99 ]</td>
<td>1 517 37 (26) 252 36 (26) 50.9 % 1.00 [-2.92, 4.92 ]</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 1016 504 100.0 % 1.49 [-1.30, 4.28 ]

Heterogeneity: Tau² = 0.0; Chi² = 0.12, df = 1 (P = 0.73); I² = 0.0%

Test for overall effect: Z = 1.05 (P = 0.30)

<table>
<thead>
<tr>
<th>2 2 weeks Paracetamol</th>
<th>Mean Difference Weight</th>
<th>Mean Difference</th>
<th>Mean Difference Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Williams 2014 (3) 509 26 (26) 249 25 (25) 49.5 % 1.00 [-2.84, 4.84 ]</td>
<td>50.5 % 1.00 [-2.80, 4.80 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (4) 498 26 (25) 249 25 (25) 49.5 % 1.00 [-2.84, 4.84 ]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 1007 498 100.0 % 1.00 [-1.70, 3.70 ]

Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 1 (P = 0.73); I² = 0.0%

Test for overall effect: Z = 0.73 (P = 0.47)

<table>
<thead>
<tr>
<th>3 4 weeks Paracetamol</th>
<th>Mean Difference Weight</th>
<th>Mean Difference</th>
<th>Mean Difference Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Williams 2014 (5) 507 18 (24) 250 17 (23) 49.2 % 1.00 [-2.53, 4.53 ]</td>
<td>50.8 % 0.0 [-3.48, 3.48 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (6) 509 17 (23) 250 17 (23) 49.2 % 1.00 [-2.53, 4.53 ]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 1016 500 100.0 % 0.49 [-1.99, 2.97 ]

Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 1 (P = 0.69); I² = 0.0%

Test for overall effect: Z = 0.39 (P = 0.70)

<table>
<thead>
<tr>
<th>4 12 weeks (short-term) Paracetamol</th>
<th>Mean Difference Weight</th>
<th>Mean Difference</th>
<th>Mean Difference Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Williams 2014 (7) 514 13 (22) 253 13 (23) 50.1 % 0.0 [-3.41, 3.41 ]</td>
<td>49.9 % -1.00 [-4.42, 2.42 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (8) 506 12 (22) 253 13 (23) 50.1 % 0.0 [-3.41, 3.41 ]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 1020 506 100.0 % -0.50 [-2.92, 1.92 ]

Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 1 (P = 0.69); I² = 0.0%

Test for overall effect: Z = 0.40 (P = 0.69)
Analysis 1.2. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 2 Disability.

Review: Paracetamol for low back pain

Comparison: 1 Acute low back pain - paracetamol versus placebo

Outcome: 2 Disability

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV(Random,95% CI)</td>
</tr>
<tr>
<td>1 1 week (immediate-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (1)</td>
<td>513</td>
<td>7.7 (6.5)</td>
<td>250</td>
<td>8.3 (6.5)</td>
<td>-0.60 [-1.58, 0.38]</td>
</tr>
<tr>
<td>Williams 2014 (2)</td>
<td>498</td>
<td>8 (6.5)</td>
<td>250</td>
<td>8.3 (6.5)</td>
<td>-0.30 [-1.29, 0.69]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1011</strong></td>
<td><strong>500</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>-0.45 [-1.15, 0.25]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.18, df = 1 (P = 0.67); I^2 = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.27 (P = 0.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (3)</td>
<td>496</td>
<td>5.4 (5.9)</td>
<td>249</td>
<td>5.3 (6.1)</td>
<td>0.10 [-0.82, 1.02]</td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>507</td>
<td>5.2 (6.1)</td>
<td>249</td>
<td>5.3 (6.1)</td>
<td>-0.10 [-1.03, 0.83]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1003</strong></td>
<td><strong>498</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.00 [-0.65, 0.65]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.00 (P = 1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (5)</td>
<td>504</td>
<td>3.2 (5.2)</td>
<td>249</td>
<td>3.3 (5.1)</td>
<td>-0.10 [-0.88, 0.68]</td>
</tr>
<tr>
<td>Williams 2014 (6)</td>
<td>504</td>
<td>3.5 (5.3)</td>
<td>249</td>
<td>3.3 (5.1)</td>
<td>0.20 [-0.58, 0.98]</td>
</tr>
</tbody>
</table>

(Continued . . .)
Study or subgroup | Paracetamol | Placebo | Mean Difference | Weight | Mean Difference |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td></td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1008</td>
<td>498</td>
<td>100.0 % 0.05 [-0.50, 0.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.0; Chi² = 0.28, df = 1 (P = 0.59); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.17 (P = 0.86)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 12 weeks (short-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (7)</td>
<td>504</td>
<td>2.4 (4.7)</td>
<td>252</td>
<td>2.4 (4.5)</td>
<td>50.6 % 0.0 [-0.69, 0.69]</td>
</tr>
<tr>
<td>Williams 2014 (8)</td>
<td>514</td>
<td>2.6 (4.9)</td>
<td>252</td>
<td>2.4 (4.5)</td>
<td>49.4 % 0.20 [-0.50, 0.90]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1018</td>
<td>504</td>
<td>100.0 % 0.10 [-0.39, 0.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 1 (P = 0.69); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.39 (P = 0.69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Regular group
(2) As-needed group
(3) As-needed group
(4) Regular group
(5) Regular group
(6) As-needed group
(7) Regular group
(8) As-needed group
### Analysis 1.3. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 3 Quality of life, physical component.

**Review:** Paracetamol for low back pain

**Comparison:** 1 Acute low back pain - paracetamol versus placebo

**Outcome:** 3 Quality of life, physical component

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random</td>
</tr>
<tr>
<td>1 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (1)</td>
<td>386</td>
<td>49.7 (10.4)</td>
<td>189</td>
<td>50.8 (9.1)</td>
<td>-1.10</td>
</tr>
<tr>
<td>Williams 2014 (2)</td>
<td>381</td>
<td>50.3 (9.3)</td>
<td>189</td>
<td>50.8 (9.1)</td>
<td>-0.50</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>767</td>
<td></td>
<td>378</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\tau^2 = 0.0$; $\chi^2 = 0.26$, $df = 1$ ($P = 0.61$); $I^2 = 0.0$

**Test for overall effect:** $Z = 1.34$ ($P = 0.18$)

<table>
<thead>
<tr>
<th>2 12 weeks (short-term)</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random</td>
</tr>
<tr>
<td>Williams 2014 (3)</td>
<td>252</td>
<td>54.9 (8.6)</td>
<td>122</td>
<td>54.7 (8.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>264</td>
<td>55.3 (7.9)</td>
<td>122</td>
<td>54.7 (8.8)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>516</td>
<td></td>
<td>244</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\tau^2 = 0.0$; $\chi^2 = 0.09$, $df = 1$ ($P = 0.77$); $I^2 = 0.0$

**Test for overall effect:** $Z = 0.61$ ($P = 0.54$)

(1) As-needed group

(2) Regular group

(3) Regular group

(4) As-needed group
### Analysis 1.4. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 4 Quality of life, mental component.

**Review:** Paracetamol for low back pain

**Comparison:** 1 Acute low back pain - paracetamol versus placebo

**Outcome:** 4 Quality of life, mental component

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (1)</td>
<td>381</td>
<td>43.7 (6.2)</td>
<td>189</td>
<td>44.4 (6.1)</td>
<td>-0.70 [ -1.77, 0.37 ]</td>
</tr>
<tr>
<td>Williams 2014 (2)</td>
<td>386</td>
<td>43.9 (7)</td>
<td>189</td>
<td>44.4 (6.1)</td>
<td>-0.50 [ -1.62, 0.62 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>767</strong></td>
<td><strong>378</strong></td>
<td></td>
<td></td>
<td><strong>-0.60 [ -1.38, 0.17 ]</strong></td>
</tr>
<tr>
<td>2 12 weeks (short-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (3)</td>
<td>252</td>
<td>45.6 (5.3)</td>
<td>122</td>
<td>44.7 (5.5)</td>
<td>0.90 [ -0.28, 2.08 ]</td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>264</td>
<td>45.6 (5.1)</td>
<td>122</td>
<td>44.7 (5.5)</td>
<td>0.90 [ -0.25, 2.05 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>516</strong></td>
<td><strong>244</strong></td>
<td></td>
<td></td>
<td><strong>0.90 [ 0.08, 1.72 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 0.06, df = 1 (P = 0.80); I² =0.0%

Test for overall effect: Z = 1.53 (P = 0.13)

Test for overall effect: Z = 2.14 (P = 0.032)

(1) Regular group

(2) As-needed group

(3) Regular group

(4) As-needed group
Analysis 1.5. Comparison I Acute low back pain - paracetamol versus placebo, Outcome 5 Function.

Review: Paracetamol for low back pain

Comparison: I Acute low back pain - paracetamol versus placebo

Outcome: 5 Function

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1 week (immediate-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (1)</td>
<td>498 6.1 (2.6)</td>
<td>250 6.2 (2.5)</td>
<td>49.7 % -0.10 [ -0.48, 0.28 ]</td>
<td>49.7 %</td>
<td>-0.10 [ -0.48, 0.28 ]</td>
</tr>
<tr>
<td>Williams 2014 (2)</td>
<td>513 6.2 (2.6)</td>
<td>250 6.2 (2.5)</td>
<td>50.3 % 0.0 [ -0.38, 0.38 ]</td>
<td>50.3 %</td>
<td>0.0 [ -0.38, 0.38 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1011</strong> 500</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-0.05 [ -0.32, 0.22 ]</td>
</tr>
<tr>
<td>2 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (3)</td>
<td>507 7.3 (2.6)</td>
<td>248 7.4 (2.5)</td>
<td>49.5 % -0.10 [ -0.48, 0.28 ]</td>
<td>49.5 %</td>
<td>-0.10 [ -0.48, 0.28 ]</td>
</tr>
<tr>
<td>Williams 2014 (4)</td>
<td>496 7.2 (2.5)</td>
<td>248 7.4 (2.5)</td>
<td>50.5 % -0.20 [ -0.58, 0.18 ]</td>
<td>50.5 %</td>
<td>-0.20 [ -0.58, 0.18 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1003</strong> 496</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-0.15 [ -0.42, 0.12 ]</td>
</tr>
<tr>
<td>3 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (5)</td>
<td>502 8.2 (2.5)</td>
<td>249 8.2 (2.4)</td>
<td>49.3 % 0.0 [ -0.37, 0.37 ]</td>
<td>49.3 %</td>
<td>0.0 [ -0.37, 0.37 ]</td>
</tr>
<tr>
<td>Williams 2014 (6)</td>
<td>502 8.1 (2.4)</td>
<td>249 8.2 (2.4)</td>
<td>50.7 % -0.10 [ -0.46, 0.26 ]</td>
<td>50.7 %</td>
<td>-0.10 [ -0.46, 0.26 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1004</strong> 498</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-0.05 [ -0.31, 0.21 ]</td>
</tr>
<tr>
<td>4 12 weeks (short-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (7)</td>
<td>502 8.7 (2.3)</td>
<td>252 8.7 (2.2)</td>
<td>48.3 % 0.0 [ -0.34, 0.34 ]</td>
<td>48.3 %</td>
<td>0.0 [ -0.34, 0.34 ]</td>
</tr>
<tr>
<td>Williams 2014 (8)</td>
<td>512 8.7 (2.1)</td>
<td>252 8.7 (2.2)</td>
<td>51.7 % 0.0 [ -0.33, 0.33 ]</td>
<td>51.7 %</td>
<td>0.0 [ -0.33, 0.33 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1014</strong> 504</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.0 [ -0.23, 0.23 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%
Test for overall effect: Z = 0.36 (P = 0.72)

(1) As-needed group
(2) Regular group
(3) Regular group
(4) As-needed group
(5) Regular group
(6) As-needed group
(7) Regular group
(8) As-needed group
Analysis 1.6. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 6 Adverse events.

Review: Paracetamol for low back pain

Comparison: 1 Acute low back pain - paracetamol versus placebo

Outcome: 6 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>1 Any adverse events (up to 12 weeks)</td>
<td>198/1063</td>
<td>98/561</td>
<td>1.07 [0.86, 1.33]</td>
<td>100.0 %</td>
<td>1.07 [0.86, 1.33]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1063</strong></td>
<td><strong>561</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 198 (Paracetamol), 98 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.57 (P = 0.57)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

2 Serious adverse events (up to 12 weeks)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Williams 2014</td>
<td>9/1096</td>
<td>5/547</td>
<td>0.90 [0.30, 2.67]</td>
<td>100.0 %</td>
<td>0.90 [0.30, 2.67]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1096</strong></td>
<td><strong>547</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 9 (Paracetamol), 5 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.19 (P = 0.85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100
Favours [paracetamol] Favours [placebo]
Analysis 1.7. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 7 Global impression of recovery.

Review: Paracetamol for low back pain
Comparison: 1 Acute low back pain - paracetamol versus placebo
Outcome: 7 Global impression of recovery

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1 week (immediate-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014 (1)</td>
<td>514</td>
<td>2.1 (2)</td>
<td>252</td>
<td>2.1 (2.2)</td>
<td>51.7%</td>
</tr>
<tr>
<td>Williams 2014 (2)</td>
<td>497</td>
<td>2.2 (2.2)</td>
<td>252</td>
<td>2.1 (2.2)</td>
<td>48.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1011</td>
<td>504</td>
<td></td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.18, df = 1 (P = 0.67); I^2 = 0.0%$
Test for overall effect: $Z = 0.41 (P = 0.68)$

2 2 weeks
| | | | | | |
| Williams 2014 (3) | 498 | 2.7 (2.1) | 248 | 2.8 (2.2) | 49.9% | -0.10 [-0.43, 0.23] |
| Williams 2014 (4) | 507 | 2.8 (2.1) | 248 | 2.8 (2.2) | 50.1% | 0.0 [-0.33, 0.33] |
| Subtotal (95% CI) | 1005 | 496 | | | 100.0% | -0.05 [-0.28, 0.18] |

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.18, df = 1 (P = 0.67); I^2 = 0.0%$
Test for overall effect: $Z = 0.42 (P = 0.68)$

3 4 weeks
| | | | | | |
| Williams 2014 (5) | 506 | 3.4 (2.1) | 249 | 3.5 (2.1) | 50.0% | -0.10 [-0.42, 0.22] |
| Williams 2014 (6) | 507 | 3.4 (2.1) | 249 | 3.5 (2.1) | 50.0% | -0.10 [-0.42, 0.22] |
| Subtotal (95% CI) | 1013 | 498 | | | 100.0% | -0.10 [-0.33, 0.13] |

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.0, df = 1 (P = 1.00); I^2 = 0.0%$
Test for overall effect: $Z = 0.87 (P = 0.38)$

4 12 weeks (short-term)
| | | | | | |
| Williams 2014 (7) | 505 | 3.8 (2) | 252 | 3.8 (2) | 50.7% | 0.0 [-0.30, 0.30] |
| Williams 2014 (8) | 514 | 3.7 (2.1) | 252 | 3.8 (2) | 49.3% | -0.10 [-0.41, 0.21] |
| Subtotal (95% CI) | 1019 | 504 | | | 100.0% | -0.05 [-0.26, 0.17] |

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.21, df = 1 (P = 0.65); I^2 = 0.0%$
Test for overall effect: $Z = 0.45 (P = 0.65)$
### Analysis 1.8. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 8 Poor sleep quality.

**Review:** Paracetamol for low back pain  
**Comparison:** 1 Acute low back pain - paracetamol versus placebo  
**Outcome:** 8 Poor sleep quality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Risk Ratio M H(Random;95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M H(Random;95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td><strong>1 1 week (immediate-term)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014</td>
<td>272/1015</td>
<td>127/496</td>
<td>100.0 % 1.05 [0.87, 1.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1015</strong></td>
<td><strong>496</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.05 [0.87, 1.25]</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>2 2 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014</td>
<td>173/1003</td>
<td>85/497</td>
<td>100.0 % 1.01 [0.80, 1.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1003</strong></td>
<td><strong>497</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.01 [0.80, 1.28]</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>3 4 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014</td>
<td>116/1007</td>
<td>52/503</td>
<td>100.0 % 1.11 [0.82, 1.52]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1007</strong></td>
<td><strong>503</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.11 [0.82, 1.52]</strong></td>
</tr>
</tbody>
</table>

Total events: 272 (Paracetamol), 127 (Placebo)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.49 (P = 0.62)

(Continued ... )
### Analysis 1.9. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 9 Patient adherence.

Review: Paracetamol for low back pain

Comparison: 1 Acute low back pain - paracetamol versus placebo

Outcome: 9 Patient adherence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Williams 2014</td>
<td>459/897</td>
<td>196/414</td>
<td>1.08 [0.96, 1.22]</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>897</strong></td>
<td><strong>414</strong></td>
<td><strong>1.08 [0.96, 1.22]</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 459 (Paracetamol), 196 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.27 (P = 0.20)
### Analysis 1.10. Comparison 1 Acute low back pain - paracetamol versus placebo, Outcome 10 Use of rescue medication.

**Review:** Paracetamol for low back pain  
**Comparison:** 1 Acute low back pain - paracetamol versus placebo  
**Outcome:** 10 Use of rescue medication

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Risk Ratio M-H</th>
<th>Weight</th>
<th>Risk Ratio M-H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I Up to 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 2014</td>
<td>6/1031</td>
<td>6/517</td>
<td>0.50 [0.16, 1.55]</td>
<td>100.0 %</td>
<td>0.50 [0.16, 1.55]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1031</td>
<td>517</td>
<td>100.0 %</td>
<td>0.50 [0.16, 1.55]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Paracetamol), 6 (Placebo)  
Heterogeneity: not applicable  
Test for overall effect: Z = 1.20 (P = 0.23)

### Analysis 2.1. Comparison 2 Chronic low back pain - paracetamol versus placebo, Outcome 1 Pain.

**Review:** Paracetamol for low back pain  
**Comparison:** 2 Chronic low back pain - paracetamol versus placebo  
**Outcome:** 1 Pain

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paracetamol</th>
<th>Placebo</th>
<th>Mean Difference IV</th>
<th>Weight</th>
<th>Mean Difference IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV Random,95% CI</td>
<td></td>
<td>IV Random,95% CI</td>
</tr>
<tr>
<td>I 1 day (immediate-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wetzel 2014</td>
<td>36 51 (21)</td>
<td>36 51 (21)</td>
<td>0.0 [ -9.70, 9.70 ]</td>
<td>100.0 %</td>
<td>0.0 [ -9.70, 9.70 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>36</td>
<td>36</td>
<td>100.0 %</td>
<td>0.0 [ -9.70, 9.70 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 0.0 (P = 1.0)
APPENDICES

Appendix 1. CENTRAL search strategy

Last searched 07 August 2015
1. acetaminophen.mp. or exp Acetaminophen/
2. Analgesics, Non-Narcotic/tu [Therapeutic Use]
3. (paracetamol or tylenol or panadol).mp.
4. 1 or 2 or 3
5. exp Osteoarthritis, Hip/ or exp Osteoarthritis/ or exp Osteoarthritis, Spine/ or exp Osteoarthritis, Knee/
6. Low back pain.mp. or exp Low Back Pain/
7. Neck pain.mp. or exp Neck Pain/
8. ("low back pain" or "back pain" or "neck pain" or backache or lumbago or "neck ache" or "spin* pain" or "knee pain" or "hip pain").mp.
9. 5 or 6 or 7 or 8
10. 4 and 9

Appendix 2. MEDLINE search strategy

Last searched 07 August 2015
1. acetaminophen.mp. OR exp acetaminophen/
2. *Analgesics, Non-Narcotic/tu, th [Therapeutic Use, Therapy]
3. analgesic*.ab,ti.
4. (aceta OR actimin OR anacin OR apacet OR "aspirin free anacin" OR acamol OR acetalgan OR adol OR aldolOR OR alvedon OR apietral OR atamel OR atasol OR benuron OR biogeic OR "biogeic kiddielets" OR buscapina OR hansex OR "ben u ron" OR calpol OR captin OR cemol OR coldex OR corbin OR crocin OR dafalgan OR daleron OR "dawa ya magi" OR depon OR dexamol OR dolex OR dolgesic OR doliplane OR dolorol OR dolpron OR "duiyixian anjifen pian" OR dapa OR dolo OR dartil OR duatrol OR dayquil OR efferalgin OR enela OR europain OR febricet OR febridol OR fensum OR feverall OR fibi OR "fibi plus" OR gelocatil OR gripin OR gesc OR genapap OR genebs OR hedex OR hedanol OR herron OR influene OR hafa OR kitadol OR lekadol OR lupocet OR lemsip OR liquiprin OR pyrigesic OR mexalen OR milidon OR minoset OR momentum OR napa OR "neo kiddielets" OR neopap OR "oraphen pd" OR pyrigesic OR pacol OR pamol OR parol OR panado OR panadol OR panamax OR panda OR panodil OR pyrigesic OR paracet OR paracetamol OR paracitl OR paralen OR param OR paramol OR parol OR perdolan OR perchalan OR pinex OR "pyongsu cetamol" OR pyrenol OR pyrigesic OR plicet OR panadrex OR paratabs OR paralgin OR phenaphen OR revanin OR rokamol OR rubophen OR redutemp OR sara OR scanol OR "sinpro n" OR "snaplets fi" OR suppar OR tachipirin OR tachipirina OR tafiro OR tapisin OR termalgin OR tempra OR thomapyrin OR tipol OR "todal classic duo" OR trephadol OR triaminic OR tylenol OR tamen OR tapanol OR tipol OR uphamol OR vermidon OR vitamol OR valorin OR xumadol OR zolben).tw.
5. OR/1-4
6. osteoarthritis.mp. OR exp osteoarthritis/
7. exp low back pain/
8. exp back pain/
9. exp neck pain/
10. ("low back pain" OR "back pain" OR "neck pain" OR backache OR lumbago OR "neck ache" OR "spin* pain" OR "knee pain" OR "hip pain").mp.
11. OR/6-10
12. 5 AND 11
13. randomized controlled trial.pt. OR exp randomized controlled trial/
14. "randomized controlled trial".mp.
15. exp random allocation/
16. placebo.mp. OR exp placebos/ OR exp placebo effect/
17. (random* adj3 trial).ab,ti.
18. "controlled clinical trial".mp. OR exp controlled clinical trial/

Paracetamol for low back pain (Review)
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Appendix 3. EMBASE search strategy

Last searched 07 August 2015

1. 'acetaminophen'/exp OR 'acetaminophen'
2. (aceta OR actimin OR anacin OR apacet OR "aspirin free anacin" OR acamol OR acetalgin OR adol OR aldol OR alvedon OR apiretal OR atamel OR atasol OR benuron OR biogesic OR "biogesic kiddlelets" OR buscapin OR banesin OR "ben u ron" OR calpol OR captin OR cemol OR coldex OR cotbin OR crocin OR dafalgin OR daleron OR "dawa ya magi" OR depon OR dexamol OR dolex OR dolgesic OR doliprane OR dolotol OR dolprox OR "duiyixian anjifen pian" OR dapa OR dolo OR datril OR duatrol OR dayquil OR efferalgan OR enelfa OR europain OR febrectal OR febricet OR febridol OR fensum OR ferverall OR fibi OR "fibi plus" OR gelocatil OR gripin OR gecic OR genapap OR genes OR hedex OR hedanol OR herrer OR influbene OR kafa OR kitadol OR lekadol OR lupocet OR lemsip OR liquiprin OR pyrigesic OR mexalen OR milidon OR minoset OR momentum OR napa OR "neo kiddlelets" OR neopap OR "oraphen pd" OR pyrigesic OR pacol OR pamol OR parol OR panado OR panadol OR panamax OR panda OR panodil OR pyrigesic OR paracet OR paracetamol OR paracetol OR paracen OR paracetamol OR paracetol OR paracen OR paramed OR paradox OR parol OR perdolan OR perfagan OR pinex OR "pyongsu cetamol" OR pytenol OR pyrigesic OR plicet OR panadrex OR paratabs OR paralgin OR phenaphen OR revanin OR rokamol OR rubophen OR redutemp OR sara OR scanol OR "sinpro n" OR "snaplets fr" OR suppap OR tachipirin OR tachipirina OR tafrol OR tapisin OR termalgin OR tempra OR thomapyrin OR tipol OR "todal classic duo" OR treuphadol OR triaminic OR tylenol OR tamen OR tapanol OR tipol OR uphamol OR vermidol OR vitamol OR valorin OR xumadol OR zolben)
3. 1 OR 2
4. 'osteoarthritiS'/exp OR 'osteoarthritiS'
5. 'low back pain'/exp OR 'low back pain'
6. 'backache'/exp OR 'backache'
7. 'neck pain'/exp OR 'neck pain'
8. 'low back pain' OR 'back pain' OR 'neck pain' OR backache OR lumbago OR 'neck ache' OR 'spin$ pain' OR 'knee pain' OR 'hip pain'
9. OR (4-8)
10. 3 AND 9
11. 'randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)'
12. 'randomization'/exp OR 'randomization'
13. 'placebo'/exp OR 'placebo'
14. randomized:ab
15. placebo:ab
16. randomly:ab
17. OR (11-16)
18. 10 AND 17

Appendix 4. CINAHL search strategy

Last searched 07 August 2015

S15. S7 AND S14
S14. S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13. "backache"
S12. "hip pain"
S11. (MH "Knee Pain") OR "knee pain"
S10. (MH "Neck Pain") OR "neck pain"
S9. (MH "Low Back Pain") OR "low back pain" OR (MH "Back Pain")
S8. (MH "Osteoarthritis") OR "osteoarthritis" OR (MH "Osteoarthritis, Spine") OR (MH "Osteoarthritis, Knee") OR (MH "Osteoarthritis, Hip")
Appendix 5. AMED search strategy

Last searched 07 August 2015

1. exp Acetaminophen/ OR acetaminophen.mp.
2. exp Analgesics/ OR Analgesics.mp.
3. exp Drug therapy/ OR drug therapy.mp.
4. analgesic*.ab,ti.
5. (aceta OR actimin OR anacin OR apacet OR "aspirin free anacin" OR acamol OR acetalgin OR adol OR aldolor OR alvedon OR apiretal OR atamel OR atasol OR benuron OR biogesic OR "biogesic kiddielets" OR buscapina OR banesin OR "ben u ron" OR calpol OR captin OR cemol OR coldex OR cotibin OR crocin OR daflagan OR daleron OR "dawa ya magi" OR depon OR dexamol OR dolex OR dolgesic OR doliprane OR dolorol OR dolpri OR "duiyixian anijen pian" OR dapa OR dolo OR datril OR duatrol OR dayquil OR efferalgan OR enelfa OR europain OR febrectal OR febrict OR febridol OR fensum OR feverall OR fibi OR "fibi plus" OR gelocatil OR gripin OR gesc OR genapap OR genes OR hedy OR hedanol OR herren OR influene OR kafa OR kiradol OR lekadol OR lupocet OR lemsip OR liquirin OR pyrigesic OR mexalen OR milidon OR minoer OR momentum OR napa OR "neo kiddielets" OR neopap OR "oraphen pd" OR pyrigesic OR pacol OR pamol OR parol OR panado OR panadol OR panamax OR panda OR panodil OR pyrigesic OR paracet OR paracetamol OR paracitl OR paralen OR paramed OR paralgin OR phenaphen OR revanin OR rokamol OR rubophen OR redu temp OR sara OR scanol OR "sinpro n" OR "snaplets fr" OR suppap OR tachipirin OR tachipirina OR tafiror OR tapis OR termalgin OR tempra OR thomapyrin OR tipol OR "togal classic duo" OR treuphadol OR triamomic OR tylenol OR tamen OR tapanol OR tipol OR uphamol OR vermidon OR vitamol OR valorin OR xumadol OR zolben).tw.
6. OR/1-5
7. exp Osteoarthritis/ OR osteoarthritis.mp.
8. exp Low back pain/ OR low back pain.mp.
9. back pain.mp. OR exp Backache/
10. exp Neck pain/ OR neck pain.mp.
11. ("low back pain" OR "back pain" OR "neck pain" OR backache OR lumbago OR "neck ache" OR "spin" pain" OR "knee pain" OR "hip pain").mp.
12. OR/7-11
13. 6 AND 12
14. exp Randomized controlled trials/ OR randomized controlled trial.mp.
15. randomized controlled trial.pt.
16. exp Random allocation/ OR random allocation.mp.
17. exp Placebos/ OR placebo.mp.
18. (random* adj:3 trial).ab,ti.
20. OR/14-19
21. 13 AND 20
Appendix 6. Web of Science search strategy

Last searched 07 August 2015

16. #15 AND #9
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
15. #14 OR #13 OR #12 OR #11 OR #10
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
14. TOPIC: (Random*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
13. TOPIC: (controlled clinical trial)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
12. TOPIC: (placebo)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
11. TOPIC: (random allocation)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
10. TOPIC: (randomized controlled trial)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
9. #3 AND #8
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
8. #7 OR #6 OR #5 OR #4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
7. TOPIC: ((spin* pain" OR "knee pain" OR "hip pain"))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
6. TOPIC: (neck pain)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
5. TOPIC: (back pain)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
4. TOPIC: (osteoarthritis)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
3. #2 OR #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
2. TOPIC: (Paracetamol OR tylenol OR panadol)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years
1. TOPIC: (acetaminophen)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years

Appendix 7. LILACS search strategy

Last searched 07 August 2015

((Acetaminophen OR paracetamol OR tylenol OR panadol) AND (osteoarthritis OR back pain OR lumbago OR backache OR neck pain OR knee pain OR hip pain))
Appendix 8. IPA search strategy

Last searched 07 August 2015
1. acetaminophen.mp.
2. (aceta or actimin or anacin or apacet or "aspirin free anacin" or acamol or acetalgin oradol or aldol OR or alvedon or apioretal or atamel or atasol or benuron or biogesic or "biogesic kiddielets" or buscamin or banesin or "ben-u-ron" or calpol or captin or cemol or coldex or cortin or crocin or dafalgan or daleron or "dawa ya magi" or depon or dexamol or dolex or dolgesic or doliprane or dolorol or dolprone or "duiyixian anjifen pian" or dapa or dolo or datril or duatrol or dayquil or efferalgan or enelfa or europain or febractal or febricid or febrisol or fenum or fevral or fibi or "fibi plus" or gelocatil or gripin or gesci or genapap or genes or hedex or hedanol or harron or influbene or kafa or kitadol or lekadox or lupocet or lomisp or liquispin or pyrigesic or mexitol or milidon or minoset or momentum or napa or "neo kiddielets" or neopap or "oraphen pd" or pyrigesic or pacol or pamol or parol or panado or panadol or panamex or panda or panodil or pyrigesic or paracet or paracetamol or paracitol or paralen or paramed or paramol or parol or perdolan or perforgan or pinex or "pyongsu cetamol" or pyrenol or pyrigesic or plicet or panadex or paratabs or paracitolin or phenapen or revanin or rokamol or rubophen or redutemp or sara or scanol or "sinpro n" or "naplets fr" or suppap or tachipirin or tachipirina or tafirol or tapsin or termalgin or tempra or thomapyrin or tipol or "todal classic duo" or treuphadol or triaminic or tylenol or tamen or tapanol or tipol or uphamol or vermidon or vitamol or valorin or xumadol or zolben).tw.
3. 1 OR 2
4. osteoarthritis.mp.
5. low back pain.mp.
6. back pain.mp.
7. neck pain.mp.
8. ("low back pain" or "back pain" or "neck pain" or backache or lumbago or "neck ache" or "spin* pain" or "knee pain" or "hip pain").mp.
9. OR/4-8
10. 3 AND 9

Appendix 9. ClinicalTrials.gov and WHO ICTRP search strategy

Last searched 07 August 2015
ClinicalTrials.gov: Search: (paracetamol OR acetaminophen) AND Condition: back pain
WHO ICTRP: Title: (paracetamol OR acetaminophen) AND Condition: back pain

Appendix 10. ’Risk of bias’ criteria

Random sequence generation (selection bias)

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
There is a low risk of selection bias if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).

There is a high risk of selection bias if the investigators describe a non-random component in the sequence generation process such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number, or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention.

Allocation concealment (selection bias)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
There is a low risk of selection bias if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes.

There is a high risk of bias if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (for example a list of random numbers); assignment envelopes were used without appropriate safeguards (for example if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly un Concealed procedures.

**Blinding of participants and personnel (performance bias)**

Performance bias due to knowledge of the allocated interventions by participants or personnel/care providers during the study

There is a low risk of performance bias if blinding of participants or personnel was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

**Blinding of outcome assessor (detection bias)**

Detection bias due to knowledge of the allocated interventions by outcome assessors

There is low risk of detection bias if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding, or:

- for participant-reported outcomes in which the participant was the outcome assessor (e.g. pain, disability): there is a low risk of bias for outcome assessors if there is a low risk of bias for participant blinding (Boutron 2005);
- for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between participants and care providers (e.g. co-interventions, length of hospitalisation, treatment failure), in which the care provider is the outcome assessor: there is a low risk of bias for outcome assessors if there is a low risk of bias for care providers (Boutron 2005);
- for outcome criteria that are assessed from data from medical forms: there is a low risk of bias if the treatment or adverse effects of the treatment could not be noticed in the extracted data (Boutron 2005).

**Incomplete outcome data (attrition bias)**

Attrition bias due to amount, nature, or handling of incomplete outcome data

There is a low risk of attrition bias if: there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data were balanced in numbers, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size, or missing data were imputed using appropriate methods (if dropouts are very large, imputation using even ‘acceptable’ methods may still suggest a high risk of bias) (van Tulder 2003). The percentage of withdrawals and dropouts should not exceed 20% for short-term follow-up and 30% for long-term follow-up and should not lead to substantial bias (these percentages are commonly used but arbitrary, not supported by literature) (van Tulder 2003).
Selective reporting (reporting bias)

Reporting bias due to selective outcome reporting
There is a low risk of reporting bias if the study protocol is available and all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way, or if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
There is a high risk of reporting bias if not all of the study’s prespecified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (for example subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Other bias

Bias due to problems not covered elsewhere in the table
There is a low risk of bias if the study appears to be free of other sources of bias not addressed elsewhere (for example study funding).

Appendix II. The GRADE approach to evidence synthesis
The quality of evidence will be categorised as follows:
- High (⪪⪫⪫): further research is very unlikely to change the confidence in the estimate of effect.
- Moderate (⪪⪫⪪): further research is likely to have an important impact on the confidence in the estimate of effect.
- Low (⪪⪪⪪): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low (⪪⪪⪪⪪): any estimate of effect is very uncertain.

The evidence available to answer each subquestion will be graded on the domains in the following manner:

1. Study design

2. Risk of bias
Limitations in the study design and implementation may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. We will examine all studies on five types of biases:
a) Selection (random sequence generation, allocation concealment, group similarities at baseline)
b) Performance (blinding of participants, blinding of healthcare providers)
c) Attrition (dropouts and intention-to-treat analysis)
d) Measurement (blinding of the outcome assessors and timing of outcome assessment)
e) Reporting bias (selective reporting)
3. Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. Inconsistency may arise from differences in: populations (e.g. drugs may have larger relative effects in sicker populations), interventions (e.g. larger effects with higher drug doses), or outcomes (e.g. diminishing treatment effect with time).

The quality of evidence will be downgraded as follows:
- by one level: when the heterogeneity or variability in results is large.
- by two levels: when the heterogeneity or variability in results is large AND there was inconsistency arising from populations, interventions, or outcomes.

4. Indirectness

Indirect population, intervention, comparator, or outcome: the question being addressed in this systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome in the included randomised trial.

The quality of evidence will be downgraded as follows:
- by one level: when there is indirectness in only one area
- by two levels: when there is indirectness in two or more areas

5. Imprecision

Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of the effect. In such a case we judge the quality of the evidence to be lower than it otherwise would be because of uncertainty in the results. Each outcome is considered separately.

For dichotomous outcomes

We will consider imprecision for either of the following two reasons:
1. There is only one study (unless the study provide data from more than 300 participants). When there is more than one study, the total number of events is less than 300 (a threshold rule-of-thumb value) (Mueller 2007).
2. 95% confidence interval around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. The threshold for ‘appreciable benefit’ or ‘appreciable harm’ is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

The quality of the evidence will be downgraded as follows:
- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)

For continuous outcomes

We will consider imprecision for either of the following two reasons:
1. There is only one study (unless the study provide data from more than 400 participants). When there is more than one study, total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β, and an effect size of 0.2 standard deviations, representing a small effect).
2. 95% confidence interval includes no effect and the upper or lower confidence limit crosses an effect size (standardised mean difference) of 0.5 in either direction.

The quality of the evidence will be downgraded as follows:
- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)
6. Publication bias

Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

The quality of evidence will be downgraded as follows:
- by one level: when the funnel plot suggests publication bias

7. Magnitude of the effect

8. Dose response gradient

9. Influence of all plausible residual confounding

CONTRIBUTIONS OF AUTHORS

Conception, design, data collection, analysis, and drafting of the protocol and previous review: Gustavo C Machado, Manuela L Ferreira, Marina B Pinheiro, and Christopher G Maher.

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Final approval of the review: all authors.

DECLARATIONS OF INTEREST

Bruno T Saragiotto: No relevant interests.
Gustavo C Machado: No relevant interests.
Manuela L Ferreira: No relevant interests.
Marina B Pinheiro: No relevant interests.
Christina Abdel Shaheed: No relevant interests.

Christopher G Maher is an author of the PACE trial, which was included in this review, however he did not participate in the 'Risk of bias' assessment or data extraction in this review. PACE was an investigator-initiated trial, funded by the National Health and Medical Research Council of Australia and GlaxoSmithKline (a manufacturer of paracetamol).
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW
This is an update of a review published in the BMJ (Machado 2015). The study protocol was previously registered on PROSPERO (registration number CRD42013006367). We followed the new recommendations of the Cochrane Back and Neck Group in this review (Furlan 2015), which was not stated in the protocol or previous version of this review as it was not yet published. However, there were no substantial changes from the protocol or the previous version of this review.

INDEX TERMS
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