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Supporting Information

Supplementary methods and results

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Appendix to: Abdel Shaheed C, Ferreira G, Dmitritchenko A, et al. The efficacy and safety of paracetamol for pain relief: an overview of systematic reviews. *Med J Aust* 2021; doi: 10.5694/mja2.50992.

The efficacy and safety of paracetamol for pain relief: an overview of systematic reviews

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Table 1. Search strategy

1.	META–ANALYSIS.mp OR systematic review.mp OR systematic$ adj25 review$ OR systematic$ adj25 overview$ OR meta-analy$ or metaanaly$ or (meta analy$) OR synthesis OR review OR academic review
2.	ANIMAL/ not HUMAN/
3.	1 NOT 2
4.	Acetaminophen.mp OR paracetamol.mp OR propacetamol.mp
5.	3 and 4

Table 2. Determination of Grading of Recommendations Assessment, Development and Evaluation criteria (GRADE) ratings for randomised controlled trials

GRADE criterion	Description
Limitation in study design	Risk of bias assessment for randomised controlled trials was determined independently by two reviewers using the Cochrane risk of bias tool which considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases e.g. pharmaceutical company funding. Trials with unclear risk or high risk of bias were downgraded. A trial was considered unclear risk when a quarter or more domains were judged as unclear risk. A trial was considered high risk when one or more domains were judged as high risk. In cases where more than one trial contributed to an effect estimate, when more than 25% of participants in the comparison were from trials at high overall risk of bias (i.e. one or more bias domains judged as high risk) we downgraded one level for the quality of evidence. We downgraded by two levels if 50% of participants in the comparison were from trials at high overall risk of bias.
Inconsistency of results	We downgraded one level if we identified important and non-explained heterogeneity through visual inspection or considerable heterogeneity in the I^2 test (> 50%). If there was evidence of serious inconsistency (I^2 test > 75%) we downgraded by two levels.
Imprecision	Dichotomous outcomes: A) When the total number of events was < 300, we downgraded the evidence by one level. B) When the 95% confidence interval around the pooled or best estimate of effect included appreciable benefit or harm we downgraded by one level. We downgraded the evidence by two levels when there was imprecision due to both A) and B). Continuous outcomes: A) When the total sample size was < 400, we downgraded the evidence by one level. B) When the 95% confidence interval included appreciable benefit or harm, we downgraded the evidence by one level. We downgraded the evidence by two levels when there was imprecision due to both A) and B).
Publication bias	Assessed using funnel plot analysis/ Egger's regression test for ten or more studies. If this information was provided by the review, we adopted these results. We did not downgrade by two levels for this domain.

Table 3. Clinical characteristics of the 36 included reviews, including pain and adverse events outcomes reported

Systematic review	Pain condition	Outcomes	Follow-up	Intervention	Comparison	Duration of therapy
Deussen et al 2011 [1]	Uterine cramping/involution after birth	Pain; Adverse events	6 h	Oral paracetamol 650 mg	Placebo	Single dose
Hazlewood et al 2012 [2]	Rheumatoid arthritis and rheumatoid synovitis	Mean pain relief 0–3 (0 no pain relief, 3 complete pain relief); Mean (%) maximum pain relief	Over 6 h	Paracetamol 1000 mg (2 x 500 mg tablets) – multiple doses over trial period oral	Placebo	Up to 17 days
Chou et al 2013 [3]	Perineal pain in early post-partum period	Proportion of people with 50% pain relief; Non serious adverse events	Various	Variable doses – 500 mg, 650 mg to 1000 mg likely oral	Placebo	All single dose
Derry et al 2013 [4]	Adults with acute migraine	Proportion of participants achieving relief of moderate to severe symptoms; Proportion of pain-free participants; At least one adverse event	2 h after dosing	Single dose oral paracetamol 1000 mg (likely immediate release formulation)	Placebo	Single dose
Porela-Tiihonen et al 2013 [5]	Cataract surgery	VAS (0–10); Adverse events	Immediately following surgery	Oral paracetamol 1 g	Vitamin C 400 mg	Single oral dose 1 hour before surgery
Li et al 2013 [6]	Cold symptoms	Pain; Headache; Achiness; Sore throat; Adverse events	2 h	Oral paracetamol 500 mg or 1000 mg	Placebo	Single oral dose
Gurusamy et al 2014 [7]	Laparoscopic cholecystectomy	Pain (0–10 VAS); Serious adverse events	4-8 hours after procedure	1 mg intravenous 3 times daily or 1 g intravenous after intubation OR paracetamol (acetaminophen) 300 mg orally every 6 h for 48 h	Placebo	Over 48 hours
Bai et al 2015 [8]	Catheter-related bladder discomfort (CRBD)	Pain (0–10 VAS); Incidence of CRBD; Incidence of moderate severity CRBD;	Over 12 h	Intravenous paracetamol 15mg/kg	Placebo	Single dose

Systematic review	Pain condition	Outcomes	Follow-up	Intervention	Comparison	Duration of therapy
De Oliviera et al 2015 [9]	Prevention of post-operative pain	Early post-operative pain (0–4 h; 0–10); Late post-operative pain (24 h); Incidence of nausea and vomiting	Before beginning of surgery or at end of surgery	Single dose intravenous paracetamol up to 2000 mg per dose	Placebo	Single dose
Hindocha et al 2015 [10]	Hysterosalpingography	Pain (0–100); Adverse events	During (ineffective) and 30 min after procedure (effective)	1 g paracetamol (dose form not reported)	Placebo	Taken 30 minutes before procedure
Ashley et al 2016 [11]	Dental pain in children	Post-operative pain reported by parent	6–7 h	80 mg paracetamol 20 minutes pre-operatively orally or paracetamol 15 minutes pre-operatively	Placebo	Single dose
McNicol et al 2016 [12]	Post-operative pain	Proportion of patients experiencing 50% pain relief; Mean difference in pain (VAS); Adverse events and serious adverse events	4 or 6 h after surgery	Intravenous propacetamol or paracetamol – paracetamol 1 g usual dose	Placebo	Single dose
Richer et al 2016 [13]	Children and adolescents with migraine	Proportion of pain-free participants	2 hours after dosing	Oral paracetamol 10 mg/kg immediate release formulation	Placebo	Single dose
Saragiotto et al 2016 [14]	Acute low back pain	Pain (0–100)	1, 2, 4, 12 weeks	Oral paracetamol up to 3990 mg daily (sustained release formulation)	Placebo	Up to 4 weeks
Sin et al 2016 [15]	People with abdominal pain	Pain (0–100) adverse events	20 and 40 min	Intravenous paracetamol 15 mg/kg	Placebo	Single dose over 3 minutes
Sjoukes et al 2016 [16]	Otitis media in children	Proportion with pain; Adverse events	48 h	Oral paracetamol 10 mg/kg 3 times daily	Placebo	48 hours
Stephens et al 2016 [17]	Episodic tension type headache	Pain,; Adverse events	2 h or over 24 h	Oral paracetamol 1000 mg as single dose or 500 mg to 1000 mg as multiple doses	Placebo	Single and multiple doses
Blank et al 2017 [18]	Abdominal surgery	Pain; Adverse events	24 h	Intravenous paracetamol up to 4 g usually over 24 h	Placebo	Multiple doses
Douzjian et al 2017 [19]	Post-cardiac surgery	Pain scores at 6, 12, 18, 24 h	—	Variable doses e.g. paracetamol 1 g intravenous every 6 h	Placebo	Multiple doses over 24 hours

Systematic review	Pain condition	Outcomes	Follow-up	Intervention	Comparison	Duration of therapy
Garcia Perdomo et al 2017 [20]	Renal colic	Pain (0–100) adverse events	15 min and 0.5 h	Intravenous paracetamol 1 g	Placebo	Single dose
Martinez et al 2017 [21]	Major surgery (neurosurgery, gynaecological and orthopaedic surgery)	Pain (0–100) Serious adverse events	Not reported	Doses unspecified	Placebo	NR
Monk et al 2017 [22]	Orthodontic treatment in adults	Pain (0–10 VAS) while biting or chewing	3, 6, 7 or 24 h	500 mg to 650 mg oral paracetamol usually 1 h before and 6 h after orthodontic procedure – up to 4 doses after procedure	Placebo	Doses as described – variable
Shirvani et al 2017 [23]	Pulpal anaesthesia in patients with irreversible pulpitis	Pain	—	Oral administration of a paracetamol 325 mg to 1000 mg monotherapy	Placebo	Single dose administered 30 min to 1 hour preoperatively
Wiffen et al 2017 [24]	Neuropathic pain	No RCTs identified				
Wiffen et al 2017 [25]	Cancer pain	Adverse events and serious adverse events (no RCTs reporting pain outcomes)	—	Paracetamol in addition to opioid analgesia	Same dose of opioid analgesia	—
Cooper et al 2018 [26]	Chronic non-cancer pain in children and adolescents	No RCTs identified				
Dixon et al 2018 [27]	Hip	NA	NA	NA	NA	NA
Guo et al 2018 [28]	Knee and Hip Arthroplasty	Pain; Adverse events (not specific to the 3 RCTs of interest)	24 h	1000 mg intravenous paracetamol or 2000 mg intravenous propacetamol every 6 hours	Placebo (in 3 RCTs)	Single and repeated dose
Lee et al 2019 [29]	Bariatric surgery	Pain (VAS)	24 h	Intravenous paracetamol every 6 h for 24 h	Placebo (saline)	Multiple doses
Leopoldino et al 2019 [30]	Knee and hip osteoarthritis	Pain (0–100); Adverse events	Immediate and short term	Oral paracetamol up to 4 g daily	Placebo	Up to 12 weeks
Ng et al 2019 [31]	Post caesarean	Pain (VAS)	Up to 48 h	Intravenous paracetamol three or four times a day for up to 48 h or intravenous paracetamol 15mg/kg before induction of anaesthesia	Placebo	Single and multiple doses

Systematic review	Pain condition	Outcomes	Follow-up	Intervention	Comparison	Duration of therapy
O'Neil et al 2019 [32]	Plastic surgery	Pain VAS or NRS	Over 24 h	Various regimens, usually 1 g paracetamol up to 4 doses within 24 h	Placebo	Single dose or multiple dose
Tolska et al 2019 [33]	Tonsillectomy	Pain VAS (0–10)	24 h	1 g intravenous every 6 h or single dose	Placebo	Single dose or multiple dose
Campbell et al 2020 [34]	Otologic	Pain (CHEOPS, OPS)	Within 1 h	Oral Paracetamol 15 mg / kg single dose	Placebo	Single dose
Ghaffarpasand et al 2020 [35]	Post-craniotomy	Pain VAS	Over 24 h	Intravenous paracetamol pre-incision or upon surgical closure and then every 6 h for a total of 24 h	Placebo	Multiple dose
Ohlsson et al 2020 [36]	Pain in newborns	PIPP score; NIPS score	3 minutes following lancing	Oral paracetamol up to 40 mg/kg 90 min before heel lance	Sterile water	Single administration

CHEOPS= The Children's Hospital of Eastern Ontario Pain Scale; NA=not applicable; NRS=numerical rating scale; NIPS=Neonatal Infant Pain Scale; OPS=objective pain scale; PIPP= Premature Infant Pain Profile Score; RCT=randomised controlled trial; VAS=visual analogue scale.

Table 4. Systematic reviews excluded after reviewing full text, with reasons for exclusion

Duplicate or older study which evaluated the same condition as a review we selected

1. Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. *CMAJ* 2014; 186: 190-199.
2. Angelopoulou MV, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: a meta-analysis. *Orthod Craniofac Res* 2012; 15: 71-83.
3. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015; 162: 46-54.
4. Cetira Filho EL, Carvalho FSR, de Barros Silva PG, et al. Preemptive use of oral nonsteroidal anti-inflammatory drugs for the relief of inflammatory events after surgical removal of lower third molars: a systematic review with meta-analysis of placebo-controlled randomized clinical trials. *J Craniomaxillofac Surg* 2020; 48: 293-307.
5. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017; 390: e21-e33.
6. Enthoven WT, Roelofs PD, Deyo RA, et al. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev* 2016;; CD012087.
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8. Liang L, Cai Y, Li A, Ma C. The efficiency of intravenous acetaminophen for pain control following total knee and hip arthroplasty: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017; 96: e8586.
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10. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache* 2015; 55: 3-20.
11. Merashly M, Uthman I. Management of knee osteoarthritis: an evidence-based review of treatment options. *J Med Liban* 2012; 60: 237-242.
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13. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev* 2016*;* CD011219.
14. Orr SL, Friedman BW, Christie S, et al. Management of adults with acute migraine in the emergency department: the American Headache society evidence assessment of parenteral pharmacotherapies. *Headache* 2016; 56: 911-940.
15. Wöber-Bingöl Ç. Pharmacological treatment of acute migraine in adolescents and children. *Paediatr Drugs* 2013; 15: 235-246.

Not directly relevant to research question (includes studies with ineligible intervention or outcomes data)

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2. Amundsen S, Nordeng H, Nezvalová-Henriksen K, et al. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol* 2015; 11: 209-219.
3. Azari L, Santoso JT, Osborne SE. Optimal pain management in total abdominal hysterectomy. *Obstet Gynecol Surv* 2013; 68: 215-227.
4. Basurto Ona X, Uriona Tuma SM, Martínez García L, et al. Drug therapy for preventing post-dural puncture headache. *Cochrane Database Syst Rev* 2013*;* CD001792.
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24. Niven DJ, Stelfox HT, Laupland KB. Antipyretic therapy in febrile critically ill adults: a systematic review and meta-analysis. *J Crit Care* 2013; 28: 303-310.
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28. Santoro D, Satta E. Pain in Renal Disease. *J Pain Palliat Care Pharmacother* 2014; 28: 409-411.
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Ineligible comparison

1. Ennis ZN, Dideriksen D, Vaegter HB, et al. Acetaminophen for chronic pain: a systematic review on efficacy. *Basic Clin Pharmacol Toxicol* 2016; 118: 184-189.
2. Falch C, Vicente D, Häberle H, et al. Treatment of acute abdominal pain in the emergency room: a systematic review of the literature. *Eur J Pain* 2014; 18: 902-913.
3. Husebo BS, Achterberg W, Flo E. Identifying and managing pain in people with alzheimer's disease and other types of dementia: a systematic review. *CNS Drugs* 2016; 30: 481-497.
4. Joshi GP, Rawal N, Kehlet H, et al. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. *Br J Surg* 2012; 99: 168-185.
5. Karlsen AP, Wetterslev M, Hansen SE, et al. Postoperative pain treatment after total knee arthroplasty: a systematic review. *PLoS One* 2017; 12: e0173107.
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7. Le May S, Ali S, Khadra C, et al. pain management of pediatric musculoskeletal injury in the emergency department: a systematic review. *Pain Res Manag* 2016; 2016: 4809394.
8. Wong JJ, Côté P, Ameis A, et al. Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Eur Spine J*. 2016; 25: 34-61.

Ineligible study type

1. Alshami AM. Knee osteoarthritis related pain: a narrative review of diagnosis and treatment. *Int J Health Sci (Qassim)* 2014; 8: 85-104.
2. Dunn LK, Naik BI, Nemergut EC, Durieux ME. Post-craniotomy pain management: beyond opioids. *Curr Neurol Neurosci Rep* 2016; 16: 93.
3. Ergenoglu P, Akin S, Yalcin Cok O, et al. Effect of intraoperative paracetamol on catheter-related bladder discomfort: a prospective, randomized, double-blind study. *Curr Ther Res Clin Exp* 2012; 73: 186-194.
4. Feltracco P, Carollo C, Barbieri S, et al. Pain control after liver transplantation surgery [published correction appears in Transplant Proc. 2015; 47: 2304]. *Transplant Proc* 2014; 46: 2300-2307.
5. Fengyan, D. Intravenous acetaminophen for perioperative pain control in adult elective neurospine surgical patients: a retrospective case-control study. *AANA J* 2017; 85: 181-188.

6. Gritsenko K, Khelemsky Y, Kaye AD, et al. Multimodal therapy in perioperative analgesia. *Best Pract Res Clin Anaesthesiol* 2014; 28: 59-79.
7. Halila GC, Czepula AIdS, Otuki MF, et al. Review of the efficacy and safety of over-the-counter medicine. *Brazilian Journal of Pharmaceutical Sciences* 2015; 51: 403-414.
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10. Moore RA, Derry C. Efficacy of OTC analgesics. *Int J Clin Pract Suppl* 2013: 21-25.
11. Moore RA, Derry S, Wiffen PJ, et al. Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *Eur J Pain* 2015; 19: 1213-1223.
12. Patniyot IR, Gelfand AA. Acute treatment therapies for pediatric migraine: a qualitative systematic review. *Headache* 2016; 56: 49-70.
13. Preiß JC, Hoffmann JC. Schmerztherapie bei chronischer Pankreatitis und chronisch-entzündlichen Darmerkrankungen [Pain management in chronic pancreatitis and chronic inflammatory bowel diseases]. *Schmerz* 2014; 28: 294-299.
14. Reid MC, Shengelia R, Parker SJ. Pharmacologic management of osteoarthritis-related pain in older adults. *Am J Nurs* 2012; 112 (3 Suppl 1): S38-S43.
15. Richette P, Latourte A, Frazier A. Safety and efficacy of paracetamol and NSAIDs in osteoarthritis: which drug to recommend? *Expert Opin Drug Saf* 2015; 14: 1259-1268.
16. Shastri N. Intravenous acetaminophen use in pediatrics. *Pediatr Emerg Care* 2015; 31: 444-450.
17. Yeh YC, Reddy P. Clinical and economic evidence for intravenous acetaminophen. *Pharmacotherapy* 2012; 32: 559-579.

Table 5. Excluded systematic reviews on the same conditions as included reviews

Reference	Description
Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. *CMAJ* 2014; 186: 190-199.	This was not a typical systematic review - more of a descriptive narrative review therefore was excluded from consideration in the sensitivity analysis (and could also go under ineligible study type in the PRISMA diagram)
Angelopoulou MV, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: a meta-analysis. *Orthod Craniofac Res* 2012; 15: 71-83.	This review included just two of the trials that were included by the more recent Monk review. To note the Monk review did not include the trial by Salmassian et al. However this would not change the direction of effect or conclusions at all, as this trial reported a positive benefit of paracetamol v placebo (for an unspecified outcome, however).
Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015; 162: 46-54.	This review reported an effect estimate of 0.63 (CrI, 0.39 to 0.88) for knee OA and concluded that all treatments except acetaminophen (paracetamol) showed clinically significant improvement from baseline pain. This is not discordant from our findings, that the medicine is superior to placebo, but only marginally which warrants discussion around its clinical utility.
Cetira Filho EL, Carvalho FSR, de Barros Silva PG, et al. Preemptive use of oral nonsteroidal anti-inflammatory drugs for the relief of inflammatory events after surgical removal of lower third molars: a systematic review with meta-analysis of placebo-controlled randomized clinical trials. *J Craniomaxillofac Surg* 2020; 48: 293-307.	Provided similar conclusions to the review of dental procedures we included.
da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017; 390: e21-e33.	This was a network meta-analysis which reported effects for paracetamol at <2000 mg, 3000 mg and 3900-4000 mg and found a statistically significant but marginal benefit for the highest dose range only. Paracetamol < 2000 mg: –0·07 (CrI –0.42 to 0.27) Paracetamol 3000 mg: –0·18 (CrI –0.68 to 0.32) Paracetamol 3900–4000 mg –0·16 (CrI –0.27 to –0.06
Enthoven WT, Roelofs PD, Deyo RA, et al. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev* 2016;; CD012087.	This review did not include a paracetamol v placebo/no treatment comparison
Jeric M, Surjan N, Jelicic Kadic A, et al. Treatment of acute migraine attacks in children with analgesics on the World Health Organization Essential Medicines List: a systematic review and GRADE evidence synthesis. *Cephalalgia* 2018; 38: 1592-1607.	This review also concluded that paracetamol provided no benefit over placebo for migraine in children.

Liang L, Cai Y, Li A, Ma C. The efficiency of intravenous acetaminophen for pain control following total knee and hip arthroplasty: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017; 96: e8586.	This review was excluded as the Guo review selected in our overview included more trials. The Liang review provides conflicting results to the Guo review as it shows some benefit of paracetamol; WMD –0.93 (95% CI –1.17, –0.68) from 4 studies (n=865) 24 hours post total joint arthroplasty (low quality evidence) whereas the Guo review provided very low quality evidence of no benefit; SMD 0.12 (–0.13, 0.36) from a total of seven studies (n=1400). We inspected the original studies from the Guo review and re–did the analysis in accordance with best practice guidelines. Our analysis showed there is inconclusive evidence of benefit (based on very low quality evidence) from multiple dose or single dose regimens of paracetamol for knee/hip arthroplasty; MD –0.5 (–1.8, 0.9 from 2 trials, n=152) and –0.20 (–3.80, 3.46 from 1 trial, n=116) respectively.
Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* 2015; 350: h1225.	Had the same conclusions as review by Leopoldino.
Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache* 2015; 55: 3-20.	Narrative review.
Merashly M, Uthman I. Management of knee osteoarthritis: an evidence-based review of treatment options. *J Med Liban* 2012; 60: 237-242.	Narrative review.
Myers J, Wielage RC, Han B, et al. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. *BMC Musculoskelet Disord* 2014; 15: 76.	This report did not provide specific results for paracetamol.
Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev* 2016;; CD011219.	We included the updated 2020 Cochrane review by the same authors.
Orr SL, Friedman BW, Christie S, et al. Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. *Headache* 2016; 56: 911-940.	This review identified one trial which showed no difference in pain free outcome at 2 hours (3/30 in the acetaminophen group (1 g single dose infusion) and 4/30 in the placebo (saline solution) group. To note, the patient group comprised migraine +/- aura. The authors concluded that *"we cannot rule out, that in some migraine attacks, such as attacks of shorter or longer duration or with higher intensity of concomitant symptoms, would significantly benefit from intravenous acetaminophen. Further studies with more patients would be required to answer this question."*
Wöber-Bingöl Ç. Pharmacological treatment of acute migraine in adolescents and children. *Paediatr Drugs* 2013; 15: 235-246.	This study reported on the (Hämäläinen 1997) study which was included in the more recent Cochrane review (Richer et al., 2016) we used in our overview.

CI=confidence interval; CrI=credible interval; WMD=weighted mean difference; SMD=standardised mean difference.

Table 6. Effect estimates extracted from included reviews or calculated by us (for conditions with randomised controlled trial evidence)

A. Mean difference (95% CI) pain reduction, on 0–10 pain scale

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Paracetamol regimen**	**Effect size***	Risk of bias	Inconsistency	Imprecision	Publication bias	Quality
Uterine cramping/involution after birth [15]	1	48	0.65g single dose	–0.4 (–2.4 to 1.6)	No	No	Yes (x2)	Not assessed	Low[b]
Rheumatoid arthritis [16]	2	55	1g multiple doses daily for up to 17 days	**–1.3 [P<0·05]**	Yes (x2)	No	Yes	Not assessed	Very low[b]
Cataract surgery [19]	1	160	1g single dose 1h before surgery	**–0.9 (–1.2 to –0.6)**	Yes	No	Yes	Not assessed	Low[b]
Common cold headache [20]	1	379	0.5–1g single dose	**–1.4 (–2.0 to –0.8)**	Yes	No	Yes	Not assessed	Low[c]
Common cold sore throat [20]	1	379	0.5–1g single dose	–0.1 (–0.9 to 0.6)	Yes	No	Yes	Not assessed	Low[c]
Post-laparoscopic cholecystectomy [21]	3	146	Multiple doses up to 3g over 48h	–0.1 (–1.0 to 0.8)	Yes (x2)	No	Yes	Not assessed	Very low[b]
Catheter-related bladder discomfort [22]	1	64	15mg/kg single dose	**–0.6 (–1.1 to –0.1)**	Yes	No	Yes (x2)	Not assessed	Very low[c]
Early post-operative pain (at rest) [23]	9	609	2g single dose	**–1.1 (–2.0 to –0.2)**	Yes	Yes (x2)	No	No	Very low[b]
Preventing late post-operative pain [23]	5	328	Up to 2g single dose before or after surgery	–0·4 (–0·9 to 0·1)	Yes	Yes	Yes	Not assessed	Very low[b]
Pain after hysterosalpingography [24]	1	88	1g 30min before procedure	**–0.2 (–0.3 to –0.0)**	Yes	No	Yes	Not assessed	Low[b]
Pain during hysterosalpingography [24]	1	88	1g single dose 30min before procedure	0.0 (–1.0 to 1.0)	Yes	No	Yes	Not assessed	Low[b]
Post-operative pain [26]	12	837	1g single dose	**–0.8 (–0.9 to –0.6)**	Yes	Yes (x2)	No	No	Very low[b]
Acute low back pain [28]	1	1643	Multiple doses up to 3.99g for up to 4 weeks	0.2 (–0.1 to 0.4)	No	No	No	Not assessed	High[a]
Chronic low back pain [28]	1	72	Multiple doses up to 4g daily	0.0 (–0.1 to 0.1)	Yes	No	Yes	Not assessed	Very low (retracted)[a]
Abdominal pain [29]	1	210	15mg/kg single dose over 3min	**–3.8 [p<0.001]**	Yes	No	Yes	Not assessed	Low[b]
Abdominal surgery [32]	8	793	Multiple doses up to 4g	–0.3 (–0.7 to 0.0)	Yes	Yes (x2)	No	Not assessed	Very low[b]
Post-cardiac surgery [33]	3	261	Multiple doses up to 4g over 24 h	–0.7 (–1.4 to 0.0)	Yes	Yes	Yes	Not assessed	Very low[c]

Condition	Trials	*N*	Paracetamol regimen	Effect size*	Quality of evidence assessment (GRADE)				
					Risk of bias	Inconsistency	Imprecision	Publication bias	Quality
Renal colic [34]	1	152	1g single dose	**–2.5 (–3.3 to –1.6)**	Yes	No	Yes	Not assessed	Low[b]
Pain in major surgery [35]	15	>524	Unspecified	**–0.5 (–0.9 to –0.1)**	Yes	No	No	Unclear	Low[b]
Pain during dental procedure [36]	4	107	0.5–0.65g 1h before procedure and up to 4 repeat doses	**–1.2 (–1.8 to –0.5)**	Yes	No	Yes	Not assessed	Low[b]
Knee and hip arthroplasty [42]	2	152	Multiple doses intravenous paracetamol 1g or propacetamol 2g	–0.5 (–1.8 to 0.9)	Yes	Yes (x2)	Yes (x2)	Not assessed	Very low[b]
Knee and hip arthroplasty [42]	1	116	Single dose intravenous paracetamol 1g	–0.2 (–3.8 to 3.5)	Yes	No	Yes (x2)	Not assessed	Very low[b]
Bariatric surgery [43]	4	349	1 g intravenous every 6h over 24h	–0.4 (–0.9 to 0.1)	Yes (x2)	No	Yes	Not assessed	Very low[b]
Knee or hip osteoarthritis [44]	5	1686	1g 4 x daily for up to 12 weeks	**–0.3 (–0.6 to –0.1)**	No	No	No	Not assessed	High[a]
Post-caesarean delivery [45]	5	388	1g intravenous single or multiple doses	–0.7 (–2.0 to 0.6)	Yes	Yes (x2)	Yes (x2)	Not assessed	Very low[b]
Orbital surgery [46]	1	150	1g intravenous single dose	**–4.8 (–6.1 to –3.5)**	Yes	No	Yes	Not assessed	Low[b]
Metastatic breast cancer [46]	1	87	1g intravenous every 6 h; 4 doses total	**–1.3 (–2.3 to –0.3)**	Yes	No	Yes	Not assessed	Low[b]
Reconstructive vaginal surgery [46]	1	90	1g intravenous every 6 h over 24 –h	–0.80 (–2.0 to 0.4)	No	No	Yes (x2)	Not assessed	Low[b]
Tonsillectomy in adults [47]	2	153	1g intravenous every 6 h or single dose	–0.4 (–1.0 to 0.3)	Yes (x2)	No	Yes	Not assessed	Very low[b]
Myringotomy in children [48]	1	43	15mg/kg single oral dose	–0.3 (–1.4 to 0.8)	Yes	No	Yes (x2)	Not assessed	Very low[b]
Craniotomy [49]	4	453	1g 4 x daily for up to 24h	**–0.8 (–1.4, –0.3)**	No	No	No	Not assessed	High[b]
Pain in newborns [50]	1	38	40mg/kg single dose 90min before heel lance	0.7 (–0.1 to 1.5)	Yes	No	Yes	Not assessed	Low[a]

B. Risk or odds ratio (95% CI)

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Paracetamol regimen**	**Effect size**	**Risk of bias**	**Inconsistency**	**Imprecision**	**Publication bias**	**Quality**
Perineal pain [17]	6	797	1g single dose	**RR, 2.4 (1.5–3.8)**	Yes	No	No	Not assessed	Moderate[b]
Acute migraine in adults [18]	3	717	1g single dose	**RR, 1.6 (1.3–1.8)**	Yes	No	No	Likely downgraded	Low[a,†]
Postoperative dental pain in children [25]	2	100	80mg single dose	RR, 0.8 (0.5–1.2)	Yes	No	Yes	Not assessed	Low[a]
Migraine in children and adolescents [27]	1	88	10mg/kg single dose	RR, 1.4 (0.8–2.6)	Yes	No	Yes	Not assessed	Low[b]
Otitis media in children [30]	1	148	10mg/kg 3 x daily for up to 48h	**RR, 0.4 (0.2–0.9)**	Yes	No	Yes	Not assessed	Low[a]
Episodic tension type headache [31]	8	5890	Up to 1g single or multiple doses	**RR, 1.3 (1.1–1.4)**	Yes	No	No	Not assessed	Moderate[b]
Pulpitis [37] (endodontic pain)	2	57	0.325g – 1g single dose	OR, 0.5 (0.1—2.1)	Yes (x2)	Yes	Yes	Not assessed	Very low[b]

CI = confidence interval; OR = odds ratio; RR = risk ratio; x2 = two downgrades were applied.
Bold: statistically significant effects ($P < 0.05$). Very low quality evidence was deemed inconclusive, even if the effect estimate was statistically significant.

* Continuous pain outcomes were converted to a 0–10 pain scale; negative values favour paracetamol. For unconverted data extracted from included reviews, see Table 13.
† It is likely the review downgraded for publication bias despite there being fewer than ten trials.
[a] GRADE/overall quality assessment rating adopted from the review.
[b] GRADE rating was determined by us.
[c] GRADE rating, risk of bias assessment determined by us with Cochrane risk of bias tool, and effect size estimate was extracted from original randomised controlled trial.

For the review of rheumatoid arthritis by Hazlewood [16], the two studies reported the same effect; we report only one *P* value.

In the review by Sin [29], the methods were reported incompletely, and it appears the "very low quality" rating in that review was not applied to the effect estimate, but instead used to describe the quality of the included trial. The GRADE rating we determined for the effect estimate in this review was "low" quality (downgraded for study limitation and imprecision).

The review by Lee [43] reported moderate level evidence of benefit for bariatric surgery, whereas we report very low quality evidence of no benefit. This is because the original meta-analysis was incorrectly performed and we downgraded overall level of evidence a further level for study limitation as one of the studies was assessed as high risk.

The review of episodic tension headache by Stephens [31] provided high quality evidence of efficacy. However, our assessment was that the level of evidence should be moderate, as there were studies at high or unclear risk of bias.

A review of post-operative pain by McNicol [26] provided low level evidence (downgraded for inconsistency and study limitation), however we downgraded a further level due to inconsistency (two downgrades applied, I^2=90%).

Table 7. Summary of reviews that provided effect estimates, overall quality of evidence ratings and risk of bias for included randomised controlled trials

Study	Provided (appropriate) effect estimate	Risk of bias of included studies satisfactory (AMSTAR-2, item 9)	Provided rating for effect estimate, such as GRADE
Deussen et al 2011 [15]	Yes	Yes	No
Hazlewood et al 2012 [16]	Yes	Yes (Cochrane risk of bias) All trials: high risk	No
Chou et al 2013 [17]	Yes	Yes	No
Derry et al 2013 [18]	Yes	Yes	Yes
Porela-Tiihonen et al 2016 [19]	No (presented results descriptively)	Yes (Jadad rating)	No
Li et al 2013 [20]	No	Yes (Cochrane risk of bias) Bachert[51], Ryan[52]: unclear risk of bias	No
Gurusamy et al 2014 [21]	Yes	Yes	No (for paracetamol monotherapy)
Bai et al 2015 [22]	No (descriptive results presented)	No (inadequate)	No
De Oliveira et al 2015 [23]	Yes	Yes (Jadad, 5 point quality scale)	No
Hindocha et al 2016 [24]	Yes	Yes	No
Ashley et al 2016 [25]	Yes	Yes	Yes
McNicol et al 2016 [26]	Yes	Yes	Yes (we revised GRADE rating)
Richer et al 2016 [27]	Yes	Yes	No
Saragiotto et al 2016 [28]	Yes	Yes	Yes
Sin et al 2016 [29]	No (presented results descriptively, effect estimate was determined from these)	Yes (Cochrane-like)	No (unclear if GRADE rating was applied to effect estimate itself)
Sjoukes et al 2016 [30]	Yes	Yes	Yes
Stephens et al 2016 [31]	Yes	Yes	Yes (we revised GRADE rating)
Blank et al 2018 [32]	Yes	Yes (Cochrane risk of bias)	No
Douzijan et al 2017 [33]	No (descriptive results presented)	No (inadequate risk of bias assessment)	No
Garcia-Pedromo et al 2017 [34]	Yes	Yes	No
Martinez et al 2017 [35] (network meta-analysis; direct effects in supplementary file)	Yes	Yes (Cochrane risk of bias)	No
Monk et al 2017 [36]	Yes	Yes	No

Study	Provided (appropriate) effect estimate	Risk of bias of included studies satisfactory (AMSTAR-2, item 9)	Provided rating for effect estimate, such as GRADE
Shirvani et al 2017 [37]	No (effect estimate provided in original review was not consistent with image in forest plot)	Yes (Cochrane risk of bias)	No
Wiffen et al 2016 [38] (neuropathic pain)	NA	NA	NA
Wiffen et al 2017 [39] (cancer pain)	NA	NA	NA
Cooper et al 2017 [40]	NA	NA	NA
Dixon et al 2018 [41]	NA	NA	NA
Guo et al 2018 [42]	No (the effect estimate provided included non-eligible studies)	Yes	No
Lee et al 2019 [43]	No (error with effect estimate, this was corrected and alerted to editor of journal)	Yes	No
Leopoldino et al 2019 [44]	Yes	Yes	Yes
Ng et al 2019 [45]	No (effect estimate was provided but we could not use this and had to determine effect estimate from original placebo-controlled RCTs)	Yes	No
O'Neil et al 2019 [46]	No	No	No
Tolska et al 2019 [47]	Yes	Yes	No
Campbell et al 2020 [48]	No	Yes	No
Ghaffarpsand et al 2020 [49]	No (effect estimate was provided but we could not use this and had to determine effect estimate from original placebo-controlled RCTs)	Yes	No
Ohlsson et al 2020 [50]	Yes	Yes	Yes

GRADE= Grading of Recommendations Assessment, Development and Evaluation; NA=not applicable; RCT=Randomised Controlled Trial; SD =Standard deviation.

The review by Porela-Tiihonen [19] only reported mean pain for both groups. We used the original study to determine SD and compute effect estimate.

The review by Richer [27] did not provide a GRADE rating for the paracetamol v placebo comparison.

Table 8. Effect size estimates extracted from systematic reviews or computed from data in original publications

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Effect estimates computed from RCTs included in the review of the common cold by Li [20]						
Bachert et al 2005 [51]	Headache 2h (0–10)	500mg: 4.28 (1.93)	79	5.72 (1.93)	78	–1.44 (–2.04 to –0.84)
		1000mg: 4.29 (1.99)	79	5.72 (1.93)	78	–1.43 (–2.04 to –0.82)
Bachert et al 2005 [51]	Achiness 2h (0–10)	500mg: 4.41 (2.08)	79	5.36 (2.06)	78	–0.95 (–1.60 to –0.30)
		1000mg: 4.30 (2.08)	79	5.36 (2.06)	78	–1.06 (–1.71 to –0.41)
Bachert et al 2005 [51]	Sore throat 2h (0–10)	500mg: 2.77 (2.41)	79	3.08 (2.36)	78	–0.31 (–1.06 to 0.44)
		1000mg: 2.95 (2.31)	79	3.08 (2.36)	78	–0.13 (–0.86 to 0.60)
Bachert et al 2005 [51]	Frontal and maxillary sinus sensitivity to percussion 2h (0–10)	500mg: 1.15 (1.54)	79	1·58 (2·00)	78	–0.43 (–0.99 to 0.13)
		1000mg: 1.11 (1.50)	79	1.58 (2.00)	78	–0.47 (–1.02 to 0.08)
Ryan et al 1987 [52] Paracetamol 650mg single dose	Pain (0–4)	2.00 (SD not reported)	32	2.09 (SD not reported)	32	–0.09 [P<0.05]
Effect estimates computed from RCTs included in the review of abdominal pain by Sin [29]						
Oguzturk et al 2012 [53]† Paracetamol 15mg/kg	VAS 20 min (0–100)	Median, 45 (range 30–70)	70	Median, 82.5 (range 70–90)	70	–37.5 [P<0.001] Effect estimates determined from data in review
	VAS 40 min (0–100)	Median, 33 (range 30–37)	70	Median, 85 (range 74–93)	70	–52.0 [P<0.001]
Effect estimates computed from RCTs in the review of catheter-related bladder discomfort by Bai [22]						
Ergenoglu et al 2012 [54] Paracetamol 15mg/kg	VAS (0–10) 1h	1.84 (1.25)	32	2.41 (0.84)	32	–0.57 (–1.09 to –0.05)

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Effect estimates computed from RCTs included in the review of cardiac surgery by Douzijan [33]						
Lahtinen et al 2002 [55] Intravenous propacetamol 2g	VAS (rest) 12h (0–10)	3.4 (2.3)	40	3.3 (2.0)	39	0.10 (–0.85 to 1.05)
Khalil et al 2005 [56] Intravenous paracetamol 1g	VAS 12h (0–10)	4.04 (0.74)	17	4.66 (0.89)	15	–0.62 (–1.19 to –0.05)
Cattabriga et al 2007 [57] Intravenous paracetamol 1g	VAS 12h (0–10)	1.5 (0.9)	75	2.8 (2.0)	75	–1.30 (–1.80 to –0.80)
Pooled effect						*0.69 (–1.42 to 0.03); I^2 = 74%*
Note: it was only possible to obtain information and pool for these three trials, identified from the review by Douzjian [33].						
Effect estimates computed from RCTs included in the review of cataract surgery by Porela Tiihonen [19]						
Kaluzny et al 2010 [58] Intra-operative pain Oral paracetamol g	VAS (0–10)	1.45 (1.17)	80	2.17 (1.81)	80	–0.72 (–1.19 to –0.25)
Kaluzny et al 2010 [58] Post-operative pain	VAS (0–10)	0.56 (0.61)	80	1.47 (1.39)	80	–0.91 (–1.24 to –0.58)
Effect estimates computed from RCTs included in the review of knee arthroplasty by Guo [42]						
Camu et al 2017 [59] Intravenous propacetamol 2g four times a day (2g propacetamol is metabolised to 1g paracetamol)	VAS (0–100)	20 (17) *SD from Murata-Ooiwa, as it was the most similar study*	58	18 (19) *SD from Murata-Ooiwa, as it was the most similar study*	28	2.00 (–6.29 to 10.3)
Murato-Ooiwa et al 2017 [60] Intravenous paracetamol 1g every 6h	VAS (0–100)	15.3 (17)	32	26.8 (19)	34	–11.5 (–20.2 to –2.81)

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Pooled effect (multiple dose trials)						***–4.68 (–17.9 to 8.54) [0–100 scale],–0.5 (–1.8 to 0.9) [0–10 scale]*** ***I^2=79%***
O'Neal et al 2017 [61] Single dose intravenous paracetamol 1g	NRS (0–10)	5.6 (9.9)	57	5.8 (9.9)	59	–0.20 (–3.80 to 3.46)
Effect estimate computed from RCTs in the review of post-craniotomy by Ghaffarpasand [49]						
Greenberg et al 2018 [62] 1g intravenous acetaminophen or placebo upon surgical closure, and every 6h thereafter, up to 18h post-operatively	6h VAS (0–100)	Median, 30 (IQR, 10–50) (SD, 29.6*)	63	Median, 45 (IQR, 20–60) (SD, 29.6*)	62	–15.0 (–25.4 to –4.6)
	6h (VAS converted to 0–10 scale)	3.0 (2.96)	63	4.5 (2.96)	62	–1.50 (–2.54 to –0.46)
Sivakumar et al 2018 [63] 1000mg/100mL intravenous acetaminophen every 8h for 48h v 100mL 0.9% normal saline on the same schedule	VAS (0–10), 6h	5.4 (2.3) *SD from Dilmen,[14] as it was the most similar study*	102	5.7 (2.7) *SD from Dilmen,[14] as it was the most similar study*	102	–3.00 (–9.90 to 3.90)
Dilmen et al 2016 [65] Intravenous paracetamol 1g or placebo	VAS (0–10), 2h	1.90 (2.04)	20	3.05 (2.71)	18	–1.15 (–2.69 to 0.39)
Artime et al 2018 [65] Intravenous acetaminophen or placebo pre-incision and then every 6h for 24h after surgery.	VAS (0–10), 2h	2.7 (2.3) *SD from Dilmen,[14] as it was the most similar study*	45	3.7 (2.7) *SD from Dilmen,[14] as it was the most similar study*	41	–1.00 (–2.07 to 0.07)
Pooled effect estimate (excludes Verchere trial [66] as this was not truly placebo-controlled)						*–0.85 (–1.44 to –0.26) (converted to 0–10 scale); I^2=27%*

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Effect estimate computed from the RCTs included in the review of post-Caesarian pain by Ng [45]						
Altenau et al 2017 [67] 1g paracetamol intravenously or 100mL saline (placebo) every 8h for 48h for a total of 6 doses	Faces Pain Scale (0–10) after 3rd dose	Median, 0 (IQR 0–4) SD, 2.96*	43	Median, 2 (IQR 0–5) SD, 3.70*	40	–2.00 (–3.45 to –0.55)
Towers et al 2018 [68] 1g of intravenous acetaminophen preoperatively over 15min infusion up to 4 times in 24h. The maximum amount of acetaminophen used in 24h was controlled at 4g v saline	Faces pain scale (0–10), 24h	5.2 (2.1)	51	5.2 (2.1)	54	0.00 (–0.80 to 0.80)
Soltani et al 2015 [69] 15mg/kg intravenous paracetamol (Apotel) diluted in 100mL normal saline 15min before induction of anesthesia.	VAS 0–10, 3h	6.45 (1.51)	40	5.10 (1.86)	40	1.35 (0.61 to 2.09)
Ozmete et al 2016 [70] Intravenous 1 g paracetamol (100mL) or 0.9% NaCl solution (100mL)	VAS 0–10, 1h	2.0 (1.86) *SD from Soltani,[19] as it was the most similar study*	30	3.0 (1.51) *SD from Soltani,[19] as it was the most similar study*	30	–1.00 (–1.86 to –0.41)
Ayatollahi et al 2014 [71] 1g intravenous paracetamol 20min before the operation	VAS (0–10) 2h	5.4 (1.16)	30	7.3 (1.11)	30	–1.90 (–2.47 to –1.33)
Pooled effect estimate						*0.68 (–1.99 to 0.64)* I^2*=92%*

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Effect estimates computed from RCTs included in the review of plastic surgery by O'Neill [46]						
Wladis et al 2016 [72] orbital surgery Control (no treatment) v 1g intravenous paracetamol immediately before the surgery began	Pain score (0–10) Immediate term post-operative	3.68 (3.24)	50	7.92 (3.36)	50	–4.24 (–5.53 to –2.95)
Wladis et al 2016 [72] orbital surgery Control (no treatment) v intravenous paracetamol (1g infusion within 30min of initiation of the surgery)	Pain score (0–10) Immediate term post-operative	3.12 (3.05)	50	7.92 (3.36)	50	–4.80 (–6.06 to –3.54)
Crisp et al 2017 [73] reconstructive vaginal surgery	0–100 VAS, pain at rest 18h	27.0 (25.9)	47	35.0 (33.0)	43	–8.00 (–20.3 to 4.32)
Ohnesorge et al 2009 [74] elective surgery for metastatic breast cancer 1g intravenous paracetamol 20min before operation and 4, 10 and 16h after the end of the operation	NRS (0–10) at 1h	3.8 (2.0) *SD estimated from graph*	26	5.1 (1.7) *SD estimated from graph*	27	–1.30 (–2.30 to –0.30)
Effect estimates computed from RCTs included in the review of otological procedures by Campbell [48]						
Bennie et al 1997 [75] Myringotomy in 43 children	CHEOPS, 30min 10-item scale [range 4–13]	6.1 (0.7)	11	6.4 (1.7)	11	–0.30 (–1.39 to 0.79)
Watcha et al 1992 [76] Myringotomy in children	Objective pain scale (0–10), 60min	Median, 0 (range 0–4) SD, 1*	14	Median, 0 (range 0–4) SD, 1*	7	0.00 (–0.91 to 0.91)

Publication	Outcome	Treatment (paracetamol): mean (SD)	Treatment sample size	Control (placebo or no active treatment): mean (SD)	Control sample size	Effect estimate: mean difference (95% CI)
Effect estimates computed from RCTs included in the review of pulpitis by Shirvani [37]						
Madani et al 2013 [77]	Treatment success (no pain to cold)	2	15	3	15	0.62 (0.09 to 4.34)
Ianiro et al 2007 [78]	Treatment success (no pain to cold)	11	14	12	13	0.31 (0.03 to 3.39)
Pooled effect estimate						*0.47 (0.10 to 2.12)* I^2*=0%*

CHEOPS=The Children's Hospital of Eastern Ontario Pain Scale; CI=confidence interval; IQR= interquartile range; MD=mean difference; NRS=Numerical Rating Scale; SD=standard deviation; VAS=visual analogue scale.

* SDs computed from reported 95% CIs or IQR (IQR/1.35).

† Three-arm trial with total of 210 participants.

Table 9. Cochrane risk of bias assessments we undertook for trials because they were not undertaken in the included systematic reviews

Review	Trial	Randomisation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data (Attrition bias)	Selective reporting	Other bias
Sin et al 2016 [29]	Oguzturk et al 2012 [53]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Guo et al 2018 [42]	Camu et al 2017 [59]	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	Unclear risk
	O'Neal et al 2017 [61]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
	Murata-Ooiwa 2017 [60]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Unclear risk
Bai et al 2015 [22]	Ergenoglu et al 2012 [54]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	NA
Douzijan et al 2017 [33]	Khalil et al 2005 [56]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk	NA
	Lahtinen et al 2002 [55]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	NA
	Cattabriga et al 2007 [57]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	NA
O'Neil et al 2019 [46]	Wladis et al 2016 [72]	High risk	High risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
	Crisp et al 2017 [73]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Ohnsorge et al 2009 [74]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Campbell et al 2020 [48]	Bennie et al 1997 [75]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
	Watcha et al 1992 [76]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk

Table 10. AMSTAR-2 ratings for the 36 included systematic reviews

Review	AMSTAR-2 item															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Deussen et al 2011 [15]	1	1	1	1	1	1	1	1	1	1	NA	NA	0	NA	NA	1
Hazlewood et al 2012 [16]	1	0	0	1	0	0	0	0	1	0	NA	NA	0	0	NA	0
Chou et al 2013 [17]	1	1	1	0	1	1	1	1	1	0	1	0	0	1	1	1
Derry et al 2013 [18]	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
Porela-Tiihonen et al 2016 [19]	1	0	1	0	0	0	0	1	1	0	NA	NA	0	0	NA	1
Li et al 2013 [20]	1	1	1	1	1	1	1	1	1	1	NA	NA	0	0	NA	1
Gurusamy et al 2014 [21]	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	1
Bai et al 2015 [22]	1	0	1	1	1	1	0	1	0	0	NA	NA	0	0	0	1
De Oliveira et al 2015 [23]	1	0	1	1	1	1	0	1	1	0	1	0	0	1	1	1
Hindocha et al 2016 [24]	1	1	1	1	1	1	1	1	1	0	NA	NA	0	0	NA	1
Ashley et al 2016 [25]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	NA	1
McNicol et al 2016 [26]	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
Richer et al 2016 [27]	1	1	1	1	1	1	1	1	1	1	NA	NA	0	1	1	1
Saragiotto et al 2016 [28]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	NA	1
Sin et al 2016 [29]	0	1	0	1	1	1	0	1	1	0	NA	NA	0	0	NA	1
Sjoukes et al 2016 [30]	1	1	1	1	1	1	1	1	1	1	NA	NA	1	0	1	1
Stephens et al 2017 [31]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	NA	1
Blank et al 2018 [32]	1	0	0	0	0	0	0	1	1	1	1	0	0	1	1	1
Douzijan et al 2017 [33]	0	0	0	0	0	0	0	1	0	0	0	0	0	0	NA	0
Garcia-Perdomo et al 2017 [34]	1	1	1	1	1	1	0	1	1	0	NA	NA	0	0	NA	1
Martinez et al 2017 [35]	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1
Monk et al 2017 [36]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	NA	1
Shirvani et al 2017 [37]	1	0	1	1	1	1	0	1	1	0	0	0	0	1	NA	1
Wiffen et al 2016 (neuropathic pain) [38]	1	1	1	1	1	1	1	1	NA	0	NA	NA	NA	NA	NA	0
Wiffen et al 2017 [39]	1	1	1	1	1	1	1	1	NA	0	NA	NA	NA	NA	NA	0
Cooper et al 2017 [40]	1	1	1	1	1	1	1	1	NA	0	NA	NA	NA	NA	NA	1
Dixon et al 2018 [41]	1	0	1	1	0	0	0	NA	NA	1	NA	NA	NA	NA	NA	1
Guo et al 2018 [42]	1	0	0	1	1	1	0	1	1	0	0	0	0	0	NA	1
Lee et al 2019 [43]	1	1	1	1	1	1	0	1	1	1	0	1	1	1	0	1
Leopoldino et al 2019 [44]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Ng et al 2019 [45]	1	0	1	1	1	1	0	1	1	1	1	0	0	1	1	1
O'Neil et al 2019 [46]	1	0	1	1	0	0	0	1	0	0	NA	0	0	0	0	1
Tolska et al 2019 2019 [47]	1	0	1	1	1	0	0	1	1	0	1	0	0	1	1	1
Campbell et al 2020 [48]	1	0	1	1	0	0	0	1	1	1	NA	0	0	0	0	1
Ghaffarpasand et al 2020 [49]	1	0	1	1	1	1	0	1	1	1	0	0	0	1	1	1
Ohlsson et al 2020 [50]	1	1	0	1	1	1	1	1	1	0	NA	NA	1	0	NA	1

Although the use of NA (not applicable) is not advised in AMSTAR-2, some items could not be assessed for reviews that included no randomised controlled trials (RCTs) or only one eligible RCT. Shaded areas are critical items. AMSTAR-2 items are as follows: 1. PICO question defined (**P**atient/population, **I**ntervention, **C**omparison, **O**utcome) 2. a priori methods i.e. registered or published protocol, 3. Explanation of study selection 4. Comprehensive literature search 5. Duplicate study selection 6. Duplicate data extraction 7. List of excluded studies included and justification provided 8. List of included studies and justification for inclusion 9. Risk of bias (ROB) assessment satisfactory 10. Funding source disclosed 11. Appropriate statistical combination of results 12. Impact of ROB assessment on statistical analysis provided 13. ROB accounted for when interpreting results 14. Explanation and discussion of heterogeneity where applicable 15. Assessment of publication bias 16. Review authors reported potential conflict of interest.

Sin [29] used a Cochrane-like tool, but the GRADE rating does not appear to have been applied to the effect estimate of interest. Monk [36] did not account for ROB assessment when interpreting the result of the paracetamol vs placebo comparison.

Table 11. Adverse events reported by included systematic reviews

Condition	Adverse event (AE) type	Trials, sample size	Effect size estimate: RR (95% CI), unless otherwise indicated	Risk of Bias	Inconsistency	Imprecision	Publication bias	Quality
Uterine cramping and involution after birth [15]	Any AE	1 RCT, n=48	2.36 (0.95–5.88)	No	No	Yes	Not assessed	Moderate[b]
Rheumatoid arthritis and rheumatoid synovitis [16]	AE	3 RCTs, n=84	Qualitative results report no difference in total AE or withdrawals	Yes (x2)	Unclear	Yes	Not assessed	Very low[b]
Perineal pain in early post partum period [17]	Non-serious AE– maternal nausea	1 RCT, n=232	0.18 (0.01–3.66)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very low[b]
Perineal pain in early post partum period [17]	Non-serious AE – maternal sleepiness	1 RCT, n=232	0.89 (0.18–4.30)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very low[b]
Perineal pain in early post partum period [17]	Non-serious AE – maternal bowel movements at doses 500 mg to 650 mg	1 RCT, n=132	1.08 (0.44–2.66)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very low[b]
Perineal pain in early post partum period [17]	Non-serious AE – maternal bowel movements at doses 1000 mg	1 RCT, n=131	0.94 (0.40–2.18)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very low[b]
Acute migraine in adults [18]	At least 1 AE	4 RCTs, n=1293	0.78 (0.64–0.95)	Yes	No	No	Yes (downgraded)	Low[a]
Cataract surgery [19]	AE	1 RCT, n=160	"no AE reported in either the paracetamol group or vitamin C group"	Yes (unclear risk)	No	Yes	Not assessed	Low[b]
Laparoscopic cholecystectomy [21]	Serious AE	1 RCT, n=69	2.18 (0.21–22.96)	Yes	No	Yes (x2)	Not assessed	Very low[b]
Prevention of post-operative pain [23]	Incidence of nausea and or vomiting	3 RCTs, n=213	OR, 0.25 (0.13–0.47) NNT, 3.3 (2.3–5.9)	Yes	No	Yes	Not assessed	Low[b]
Postoperative pain (paracetamol vs placebo) [26]	Any AE	12 RCTs, n=950	1.06 (0.93–1.19)	Yes (x2)	No	Yes	No	Very low[b]

Condition	Adverse event (AE) type	Trials, sample size	Effect size estimate: RR (95% CI), unless otherwise indicated	Risk of Bias	Inconsistency	Imprecision	Publication bias	Quality
Post-operative pain (propacetamol vs placebo) [26]	Any AE	10 RCTs, n=1409	1.17 (1.02–1.35)	Yes	No	No	No	Low[b]
Post-operative pain paracetamol [26]	Serious AE	6 RCTs, n=634	1.12 (0.19–6.59)	Yes	No	Yes	Not assessed	Low[b]
Post-operative pain propacetamol [26]	Serious AE	5 RCTs, n=336	0.0 (0.0–0.0)	Yes	No	No	Not assessed	Moderate[b]
Migraine in children and adolescents [27]	AE	1 RCT, n=88	"No significant difference"	Yes	No	Yes	Not assessed	Low[b]
Low back pain [28]	Any AE	1 RCT, n=1624	1.07 (0.86–1.33)	No	No	No	Not assessed	High[a]
Low back pain [28]	Serious AE (up to 12 weeks follow up)	1 RCT, n=1624	0.90 (0.30–2.67)	No	No	Yes	Not assessed	Moderate[b]
Abdominal pain [29]	AE – new onset or worsening of nausea or vomiting	1 RCT, n=140	13 (19%) patients receiving paracetamol, and one receiving placebo (1%) .	Yes	No	Yes	Not assessed	Low[b]
Otitis media in children [30]	AE	1 RCT, n=148	1.03 (0.21–4.93)	Yes	No	Yes (x2)	Not assessed	Very low[a]
Episodic tension type headache [31]	Any AE	11 RCTs, n=5605	1.12 (0.94–1.32)	No	No	No	No	High[a]
Episodic tension type headache [31]	Gastrointestinal AE	10 RCTs, n=5526	1.12 (0.86–1.45)	No	No	Yes	No	Moderate[b]
Episodic tension type headache [31]	Gastrointestinal AE	4 RCTs, n=4036	1.47 (0.83–2.61)	No	No	Yes	Not assessed	Moderate[b]
Post-cardiac surgery [33]	Nausea and vomiting	1 RCT, n=32 (Khalil)	Lower incidence of nausea, but not vomiting [P<0.05] less sedation (at 12 and 18h with paracetamol P<0.05)	Yes	No	Yes	Not assessed	Low[b]
Post-cardiac surgery [33]	Nausea and vomiting	1 RCT, n=113 (Cattabriga)	"No difference in the rate of nausea and vomiting"	Yes	No	Yes	Not assessed	Low[b]
Renal colic [34]	At least 1 AE	1 RCT, n=152	Original trial cites no difference: 1.52 (0.67–3.46) (Bektas)	Yes	No	Yes	Not assessed	Low[b]

Condition	Adverse event (AE) type	Trials, sample size	Effect size estimate: RR (95% CI), unless otherwise indicated	Risk of Bias	Inconsistency	Imprecision	Publication bias	Quality
Major surgery 2017 [35]	Serious AE	3 RCTs, n= 230	OR, 3.09 (0.33–28.8)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very low[b]
Bariatric surgery [43]	Swelling of the face and rash	AE reported for only 1 RCT, n=99	"One patient in the IV acetaminophen group experienced generalized swelling of the face and had a rash, which then led this patient to be removed from the study"	Yes	No	Yes	Not assessed	Low[b]
Spinal pain and osteoarthritis [44]	Liver AE (spinal pain and osteoarthritis)	3 RCTs, n=1237	3.8 (1.9–7.4)	Yes	No	No	Not assessed	Moderate[b]
Spinal pain and osteoarthritis [44]	Serious AE (spinal pain and osteoarthritis)	6 RCTs, n=3209	1.4 (0.7–2.5)	Yes	No	Yes	Not assessed	Low[b]
Spinal pain and osteoarthritis [44]	Any AE (spinal pain and osteoarthritis)	8 RCTs, n=3252	1.0 (0.9–1.1)	Yes	No	No	Not assessed	Moderate[b]
Post-caesarean delivery [45]	AE	1 RCT, n=60	One study (Ozmete, 2016) reported no significant difference in AE	Yes	Yes	Yes	Not applicable	Very low[b]
Orbital surgery [46]	AE – various	1 RCT, n=150	Reported no significant complications or AE	Yes	No	Yes	Not assessed	Low[b]
Reconstructive vaginal surgery [46]	AE – various	1 RCT, n=90	Reported no significant complications or AE	No	No	Yes	Not assessed	Moderate[b]
Elective surgery for metastatic breast cancer [46]	AE – various	1 RCT, n=87	Did not report an increased risk of nausea, vomiting or sedation	Yes	No	Yes	Not assessed	Low[b]
Myringotomy in Children [48]	Nausea and vomiting	Unclear	AE reported in 7% of children receiving acetaminophen. No comparison with placebo	Yes	No	Yes	Not assessed	Low[b]

NNT=number needed to treat; OR=odds ratio; RCT=randomised controlled trial; RR=risk ratio; (x2) = two downgrades applied.

[a] GRADE/overall quality assessment rating adopted from review.

[b] GRADE rating determined by us.

We report adverse events as "any adverse events" or as "serious adverse events" (life-threatening events or events resulting in hospital admission) if the definition in the systematic review was sufficiently clear.

Table 12. Sensitivity analysis, applying only one downgrade for each GRADE domain, when appropriate (for conditions with randomised controlled trial evidence)*

A. Mean difference (95% CI) pain reduction, on 0–10 pain scale

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Paracetamol regimen**	**Effect size***	Risk of bias	Inconsistency	Imprecision	Publication bias	Quality
Uterine cramping/involution after birth [15]	1	48	0.65g single dose	–0.4 (–2.4 to 1.6)	No	No	Yes	Not assessed	Moderate[b]
Rheumatoid arthritis [16]	2	55	1g multiple doses daily for up to 17 days	**–1.3 [P<0·05]**	Yes	No	Yes	Not assessed	Low[b]
Cataract surgery [19]	1	160	1g single dose 1h before surgery	**–0.9 (–1.2 to –0.6)**	Yes	No	Yes	Not assessed	Low[b]
Common cold headache [20]	1	379	0.5–1g single dose	**–1.4 (–2.0 to –0.8)**	Yes	No	Yes	Not assessed	Low[c]
Common cold sore throat [20]	1	379	0.5–1g single dose	–0.1 (–0.9 to 0.6)	Yes	No	Yes	Not assessed	Low[c]
Post-laparoscopic cholecystectomy [21]	3	146	Multiple doses up to 3g over 48h	–0.1 (–1.0 to 0.8)	Yes	No	Yes	Not assessed	Low[b]
Catheter-related bladder discomfort [22]	1	64	15mg/kg single dose	**–0.6 (–1.1 to –0.1)**	Yes	No	Yes	Not assessed	Low[c]
Early post-operative pain (at rest) [23]	9	609	2g single dose	**–1.1 (–2.0 to –0.2)**	Yes	Yes	No	No	Low[b]
Preventing late post-operative pain [23]	5	328	Up to 2g single dose before or after surgery	–0·4 (–0·9 to 0·1)	Yes	Yes	Yes	Not assessed	Very low[b]
Pain after hysterosalpingography [24]	1	88	1g 30min before procedure	**–0.2 (–0.3 to –0.0)**	Yes	No	Yes	Not assessed	Low[b]
Pain during hysterosalpingography [24]	1	88	1g single dose 30min before procedure	0.0 (–1.0 to 1.0)	Yes	No	Yes	Not assessed	Low[b]
Pain during dental procedure [36]	4	107	0.5–0.65g 1h before procedure and up to 4 repeat doses	**–1.2 (–1.8 to –0.5)**	Yes	No	Yes	Not assessed	Low[b]
Post-operative pain [26]	12	837	1g single dose	**–0.8 (–0.9 to –0.6)**	Yes	Yes	No	No	Low[a]
Acute low back pain [28]	1	1643	Multiple doses up to 3.99g for up to 4 weeks	0.2 (–0.1 to 0.4)	No	No	No	Not assessed	High[a]
Chronic low back pain [28]	1	72	Multiple doses up to 4g daily	0.0 (–0.1 to 0.1)	Yes	No	Yes	Not assessed	Very low (retracted)[a]
Abdominal pain [29]	1	210	15mg/kg single dose over 3min	**–3.8 [p<0.001]**	Yes	No	Yes	Not assessed	Low[b]

Condition	Trials	*N*	Paracetamol regimen	Effect size*	Quality of evidence assessment (GRADE)				
					Risk of bias	Inconsistency	Imprecision	Publication bias	Quality
Abdominal surgery [32]	8	793	Multiple doses up to 4g	–0.3 (–0.7 to 0.0)	Yes	Yes	No	Not assessed	Very low[b]
Post-cardiac surgery [33]	3	261	Multiple doses up to 4g over 24 h	–0.7 (–1.4 to 0.0)	Yes	Yes	Yes	Not assessed	Very low[c]
Renal colic [34]	1	152	1g single dose	**–2.5 (–3.3 to –1.6)**	Yes	No	Yes	Not assessed	Low[b]
Pain in major surgery [35]	15	>524	Unspecified	**–0.5 (–0.9 to –0.1)**	Yes	No	No	Unclear	Low[b]
Knee and hip arthroplasty [42]	2	152	Multiple doses intravenous paracetamol 1g or propacetamol 2g	–0.5 (–1.8 to 0.9)	Yes	Yes	Yes	Not assessed	Very low[b]
Knee and hip arthroplasty [42]	1	116	Single dose intravenous paracetamol 1g	–0.2 (–3.8 to 3.5)	Yes	No	Yes	Not assessed	Low[b]
Bariatric surgery [43]	4	349	1 g intravenous every 6h over 24h	–0.4 (–0.9 to 0.1)	Yes	No	Yes	Not assessed	Low[b]
Knee or hip osteoarthritis [44]	5	1686	1g 4 x daily for up to 12 weeks	**–0.3 (–0.6 to –0.1)**	No	No	No	Not assessed	High[a]
Post-caesarean delivery [45]	5	388	1g intravenous single or multiple doses	–0.7 (–2.0 to 0.6)	Yes	Yes	Yes	Not assessed	Very low[b]
Orbital surgery [46]	1	150	1g intravenous single dose	**–4.8 (–6.1 to –3.5)**	Yes	No	Yes	Not assessed	Low[b]
Metastatic breast cancer [46]	1	87	1g intravenous every 6 h; 4 doses total	**–1.3 (–2.3 to –0.3)**	Yes	No	Yes	Not assessed	Low[b]
Reconstructive vaginal surgery [46]	1	90	1g intravenous every 6 h over 24 –h	–0.80 (–2.0 to 0.4)	No	No	Yes	Not assessed	Moderate[b]
Tonsillectomy in adults [47]	2	153	1g intravenous every 6 h or single dose	–0.4 (–1.0 to 0.3)	Yes	No	Yes	Not assessed	Low[b]
Myringotomy in children [48]	1	43	15mg/kg single oral dose	–0.3 (–1.4 to 0.8)	Yes	No	Yes	Not assessed	Low[b]
Craniotomy [49]	4	453	1g 4 x daily for up to 24h	**–0.8 (–1.4, –0.3)**	No	No	No	Not assessed	High[b]
Pain in newborns [50]	1	38	40mg/kg single dose 90min before heel lance	0.7 (–0.1 to 1.5)	Yes	No	Yes	Not assessed	Low[a]

B. Risk or odds ratio (95% CI)

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Paracetamol regimen**	**Effect size**	**Risk of bias**	**Inconsistency**	**Imprecision**	**Publication bias**	**Quality**
Perineal pain [17]	6	797	1g single dose	**RR, 2.4 (1.5–3.8)**	Yes	No	No	Not assessed	Moderate[b]
Acute migraine in adults [18]	3	717	1g single dose	**RR, 1.6 (1.3–1.8)**	Yes	No	No	Likely downgraded	Low[a,†]
Postoperative dental pain in children [25]	2	100	80mg single dose	RR, 0.8 (0.5–1.2)	Yes	No	Yes	Not assessed	Low[a]
Migraine in children and adolescents [27]	1	88	10mg/kg single dose	RR, 1.4 (0.8–2.6)	Yes	No	Yes	Not assessed	Low[b]
Otitis media in children [30]	1	148	10mg/kg 3 x daily for up to 48h	**RR, 0.4 (0.2–0.9)**	Yes	No	Yes	Not assessed	Low[a]
Episodic tension type headache [31]	8	5890	Up to 1g single or multiple doses	**RR, 1.3 (1.1–1.4)**	Yes	No	No	Not assessed	Moderate[b]
Pulpitis [37] (endodontic pain)	2	57	0.325g – 1g single dose	OR, 0.5 (0.1—2.1)	Yes	Yes	Yes	Not assessed	Very low[b]

CI = confidence interval; OR = odds ratio; RR = risk ratio.
Bold: statistically significant effects ($P < 0.05$). Very low quality evidence was deemed inconclusive, even if the effect estimate was statistically significant.

* Continuous pain outcomes were converted to a 0–10 pain scale; negative values favour paracetamol. Shaded boxes indicate cells that differ from those in the main analysis (Table 6).
† It is likely the review downgraded for publication bias despite there being fewer than ten trials.
[a] GRADE/overall quality assessment rating adopted from the review.
[b] GRADE rating was determined by us.
[c] GRADE rating, risk of bias assessment determined by us with Cochrane risk of bias tool, and effect size estimate was extracted from original randomised controlled trial.

For the review of rheumatoid arthritis by Hazlewood [16], the two studies reported the same effect; we report only one *P* value.

Table 13. Summary of all effect estimates directly extracted from reviews or directly determined for our review

A. Mean difference (95% CI) pain reduction

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Outcome measure**	**Effect size**	**Risk of bias**	**Inconsistency**	**Imprecision**	**Publication bias**	**Quality**
Uterine cramping [15]	1	48	Pain intensity (0-3)	-0.12 (-0.71 to 0.47)	No	No	Yes (x2)	Not assessed	Low[b]
Rheumatoid arthritis [16]	2	55	Mean pain relief (0-3) at 1 h (0 no pain relief, 3 complete pain relief)	**0.4 [1.2 vs 0.8 p<0.05] (favouring paracetamol)**	Yes (x2)	No	Yes	Not assessed	Very Low[b]
Rheumatoid synovitis	1	30	Mean (%) maximum pain relief in the immediate term	14.9% [50.7% vs 35.8% p<0.05] (favouring paracetamol)	Yes	No	Yes	Not assessed	Low[b]
Cataract surgery [19]	1	160	Postoperative pain (VAS 0–10)	-0.91 (-1.24 to -0.58) 95% CI determined from SD	Yes (unclear risk)	No	Yes	Not assessed	Low[b]
Common cold [20]	1	379	Sore throat at 2 h (0–10) with 500 mg dose. Data from Bachert trial [51]	-0.31 (1.06 to 0.44)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Sore throat at 2 h (0–10) with 1000 mg dose. Data from Bachert trial [51]	-0.13 (-0.86 to 0.60)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Frontal and maxillary sinus sensitivity to percussion at 2 h (0–10) with 500 mg dose. Data from Bachert trial [51]	-0.43 (-0.99 to 0.13)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Frontal and maxillary sinus sensitivity to percussion at 2 h (0–10) with 1000 mg dose. Data from Bachert trial [51]	-0.47 (-1.02 to 0.08)	Yes	No	Yes	Not assessed	Low[c]

Common cold [20]	1	64	Pain intensity at 1 h (4 point pain scale no pain to severe pain) with a 650 mg dose of paracetamol. Data from Ryan trial [52]	-0.09 [p<0.05] (2.00 vs 2.09 paracetamol vs placebo groups respectively)	Yes	No	Yes (x2)	Not assessed	Very Low[c]
Common cold [20]	1	379	Headache at 2 h (0–10; 0=none, 10=severe) with 500 mg dose. Data from Bachert trial [51].	-1.44 (-2.04 to -0.84)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Headache at 2 h (0–10; 0=none, 10=severe) with 1000 mg dose. Data from Bachert trial [51].	-1.43 (-2.04 to -0.82)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Achiness at 2 h (0–10; 0=none, 10=severe) with 500 mg dose. Data from Bachert trial [51].	-0.95 (-1.60 to -0.30)	Yes	No	Yes	Not assessed	Low[c]
Common cold [20]	1	379	Achiness at 2 h (0–10; 0=none, 10=severe) with 1000 mg dose. Data from Bachert trial [51].	-1.06 (-1.71 to -0.41)	Yes	No	Yes	Not assessed	Low[c]
Laparoscopic cholescystectomy [21]	3	146	Pain (0–10 VAS) 4 to 8 h after laparoscopic cholecystectomy	-0.10 (-1.02 to 0.82)	Yes (x2)	No	Yes	Not assessed	Very Low[b]
Catheter related bladder discomfort (percutaneous nephrolithotomy) [22]	1	64	Intensity of catheter-related bladder discomfort (CRBD) at 1 h. Data from the Ergenoglu trial [54]	-0.57 (-1.09 to -0.05) 95% CI determined from SDs	Yes	No	Yes (x2)	Not assessed	Very Low[c]
Prevention of late post-operative pain [23]	5	328	Late postoperative pain (24 h) at rest (0–10)	WMD, -0.4 (-0.9, 0.05)	Yes	Yes	Yes	Not assessed	Very low[b]

Prevention of early post-operative pain [23]	3	214	Early post-operative pain at movement (0 to 4 h) (0–10)	WMD, -1.9 (-2.80 to -1.0)	Yes	Yes	Yes	Not assessed	Very low[b]
Prevention of early post-operative pain [23]	9	609	Early postoperative pain at rest (0 to 4h) (0–10 NRS)	WMD, -1.1 (-2.0 to -0.20)	Yes	Yes (x2) I^2=87%	No	No	Very low[b]
Hysterosalpingography [24]	1	88	Pain (0–100) 30 min after hysterosalpingography	-1.61 (-2.94 to -0.28)	Yes	No	Yes	Not assessed	Low[b]
Hysterosalpingography [24]	1	88	Pain (0–100) during hysterosalpingography	0.07 (-9.92 to 10.06)	Yes	No	Yes	Not assessed	Low[b]
Post-operative pain [26]	12	837	Pain (VAS 0–100) following administration of intravenous paracetamol or propacetamol	-7.48 (-8.98 to -5.97)	Yes	Yes (x2) I^2=90%	No	No	Very Low[b] (original rating was Low)
Chronic low back pain [28]	1	72	Pain (0–100) at 1 day	0.00 (-9.70 to 9.70)	Yes	No	Yes	Not assessed	Very Low[a] (trial retracted)
Acute low back pain [28]	1	1643	Pain (0–100) at 1 week	1.49 (-1.30 to 4.28)	No	No	No	Not assessed	High[a]
Abdominal pain [29]	1	210	VAS (0–100) at 20 min. Data from Oguzturk trial [53]	-37.5 [p< 0.001]	Yes	No	Yes	Not assessed	Low[b]
Abdominal pain [29]	1	210	VAS (0–100) at 40 min. Data from Oguzturk trial [53]	-52.0 [p< 0.001]	Yes	No	Yes	Not assessed	Low[b]
Abdominal surgery [32]	8	793	24-hour pain score (0–10)	-0.34 (-0.69 to 0.01)	Yes	Yes (x2) I^2=92%	No	Not assessed	Very Low[b]
Cardiac surgery [33]	3	261	Pain scores (VAS at rest 0–10)	-0.69 (-1.42 to 0.03)	Yes (unclear risk)	Yes (I^2=74%)	Yes	Not assessed	Very Low[c]
Renal colic [34]	1	152	Pain at 15 min (0–100)	-24.77 (-33.19 to -16.35)	Yes	No	Yes	Not assessed	Low[b]
Major surgery [35]	15	>524	Pain (0–100) – direct effect	-4.9 (-8.8 to -1.0)	Yes	No	No	Unclear	Low[b]
Dental pain/orthodontic treatment [36]	4	107	Pain (VAS) 0–100 at 2 h	-11.90 (-18.36 to -5.44)	Yes (unclear risk)	No	Yes	Not assessed	Low[b]
Neuropathic pain [38]	-	-	-	-	-	-	-	-	Not

									applicable
Cancer pain in adults [39]	-	-	-	-	-	-	-	-	Not applicable
Non-cancer pain in children and adolescents [40]	-	-	-	-	-	-	-	-	Not applicable
Hip fracture [41]	-	-	-	-	-	-	-	-	Not applicable
Knee and hip arthroplasty [42]	2	152	Pain scores at 24 h (0–100 pain scale) with multiple dose regimen	-4.68 (-17.91 to 8.54)	Yes	Yes (x2) I^2=79%	Yes (x2)	Not assessed	Very Low[b]
Knee and hip arthroplasty [42]	1	116	Pain scores at 24 h (0–10 pain scale) with single dose regimen	-0.20 (-3.80 to 3.46)	Yes (unclear risk)	No	Yes (x2)	Not assessed	Very Low[b]
Bariatric surgery [43]	4	349	VAS (0–10) immediate term	-0.39 (-0.88 to 0.10)	Yes (x2)	No	Yes	Not applicable	Very Low[b]
Knee and hip osteoarthritis [44]	5	1686	Immediate term pain (0–100 scale)	−3.3 (−5.8 to −0.8)	No	No	No	Not assessed	High[a]
Knee and hip osteoarthritis [44]	7	2355	Short term pain (0–100) scale	-3.23 (−5.43 to −1.02)	No	No	No	Not assessed	High[a]
Post-caesarean pain [45]	5	388	Pain scale (0–10) within 24 h	-0.68 (-1.99 to 0.64)	Yes	Yes (x2)	Yes (x2)	Not applicable	Very Low[b]
Orbital surgery [46]	1	150	VAS 0–10 –immediate term post-operative	-4.80 (-6.06 to -3.54)	Yes	No	Yes	Not assessed	Low[b]
Reconstructive vaginal surgery [46]	1	90	VAS (0–100) at 18 h	-8.00 (-20.32 to 4.32)	No	No	Yes (x2)	Not assessed	Low[b]
Elective surgery for metastatic breast cancer [46]	1	87	NRS (0–10) at 1 h	-1.30 (-2.30 to -0.30)	Yes	No	Yes	Not assessed	Low[b]
Tonsillectomy in adults [47]	2	153	(0–10 pain scale)	-0.36 (-1.02 to 0.30)	Yes (x2)	No	Yes	Not applicable	Very Low[b]
Myringotomy in children [48]	1	43	CHEOPS (10 point scale) at 30 min	-0.30 (-1.39 to 0.79)	Yes	No	Yes (x2)	Not assessed	Very Low[b]
Craniotomy	4	453	VAS (0–100) within 6 h	-8.5 (-14.4 to -2.6)	No	No	No	Not applicable	High[b]
Pain in newborns	1	38	Premature Infants Pain Profile (PIPP) score (maximum score within 3 min following lancing) (0-21) with oral paracetamol up to 40 mg	1.48 (-0.11 to 3.07)	Yes	No	Yes	Not assessed	Low[a]

										/kg 90 minutes before heel lance vs sterile water	

† Effect estimates expressed as Mean Difference (MD) for continuous outcomes. Negative values favour paracetamol unless otherwise indicated.
†† it is likely the review downgraded for publication bias despite there being < 10 trials.
[a] GRADE/overall quality assessment rating adopted from the review
[b] GRADE rating was determined by us
[c] GRADE rating, ROB assessment determined by us and effect size estimate determined by us (usually extracted from original RCT). Note: ROB assessment determined using the Cochrane risk of bias tool
For the review of Rheumatoid Arthritis, the two studies showed the same effect independently, we selected one p-value only.
NRS=numerical rating scale; VAS=visual analogue scale; MD=mean difference; WMD=weighted mean difference. Note that this table includes additional extracted data not included in the main manuscript. The main manuscript focuses on the key findings.

B. Risk or odds ratio (95% CI)

					Quality of evidence assessment (GRADE)				
Condition	**Trials**	***N***	**Outcome measure**	**Effect size**	**Risk of bias**	**Inconsistency**	**Imprecision**	**Publication bias**	**Quality**
Perineal pain [17]	5	482	50% pain relief at doses 500 mg to 650 mg	RR, 1.86 (1.20 to 2.87)	Yes (unclear risk)	No	No	Not assessed	Moderate[b]
Perineal pain [17]	6	797	50% pain relief at doses 1000 mg	RR, 2.42 (1.53 to 3.81)	Yes (unclear risk)	No	No	Not assessed	Moderate[b]
Acute migraine in adults [18]	3	717	Proportion of participants achieving relief of moderate to severe symptoms at 2 h	RR, 1.55 (1.32 to 1.83)	Yes	No	No	Likely downgraded	Low[a]††
Acute migraine in adults [18]	3	717	Proportion of pain-free participants 2 h after dosing	RR, 1.80 (1.24 to 2.62)	Yes	No	No	Likely downgraded	Low[a]††
Cataract surgery [19]	1	160	Proportion of patients experiencing moderate to severe pain (%)	RR, 0.10 (0.01 to 0.76)	Yes (unclear risk)	No	Yes	Not assessed	Low[b]
Dental pain in children [25]	2	100	Postoperative pain at 6 to 7 h reported by parent	RR, 0.81 (0.53 to 1.22)	Yes	No	Yes	Not assessed	Low[a]
Post-operative pain [26]	5	393	50% pain relief 4 h after surgery following administration of intravenous paracetamol	RR, 4.80 (2.30 to 10.00)	Yes	Yes I^2=90%	No	No	Low[b] (original rating Moderate)
Post-operative pain [26]	8	756	50% pain relief 4 h after surgery	RR, 2.19 (1.74 to 2.77)	Yes	No	No	No	Moderate[a]
Migraine in children and adolescents [27]	1	88	Proportion of pain-free participants 2 hours after dosing	RR, 1.40 (0.75 to 2.58)	Yes (unclear risk)	No	Yes	Not assessed	Low[b]
Otitis media in children [30]	1	148	Proportion of children with pain at 48 h	RR, 0.38 (0.17 to 0.85)	Yes (unclear risk)	No	Yes	Not assessed	Low[a]
Episodic tension type headache [31]	8	5890	Proportion pain free at 2 h	RR, 1.3 (1.1 to 1.4)	Yes	No	No	Not assessed	Moderate[b] (original rating High)
Pulpal anaesthesia in patients with irreversible pulpitis [37]	2	57	Pain relief/"success" – immediate term	OR, 0.47 (0.10 to 2.12)	Yes (x2)	Yes	Yes	Not assessed	Very Low[b]

† Effect estimates expressed as Risk Ratio (RR) or Odds Ratio (OR) for dichotomous outcomes. Negative values favour paracetamol unless otherwise indicated.
†† it is likely the review downgraded for publication bias despite there being < 10 trials.
[a] GRADE/overall quality assessment rating adopted from the review
[b] GRADE rating was determined by us
[c] GRADE rating, ROB assessment determined by us and effect size estimate determined by us (usually extracted from original RCT). Note: ROB assessment determined using the Cochrane risk of bias tool.
NRS=numerical rating scale; VAS=visual analogue scale; RR=risk ratio; OR=odds ratio. Note that this table includes additional extracted data not included in the main manuscript. The main manuscript focuses on the key findings.

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