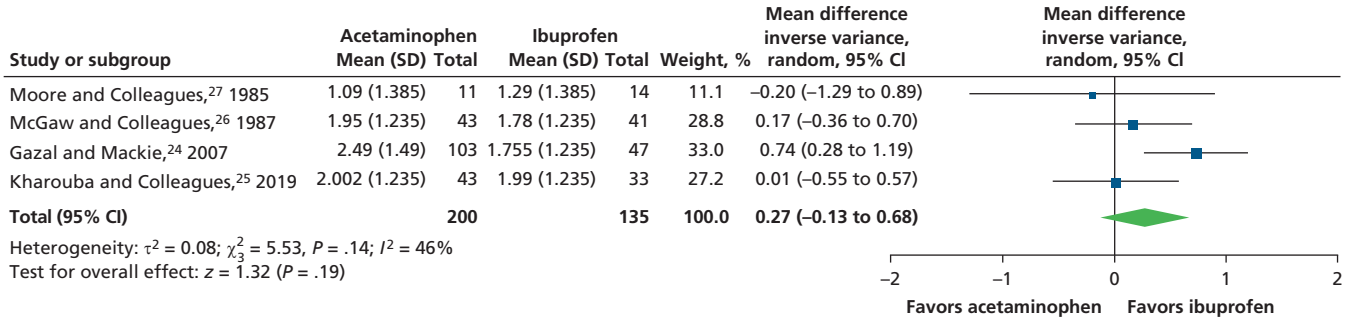
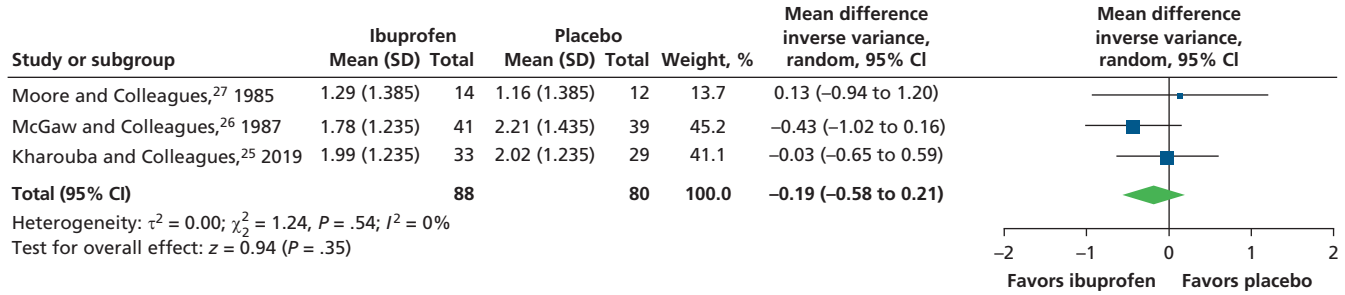
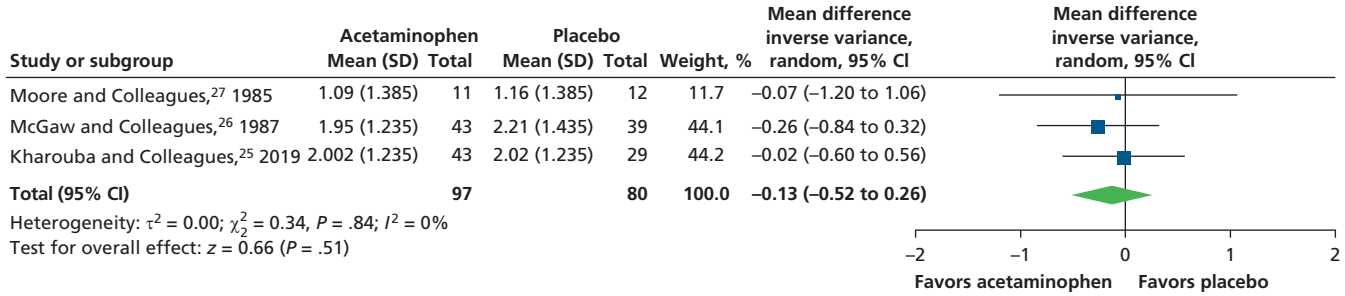


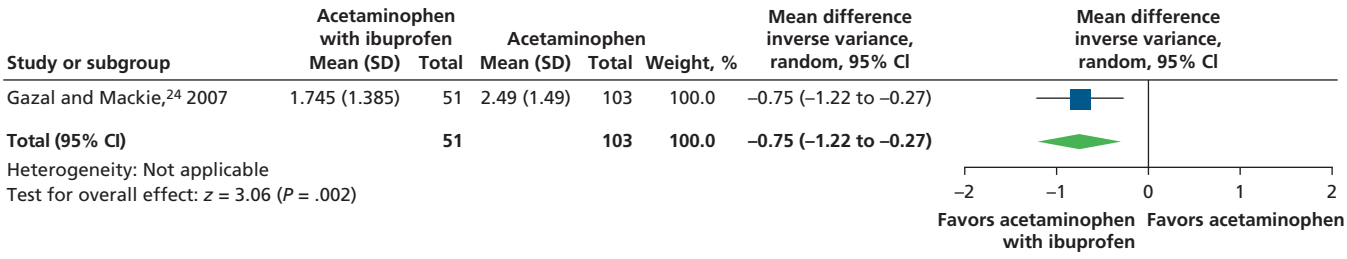
eFigure 1. Pain intensity at 4 hours, acetaminophen vs ibuprofen.



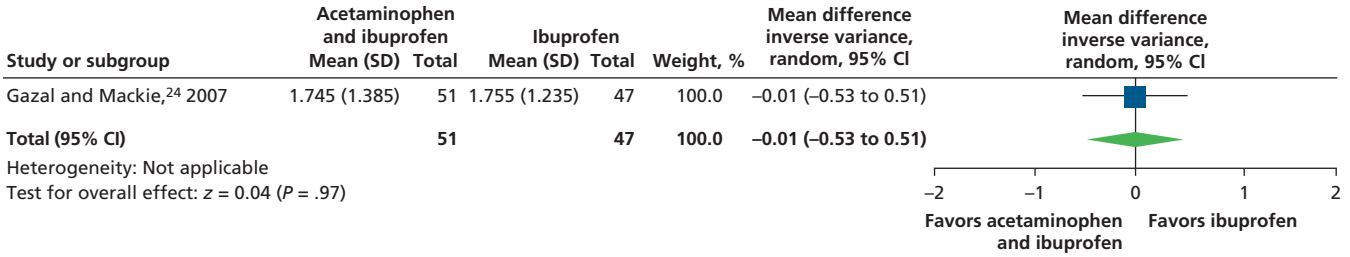
eFigure 2. Pain intensity at 4 hours, ibuprofen vs a placebo.



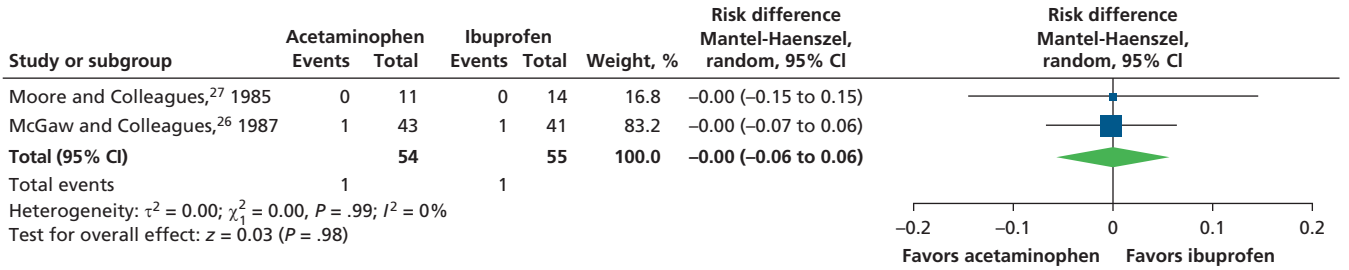
eFigure 3. Pain intensity at 4 hours, acetaminophen vs a placebo.



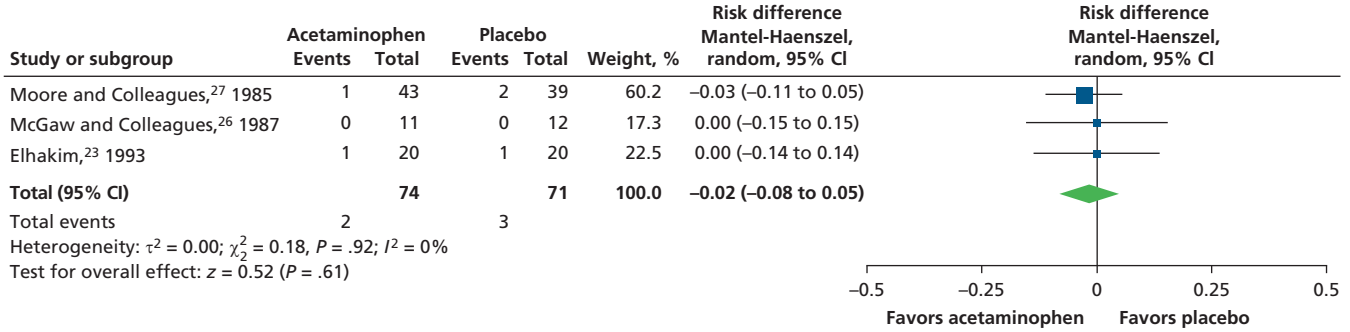
eFigure 4. Pain intensity at 15 minutes after recovery from general anesthesia, acetaminophen with ibuprofen vs acetaminophen.



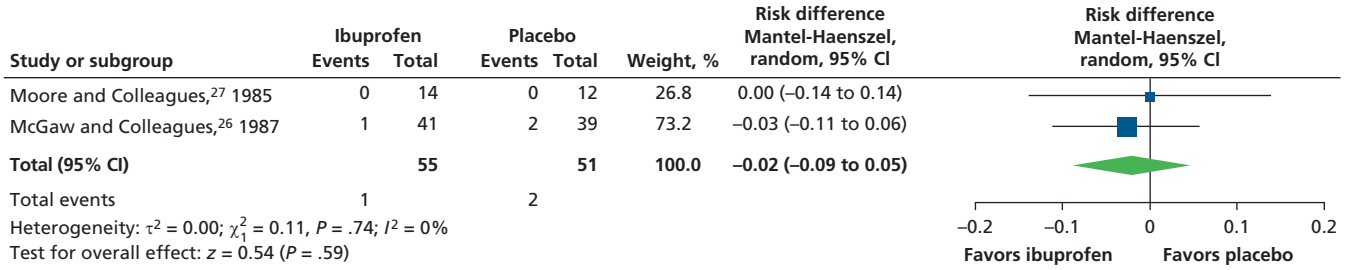
eFigure 5. Pain intensity at 15 minutes after recovery from general anesthesia, acetaminophen and ibuprofen vs ibuprofen.



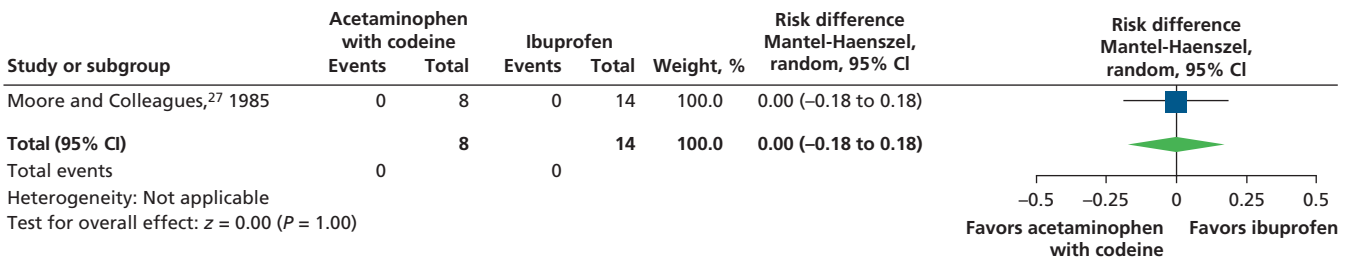
eFigure 6. Any adverse effect, acetaminophen vs ibuprofen.



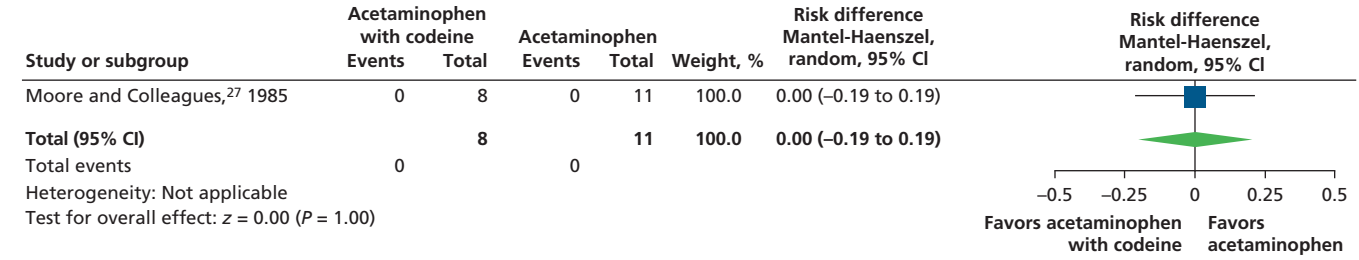
eFigure 7. Any adverse effect, acetaminophen vs a placebo.



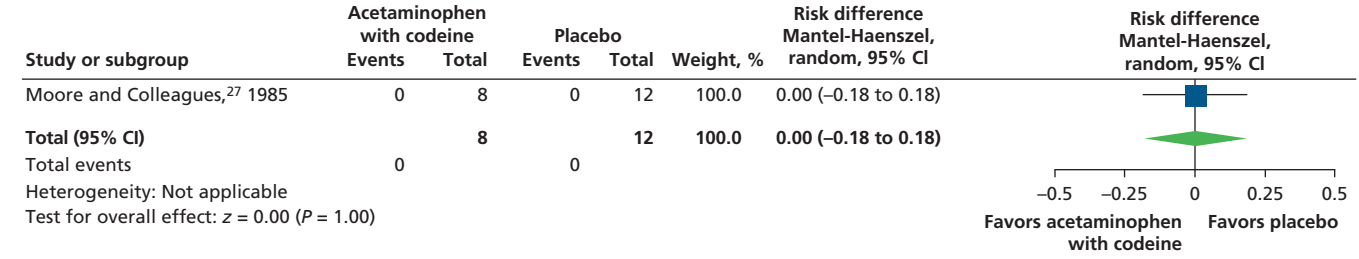
eFigure 8. Any adverse effect, ibuprofen vs a placebo.



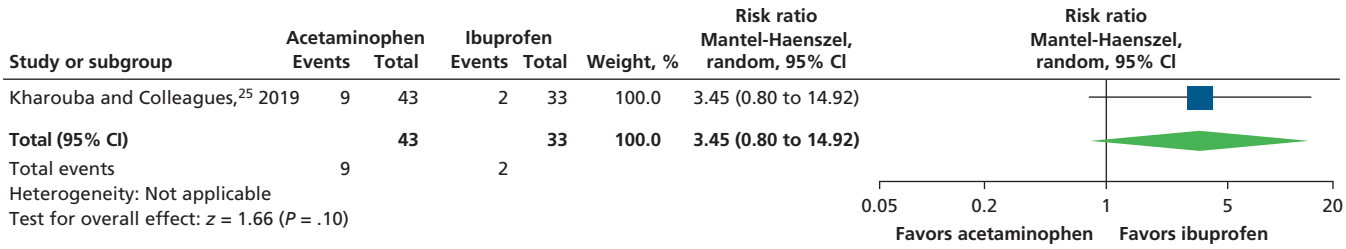
eFigure 9. Any adverse effect (not specified), acetaminophen with codeine vs ibuprofen. $P = 1$ is an artifact of the software system.



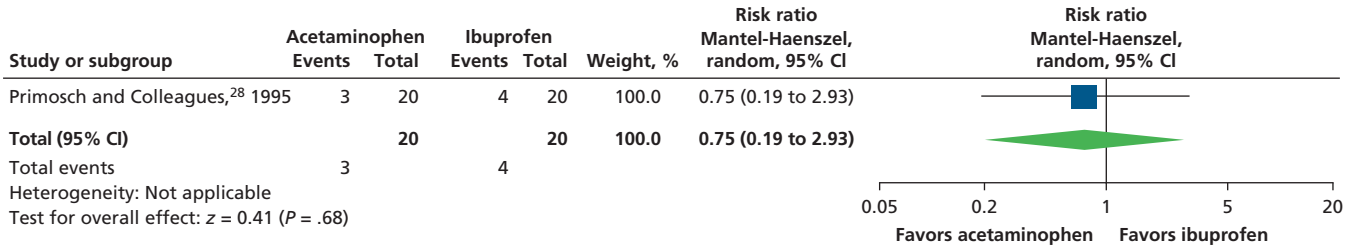
eFigure 10. Any adverse effect (not specified), acetaminophen with codeine vs acetaminophen. $P = 1$ is an artifact of the software system.



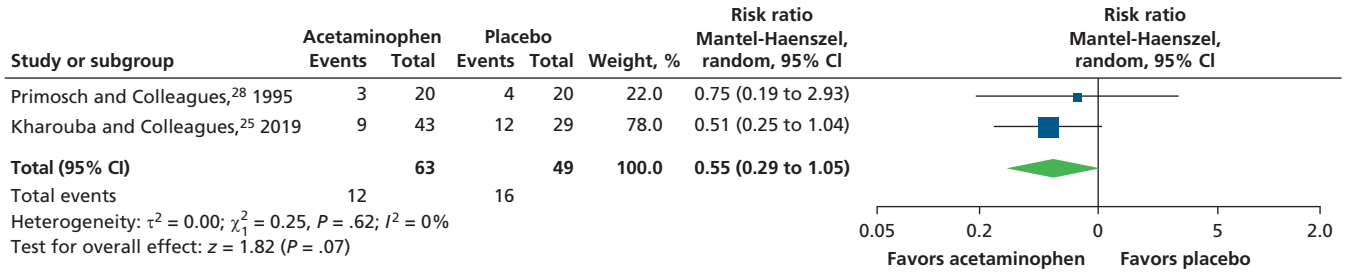
eFigure 11. Any adverse effect (not specified), acetaminophen with codeine vs a placebo. $P = 1$ is an artifact of the software system.



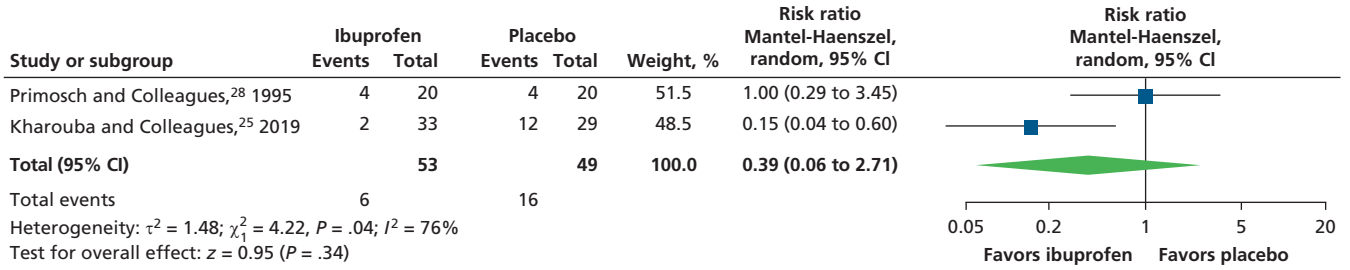
eFigure 12. Rescue analgesia at 4 hours, acetaminophen vs ibuprofen.



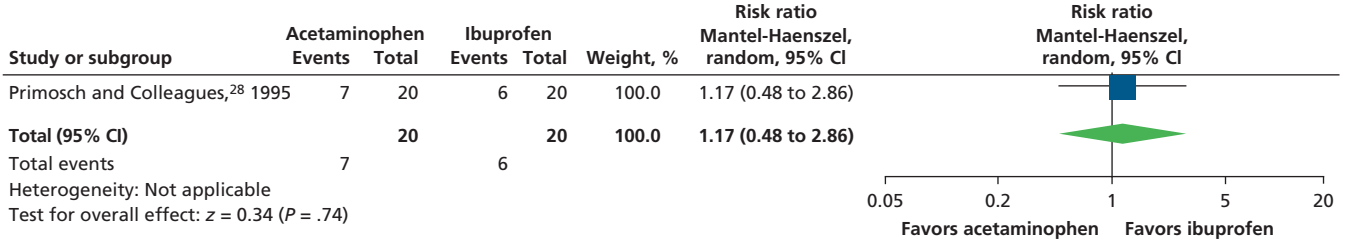
eFigure 13. Rescue analgesia at 7 hours, acetaminophen vs ibuprofen.



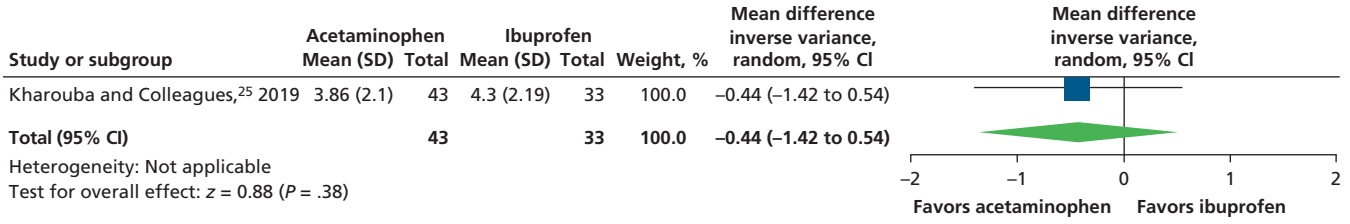
eFigure 14. Rescue analgesia at longest follow-up, acetaminophen vs a placebo.



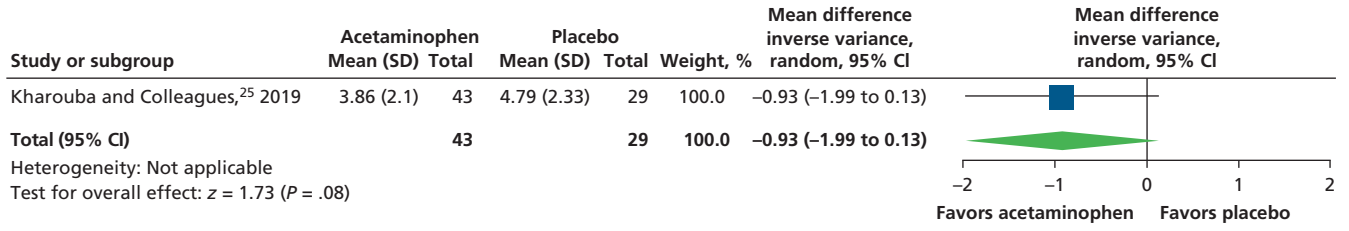
eFigure 15. Rescue analgesia at longest follow-up, ibuprofen vs a placebo.



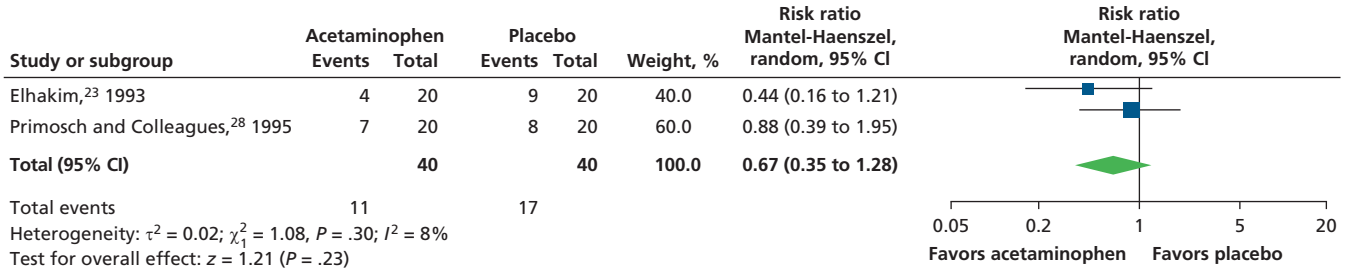
eFigure 16. Presence of pain at longest follow-up, acetaminophen vs ibuprofen



eFigure 17. Children's behavior during extraction, acetaminophen vs ibuprofen.



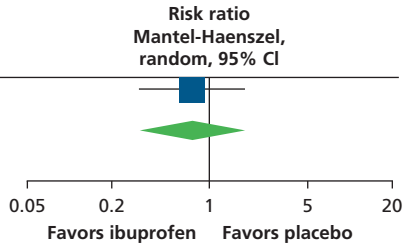
eFigure 18. Children's behavior during extraction, acetaminophen vs a placebo.



eFigure 19. Presence of pain at longest follow-up, acetaminophen vs a placebo.

Study or subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight, %	Risk ratio Mantel-Haenszel, random, 95% CI
Primosch and Colleagues,[28] 1995	6	20	8	20	100.0	0.75 (0.32 to 1.77)
Total (95% CI)		**20**		**20**	**100.0**	**0.75 (0.32 to 1.77)**
Total events	6		8			

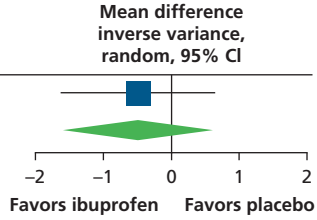
Heterogeneity: Not applicable
Test for overall effect: $z = 0.66$ ($P = .51$)



eFigure 20. Presence of pain at 7 hours, ibuprofen vs a placebo.

Study or subgroup	Ibuprofen Mean (SD)	Ibuprofen Total	Placebo Mean (SD)	Placebo Total	Weight, %	Mean difference inverse variance, random, 95% CI
Kharouba and Colleagues,[25] 2019	4.3 (2.19)	33	4.79 (2.33)	29	100.0	–0.49 (–1.62 to 0.64)
Total (95% CI)		**33**		**29**	**100.0**	**–0.49 (–1.62 to 0.64)**

Heterogeneity: Not applicable
Test for overall effect: $z = 0.85$ ($P = .40$)



eFigure 21. Children's behavior during extraction, ibuprofen vs a placebo.

eTable 1. PRISMA* checklist.

SECTION AND TOPIC	ITEM NO.	CHECKLIST ITEM	LOCATION WHERE ITEM IS REPORTED
Title			
Title	1	Identify the report as a systematic review.	P2†
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist at http://www.prisma-statement.org/Extensions/Abstracts?AspxAutoDetectCookieSupport=1.	P2
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P3
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	P4, eTable 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (for example, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P4
	10b	List and define all other variables for which data were sought (for example, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P4
Effect measures	12	Specify for each outcome the effect measure(s) (for example, risk ratio, mean difference) used in the synthesis or presentation of results.	P4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (for example, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis) (item no. 5).	P4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (for example, subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable

* PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[14] † P: Page.

eTable 1. Continued

SECTION AND TOPIC	ITEM NO.	CHECKLIST ITEM	LOCATION WHERE ITEM IS REPORTED
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P4
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P5
Study characteristics	17	Cite each included study and present its characteristics.	P5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P5, Appendix
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (for example, confidence or credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	P5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (for example, confidence or credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P6-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Appendix
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Appendix
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P7
	23b	Discuss any limitations of the evidence included in the review.	P8
	23c	Discuss any limitations of the review processes used.	Not applicable
	23d	Discuss implications of the results for practice, policy, and future research.	P7-8
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	P8
Competing interests	26	Declare any competing interests of review authors.	P8
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

eTable 2. Sample search strategy.

Database: OVID MEDLINE Epub Ahead of Print, In-Process, and Other Nonindexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946 through Present
1 (pain* and (dental or teeth or tooth or oral or mouth or odont* or endodont*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58334)
2 (pain/ or acute pain/ or exp pain, postoperative/) and (dental or teeth or tooth or oral or mouth or odont* or endodont*).ti,ab. (11066)
3 1 or 2 (58338)
Annotation: dental pain limiter
4 Toothache/ or Pulpitis/ or exp periapical periodontitis/ (10036)
5 (toothache* or odontalg* or pulpitis or apical periodontitis or periapical abscess or endodont*).mp. (30122)
6 4 or 5 (31297)
Annotation: endodontic population
7 3 and 6 (3406)
Annotation: endodontic dental pain
8 Molar, Third/ (6670)
9 exp Tooth Extraction/ (20340)
10 (((third or wisdom or impact* or unerupt*) adj3 (teeth or tooth or molar)) or ((teeth or tooth or molar) adj3 (extract* or remov* or surg*))).mp. (44553)
11 or/8-10 (45201)
Annotation: third molar extraction
12 3 and 11 (3905)
Annotation: third molar extraction pain
13 7 or 12 (6947)
14 3 and (6 or 11) (6947)
Annotation: logic check: dental pain and (endodontic or third molar)
15 random:.tw. or placebo:.mp. or double-blind:.tw. (1291591)
16 ((treatment or control) adj3 group*).ab. (624172)
17 (allocat* adj5 group*).ab. (26592)
18 ((clinical or control*) adj3 trial).ti,ab,kw. (297366)
19 or/15-18 (1798368)
Annotation: modified HIRU RCT filter
20 14 and 19 (2275)
21 exp animals/ not humans.sh. (4768153)
22 20 not 21 (2258)
23 (dh or dt or pc or rh or rt or su or th).fs. (7033700)
24 exp Analgesia/ (44555)
25 exp Analgesics/ (538503)
26 analges*.mp. (197813)
27 treat*.mp. (6135100)
28 therap*.mp. (6259786)
29 intervention*.mp. (1088700)
30 manag*.mp. (1565947)
31 prevent*.mp. (2435611)
32 (surgery or surgical).mp. (3112981)
33 exp Drug Therapy/ (1377452)
34 exp Therapeutics/ (4661006)
35 (antibiotic* or opioid* or steroid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (841008)

eTable 2. Continued

Database: OVID MEDLINE Epub Ahead of Print, In-Process, and Other Nonindexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946 through Present
36 or/23-35 (14241897)
37 22 and 36 (2158)
38 "28858553".fc_acno. (1)
39 "27769675".fc_acno. (1)
40 "27461787".fc_acno. (1)
41 "32318443".fc_acno. (1)
42 "32065309".fc_acno. (1)
43 "29959306".fc_acno. (1)
44 or/38-43 (6)
45 37 and 44 (6)

eTable 3. Risk of bias assessment.

STUDY	RANDOMIZATION	DEVIATIONS FROM THE INTENDED INTERVENTION	MISSING OUTCOME DATA	MEASUREMENT OF OUTCOME	SELECTION OF THE REPORTED RESULTS
Pain Intensity at 4 H					
Moore and colleagues,[27] 1985	Probably low	Low	High		High
McGaw and colleagues,[26] 1987	Probably low	Low	Low	Low	High
Gazal and Mackie,[24] 2007	Low	Low	Low	Low	Low
Kharouba and colleagues,[25] 2019	Low	Low	Probably low	Low	High
Pain Relief at 4 H					
Moore and colleagues,[27] 1985	Probably low	Low	Low	Low	High
McGaw and colleagues,[26] 1987	Probably low	Low	High	Probably low	High
Global Subjective Efficacy Rating at 4 H					
Moore and colleagues,[27] 1985	Probably low	Low	High	Probably low	High
McGaw and colleagues,[26] 1987	Probably low	Low	Low	Low	High
Rescue Analgesia					
Elhakim,[23] 1993	Probably high	High	Probably low	Probably low	High
Primosch and colleagues,[28] 1995	Low	Low	Low	Low	Low
Kharouba and colleagues,[25] 2019	Low	Low	Probably high	Low	Low
Any Adverse Effect					
Moore and colleagues,[27] 1985	Probably low	Low	High	Probably low	Probably high
McGaw and colleagues,[26] 1987	Probably low	Low	Low	Low	Probably high
Elhakim,[23] 1993	Probably high	Probably high	Probably low	Low	Low
Number of Patients with Pain at Longest Follow-up (1-7 H)					
Elhakim,[23] 1993	Probably high	Probably high	Probably low	Low	Low
Primosch and colleagues,[28] 1995	Low	Low	Low	Low	Low
Child's Behavior					
Kharouba and colleagues,[25] 2019	Low	Low	Probably low	Low	Low
Pain Intensity at 24 H					
Kharouba2 and colleagues,[25] 019	Low	Low	Probably low	Low	High
Pain at 15 Min After Recovery From Anesthesia					
Gazal and Mackie,[24] 2007	Low	Low	Low	Low	Low

eTable 4. Acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg) vs acetaminophen (15 mg/kg or 20 mg/kg) for acute dental pain in children.

OUTCOME	PARTICIPANTS, NO. (STUDIES)	RELATIVE EFFECT (95% CI)*	ANTICIPATED ABSOLUTE EFFECTS (95% CI)			CERTAINTY (GRADE†)	WHAT HAPPENS
			With Acetaminophen (15 mg/kg or 20 mg/kg)	With Acetaminophen (15 mg/kg) and Ibuprofen (5 mg/kg)	Difference		
Pain Intensity Assessed With Scale From 1 (None) to 4 (Severe); Follow-up, 15 Min After Recovery From General Anesthesia	154 (1 randomized controlled trial)	Data not generated	Mean pain intensity, 2.49 points	Data not generated	Mean difference, 0.75 points lower (1.22 lower to 0.27 lower)	Moderate‡	Acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg) probably reduces pain intensity 15 min after recovery from general anesthesia by an important amount compared with acetaminophen (15 mg/kg or 20 mg/kg.
Adverse Effect, Not Measured	–§	–	–	–	–	–	–
Rescue Analgesia, Not Measured	–	–	–	–	–	–	–
Pain Relief, Not Measured	–	–	–	–	–	–	–
Global Subjective Efficacy, Not Measured	–	–	–	–	–	–	–
Total Pain Relief, Not Measured	–	–	–	–	–	–	–
Summed Pain Intensity Difference, Not Measured	–	–	–	–	–	–	–

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† GRADE: Grading of Recommendations Assessment, Development and Evaluation. The GRADE Working Group grades of evidence are as follows. High certainty: Very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[21,22] ‡ Using a threshold of 0.3 points (based on 10% of the range of the scale), the lower bound of the 95% CI suggests an important difference favoring acetaminophen (15 mg/kg) and (ibuprofen 5 mg/kg), whereas the upper bound of the 95% CI suggests a negligible benefit of this intervention. Therefore, we rated down 1 level owing to imprecision. § –: Data not found.

eTable 5. Acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg) vs ibuprofen (5 mg/kg) for acute dental pain in children.

OUTCOME	PARTICIPANTS, NO. (STUDIES)	RELATIVE EFFECT (95% CI)*	ANTICIPATED ABSOLUTE EFFECTS (95% CI)			CERTAINTY (GRADE†)	WHAT HAPPENS
			With Ibuprofen (5 mg/kg)	With Acetaminophen (15 mg/kg) and Ibuprofen (5 mg/kg)	Difference		
Pain Intensity Assessed With Scale From 1 (None) to 4 (Severe); Follow-up, 15 Min After Recovery From Anesthesia	98 (1 randomized controlled trial)	Data not generated	Mean pain intensity, 1.76 points	Data not generated	Mean difference, 0.01 points lower (0.53 lower to 0.51 higher)	Moderate‡	Acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg) probably reduces pain intensity 15 min after recovery from anesthesia by a negligible amount compared with ibuprofen (5 mg/kg).
Adverse Effect, Not Measured	–§	–	–	–	–	–	–
Rescue Analgesia, Not Measured	–	–	–	–	–	–	–
Pain Relief, Not Measured	–	–	–	–	–	–	–
Global Subjective Efficacy, Not Measured	–	–	–	–	–	–	–
Total Pain Relief, Not Measured	–	–	–	–	–	–	–
Summed Pain Intensity Difference, Not Measured	–	–	–	–	–	–	–

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† GRADE: Grading of Recommendations Assessment, Development and Evaluation. The GRADE Working Group grades of evidence are as follows. High certainty: Very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[21,22] ‡ Using a threshold of 0.3 points (based on 10% of the range of the scale), the lower bound of the 95% CI suggests an important difference favoring acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg), whereas the upper bound of the 95% CI suggests an important difference favoring ibuprofen (5 mg/kg). Therefore, we rated down 1 level owing to imprecision. § –: Data not found.

eTable 6. Acetaminophen (240 mg) with codeine (24 mg) vs aluminum ibuprofen (200 mg) for acute dental pain in children.

OUTCOME	PARTICIPANTS, NO. (STUDIES)	RELATIVE EFFECT (95% CI)*	ANTICIPATED ABSOLUTE EFFECTS (95% CI)			CERTAINTY (GRADE†)	WHAT HAPPENS
			With Aluminum Ibuprofen (200 mg)	With Acetaminophen (240 mg) with Codeine (24 mg)	Difference		
Any Adverse Effects (Not Specified); Follow-up, 4 H	22 (1 RCT‡)	Not estimable	0.0%	0.0%	0.0% fewer (18% fewer to 18% more)	Very Low§,¶	There is very low certainty evidence on the difference between acetaminophen (240 mg) with codeine (24 mg) and aluminum ibuprofen (200 mg) with regard to incidence of adverse effects.
Pain Intensity Assessed With Ordinal Scale From 1 (None) to 4 (Severe); Follow-up, 4 H	22 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) decreased pain intensity compared with aluminum ibuprofen (200 mg) (MD,# −0.29 points). To compare, the mean pain intensity in the aluminum ibuprofen group was 1.29 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine 24mg may reduce pain intensity at 4 h by a negligible amount compared with aluminum ibuprofen (200 mg).
Pain Relief Assessed With Ordinal Scale From 1 (Complete) to 5 (None); Follow-up, 4 H	22 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) increased pain relief compared with aluminum ibuprofen (200 mg) (MD, −0.29 points). To compare, the mean pain relief in the aluminum ibuprofen group was 1.29 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine 24 mg may increase pain relief at 4 h by a negligible amount compared with aluminum ibuprofen (200 mg).
Global Efficacy Rating Assessed With Ordinal Scale From 1 (Excellent) to 5 (Discontinued); Follow-up 4 H	22 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) was rated as less efficacious at the end of the study period than aluminum ibuprofen (200 mg) (MD, 0.24 points). To compare, the mean global rating in the aluminum ibuprofen group was 1.64 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may be rated as less efficacious at 4 h by a negligible amount than aluminum ibuprofen (200 mg).
Total Pain Relief, Not Measured	–‡‡	–	–	–	–	–	–
Summed Pain Intensity Difference, Not Measured	–	–	–	–	–	–	–
Rescue Analgesia, Not Measured	–	–	–	–	–	–	–

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† GRADE: Grading of Recommendations Assessment, Development and Evaluation. The GRADE Working Group grades of evidence are as follows. High certainty: Very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[21,22] ‡ RCT: Randomized controlled trial. § This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. There are also concerns regarding selective outcome reporting as the number of patients analyzed for this outcome was unclear. Therefore, we rated down 1 level owing to risk of bias. ¶ The optimal information size of 100 participants was not met. Therefore, we rated down 2 levels owing to imprecision. # MD: Mean difference. ** This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. There was also a high risk of selective outcome reporting owing to the lack of measures of variability. Therefore, we rated down 1 level owing to risk of bias. †† The optimal information size of 100 participants was not met. Therefore, we rated down 1 level owing to imprecision. ‡‡ –: Data not found.

eTable 7. Acetaminophen (240 mg) with codeine (24 mg) vs acetaminophen (240 mg or 360 mg) for acute dental pain in children.

OUTCOME	PARTICIPANTS, NO. (STUDIES)	RELATIVE EFFECT (95% CI)*	ANTICIPATED ABSOLUTE EFFECTS (95% CI)			CERTAINTY (GRADE†)	WHAT HAPPENS
			With Acetaminophen (240 mg or 360 mg)	With Acetaminophen (240 mg) With Codeine (24 mg)	Difference		
Any Adverse Effects (Not Specified); Follow-up, 4 H	19 (1 RCT‡)	Not estimable	0.0%	0.0%	0.0% fewer (19% fewer to 19% more)	Very low§,¶	There is very low certainty evidence on the difference between acetaminophen (240 mg) with codeine 24 mg and acetaminophen (240 mg or 360 mg) with regard to incidents of adverse effects.
Pain Intensity Assessed With Ordinal Scale Fr**om 1 (None) to 4 (Severe); Follow-up, 4 H**	19 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) decreased pain intensity compared with acetaminophen (240 mg or 360 mg) alone (MD,# −0.09 points). To compare, the mean pain intensity in the acetaminophen group was 1.09 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may decrease pain intensity at 4 h by a negligible amount compared with acetaminophen (240 mg or 360 mg) alone.
Pain Relief Assessed With: Ordinal Scale From 1 (Complete) to 5 (None); Follow-up; 4 H	19 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) increased pain relief compared with acetaminophen (240 mg or 360 mg) alone (MD, −0.36 points). To compare, the mean pain relief in the acetaminophen group was 1.36 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may increase pain relief at 4 h by a negligible amount compared with acetaminophen (240 mg or 360 mg) alone.
Global Rating Assessed With: Ordinal Scale From 1 (Excellent) to 5 (Discontinued); Follow-up, 4 H	19 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) was rated as more efficacious at the end of the study period than acetaminophen (240 mg or 360 mg) alone (MD, −0.57 points). To compare, the mean global rating in the acetaminophen group was 2.45 points. No SDs or *P* values were provided for this time point.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may be rated as more efficacious at 4 h by an important amount than acetaminophen (240 mg or 360 mg) alone.
Total Pain Relief, Not Measured	–‡‡	–	–	–	–	–	–
Summed Pain Intensity Difference, Not Measured	–	–	–	–	–	–	–
Rescue Analgesia, Not Measured	–	–	–	–	–	–	–

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† GRADE: Grading of Recommendations Assessment, Development and Evaluation. The GRADE Working Group grades of evidence are as follows. High certainty: Very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[21,22] ‡ RCT: Randomized controlled trial. § This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. There are also concerns regarding selective outcome reporting as the number of patients analyzed for this outcome was unclear. Therefore, we rated down 1 level owing to risk of bias. ¶ The optimal information size of 100 participants was not met. Therefore, we rated down 2 levels owing to imprecision. # MD: Mean difference. ** This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. There was also a high risk of selective outcome reporting owing to the lack of measures of variability. Therefore, we rated down 1 level owing to risk of bias. †† The optimal information size of 100 participants was not met. Therefore, we rated down 1 level owing to imprecision. ‡‡ –: Data not found.

eTable 8. Acetaminophen (240 mg) with codeine (24 mg) vs a placebo for acute dental pain in children.

OUTCOME	PARTICIPANTS, NO. (STUDIES)	RELATIVE EFFECT (95% CI)*	ANTICIPATED ABSOLUTE EFFECTS (95% CI)			CERTAINTY (GRADE†)	WHAT HAPPENS
			With a Placebo	With Acetaminophen (240 mg) With Codeine (24 mg)	Difference		
Any Adverse Effects (Not Specified); Follow-up, 4 H	20 (1 RCT‡)	Not estimable	0.0%	0.0%	0.0% fewer (18% fewer to 18% more)	Very low§,¶	There is very low certainty evidence on the difference between acetaminophen (240 mg) with codeine (24 mg) and a placebo with regard to incidents of adverse effects.
Pain Intensity Assessed With Ordinal Scale From 1 (None) to 4 (Severe); Follow-up, 4 H	20 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) decreased pain intensity compared with a placebo (MD,# −0.16 points). To compare, the mean pain intensity in the placebo group was 1.16 points. SDs and exact *P* values were not provided; the authors stated that there was no significant difference between interventions.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may decrease pain intensity at 4 h by a negligible amount compared with a placebo.
Pain Relief Assessed With Ordinal Scale From 1 (Complete) to 5 (None); Follow-up; 4 H	20 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) increased pain relief compared with a placebo (MD, −0.17 points). To compare, the mean pain relief in the placebo group was 1.17 points. SDs and exact *P* values were not provided; the authors stated that there was no significant difference between interventions.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may increase pain relief at 4 h by a negligible amount compared with a placebo.
Global Rating Assessed With Ordinal Scale From 1 (Excellent) to 5 (Discontinued); Follow-up, 4 H	20 (1 RCT)	Acetaminophen (240 mg) with codeine (24 mg) was rated as more efficacious at the end of the study period than a placebo (MD, −0.87 points). To compare, the mean global rating in the placebo group was 2.75 points. SDs and exact *P* values were not provided; the authors stated that there was no significant difference between interventions.				Low**,††	Acetaminophen (240 mg) with codeine (24 mg) may be rated as more efficacious at 4 h by an important amount than a placebo.
Total Pain Relief, Not Measured	–‡‡	–	–	–	–	–	–
Summed Pain Intensity Difference, Not Measured	–	–	–	–	–	–	–
Rescue Analgesia, Not Measured	–	–	–	–	–	–	–

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† GRADE: Grading of Recommendations Assessment, Development and Evaluation. The GRADE Working Group grades of evidence are as follows. High certainty: Very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.[21,22] ‡ RCT: Randomized controlled trial. § This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. For the outcome of adverse effects, there were also concerns regarding selective outcome reporting. Therefore, we rated down 1 level owing to risk of bias. ¶ The optimal information size of 100 participants was not met. Therefore, we rated down 2 levels owing to imprecision. # MD: Mean difference. ** This study was at a high risk of bias owing to missing outcome data for more than 20% of eligible patients. There was also a high risk of selective outcome reporting owing to the lack of measures of variability. Therefore, we rated down 1 level owing to risk of bias. †† The optimal information size of 100 participants was not met. Therefore, we rated down 1 level owing to imprecision. ‡‡ –: Data not found.