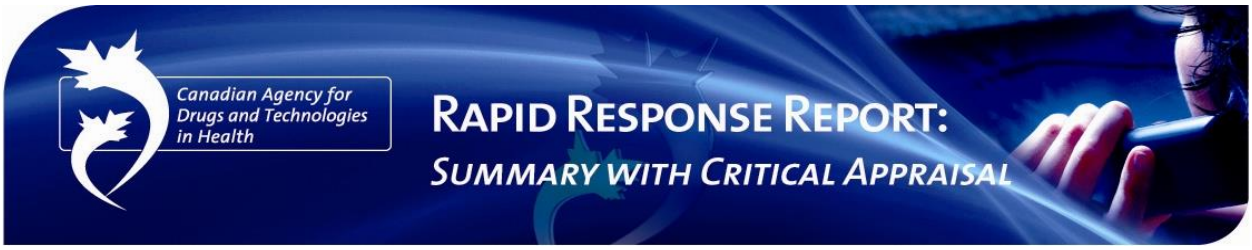

TITLE: 1000 mg versus 600/650 mg Acetaminophen for Pain or Fever: A Review of the Clinical Efficacy

DATE: 17 June 2016

CONTEXT AND POLICY ISSUES

Acetaminophen, or paracetamol, a non-opiate, centrally acting analgesic and antipyretic agent, is a widely used over-the-counter drug for pain or fever.[1] In Canada, over 4 billion doses of acetaminophen (e.g., pills) are sold each year, and approximately 15% of these sales are prescription products.[2] Acetaminophen is generally well tolerated with minor side effects such as nausea, stomach pain and rash, but there is a risk of liver toxicity after overdose.[3-7]

Acetaminophen overdoses are responsible for an estimated 4,000 hospitalizations a year in Canada.[8] There are more than 250 cases of serious liver injury in Canada each year related to acetaminophen, and over half of those are due to unintentional overdose.[8] Acetaminophen usually comes in two forms: regular strength (300/325 mg pills) and extra strength (500 mg pills). The nonprescription acetaminophen label instructs adults or children ≥12 years old to take single doses of 650 mg (2x325mg) every 4 to 6 hours, or 1000 mg (2x500mg) every 6 hours while symptoms last (the maximum recommended daily dose is 4 grams). Health Canada is considering additional steps to minimize the risk of liver damage and improve acetaminophen safety such as suggesting a decrease in the maximum recommended daily dose.[9]

This Rapid Response report aims to review the recent evidence on the clinical efficacy of acetaminophen 1000 mg versus 600/650 mg for pain and fever.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy of 1000 mg acetaminophen compared with 600/650 mg acetaminophen for the treatment of pain?

2. What is the comparative clinical efficacy of 1000 mg acetaminophen compared with 600/650 mg acetaminophen for managing fever?

KEY FINDINGS

Acetaminophen 1000 mg single dose led to a higher percentage of people with at least 50% of pain relief over six hours, and a larger decrease in pain intensity, as compared to acetaminophen 650 mg in various acute post-operative pain conditions. Statistical significance of the differences in efficacy between the two doses was not reported in some studies. And in one study the number needed to treat to achieve benefit for one patient was not statistically different between doses. The risk of adverse events was similar between the two doses, and there were no serious adverse events reported with both doses. There was no evidence found on the comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the management of fever. Comparative studies on the recommended maximum daily dose and long term use of acetaminophen are needed.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses. A second, focused search, with main concepts appearing in title or major subject heading was conducted, with a filter applied for randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and May 17, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults experiencing pain or fever
Intervention	1000 mg oral acetaminophen
Comparator	650 mg/600 mg oral acetaminophen
Outcomes	Pain management, fever reduction, safety and harms
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2011, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic review and clinical trials was assessed using the AMSTAR[10] and Downs and Black[11] checklists, respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 690 citations. After screening of abstracts from the literature search and from other sources, five potentially relevant studies were selected for full-text review. Three studies were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

Study design, population, interventions and comparators, outcomes

A detailed summary of the characteristics of the included systematic reviews and clinical studies is provided in Appendices 2 and 3, respectively.

Two systematic reviews of reviews,[12,13] and one RCT[14] were included. One systematic review[12] included systematic reviews or meta-analyses comparing ibuprofen and different doses of oral acetaminophen in different pain conditions in adults and children. One systematic review[13] included Cochrane reviews of RCTs comparing the efficacy and safety single dose oral analgesics for acute postoperative pain in patients ≥ 15 years old; data was from 13 trials on acetaminophen 600/650 mg (1522 patients) and from 19 trials on acetaminophen 975/1000 mg (2342 patients). The two systematic reviews are from the same group of authors and reported overlapping data. The RCT is a double-blind, placebo-controlled trial and compared efficacy and safety of single dose acetaminophen 1000 mg to acetaminophen 650 mg for the treatment of postsurgical dental pain in patients aged 16 to 50 years.[14]

Summary of Critical Appraisal

The included systematic reviews of reviews performed meta-analyses, provided an a priori design and performed a comprehensive literature search.[12,13] One review was a Cochrane review and included reviews of RCTs, and satisfied all the criteria specified in the AMSTAR measurement tool (e.g. comprehensive literature search, duplicate article selection and data extraction, quality appraisal of the included evidence, lists of included and excluded studies, and clear conflict of interest statement).[13] One review included reviews that included both RCTs and non-RCTs, did not provide a list of included or excluded studies and study characteristics, and did not report a quality assessment of included studies, with no obvious independent selection and data extraction procedure.[12] It is not clear whether publication bias was assessed in both reviews.

The included clinical study was an RCT and had hypotheses, method of selection from source population and representation, main outcomes, interventions, patient characteristics, main

findings, estimates of random variability and actual probability values, and losses to follow-up clearly described.[14] Demographics and patients characteristics were balanced between groups. The randomization method was clearly described, patients were randomly assigned to receive study medication, the study was double-blinded, and the patient population was representative of the types of patients who would receive the intervention.

The included systematic reviews and studies reported data on single doses of acetaminophen; the generalizability of the findings to the efficacy and safety of acetaminophen resulting from the use of maximum daily doses and long term use may thus be limited.

Details of the strengths and limitations of the included studies are summarized in Appendix 4.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 5.

1. What is the comparative clinical efficacy of 1000 mg acetaminophen compared with 600/650 mg acetaminophen for the treatment of pain?

One review included systematic reviews/meta analyses that compared the efficacy of ibuprofen and acetaminophen at different doses in reducing pain in various pain conditions in adults and children.[12] The data that is relevant to this Rapid Response review was on the efficacy of single dose acetaminophen in acute post-operative pain that was from a 2008 study which included 51 double-blind RCTs (5762 participants) published from 1996 to 2008.[15] Nineteen studies (1886 participants) compared acetaminophen 600/650 mg to placebo and 28 studies (3232 participants) compared acetaminophen 975 mg - 1000 mg with placebo. The remaining studies examined doses not of interest for this review. Efficacy was defined as the percentage of patients with at least 50% of pain relief over 6h. In all surgery, as well as in dental pain, acetaminophen 1000 mg was more efficacious than acetaminophen 600/650 mg. Number-needed-to-treat (NNT) data showed that it took fewer patients receiving acetaminophen 1000 mg in order to get one patient with beneficial effect, compared to acetaminophen 600/650 mg. The difference in NNT was not statistically significant. Details on NNT are listed in Appendix 5.

All surgery

The systematic review of reviews[12] reported that 46% of patients taking acetaminophen 1000 mg had at least 50% of pain relief over 6 hour compared to 38% taking 600/650 mg (statistical significance not provided).

Dental

The systematic review of reviews[12] reported that 41% of patients taking acetaminophen 1000 mg had at least 50% of pain relief over 6 hour compared to 35% taking 600/650 mg (statistical significance not provided).

A double-blind, randomized placebo-controlled trial compared the efficacy and safety of single dose acetaminophen 1000 mg to acetaminophen 650 mg for the treatment of postsurgical dental pain in patients aged 16 to 50 years.[14] Data showed that acetaminophen 1000 mg provided statistically significantly greater efficacy in treating postsurgical dental pain compared

with acetaminophen 650 mg. Efficacy was defined as the sum of pain relief and pain intensity difference from baseline scores over 6 hours (SPRID6), using the VAS (Visual Analog Scale)

There was a 24% improvement in mean SPRID6 in patients treated with acetaminophen 1000 mg compared with patients treated with acetaminophen 650 mg (529.4 vs 427.3; *P*< 0.001). 18.8% of patients taking acetaminophen 1000 mg reported adverse events compared to 17.4% taking 600/650 mg.

Other (non-dental)

59% of patients taking acetaminophen 1000 mg had at least 50% of pain relief over 6 hour compared to 43% taking 600/650 mg (statistical significance not provided).

Safety

One Cochrane review included reviews of RCTs that compared efficacy and safety single dose oral analgesics for acute postoperative pain in patients ≥ 15 years old.[13] This review reported the same efficacy data than the previous review and additionally reported safety data for acetaminophen 975/1000 mg and acetaminophen 600/650 mg. 18% of patients taking acetaminophen 1000 mg had at least one adverse event (headache, nausea or dizziness) compared to 16% taking 600/650 mg. The risk of having adverse events is similar between the two doses.

The RCT[14] reported that for the treatment of postsurgical dental pain, there were no serious adverse and no withdrawals from treatment due to adverse events in all groups. The adverse events reported by ≥5% of patients were nausea, vomiting and dizziness.

2. What is the comparative clinical efficacy of 1000 mg acetaminophen compared with 600/650 mg acetaminophen for the treatment of fever?

There was no evidence found on the comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the management of fever.

Limitations

Evidence on the comparative efficacy and safety of acetaminophen 1000 mg and 650 mg was limited to post-surgical pain conditions only. The statistical significance of some outcomes was unclear, increasing the uncertainty of the conclusions. Furthermore, the clinical significance of the observed differences is unknown. All studies reported data on single dose acetaminophen; more studies on the currently recommended maximum daily dose and long-term use of acetaminophen are needed. There was no evidence found on the comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the management of fever.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Acetaminophen 1000 mg single dose led to a higher percentage of people with at least 50% of pain relief over 6 hour, and a larger decrease in pain intensity, as compared to acetaminophen 650 mg in various acute post-operative pain conditions. Statistical significance of the differences in efficacy between the two doses was not reported in some studies. The NNT was lower for patients receiving acetaminophen 1000 mg in order to get one patient with beneficial effect, compared to acetaminophen 600/650 mg, but this difference was not statistically significant. The risk of adverse events was similar between the two doses, and there was no serious adverse events reported with both doses. The generalizability of the findings on the long term efficacy and safety of acetaminophen from the included systematic reviews and study may be limited since the reported data were on single dose acetaminophen.

Our conclusions agree with reports from The Food and Drug Administration (FDA) in 2002 that found early evidence, provided by the manufacturer, that 1000 mg single dose is more effective than 650 mg single dose in various pain conditions.[16,17] The FDA report encourages using the lowest effective dose and suggests to reduce the maximum single dose from 1000 mg to 650 mg, though the rationale for this recommendation was not provided; comparative studies on the currently recommended maximum daily dose (4 grams) and long term use of acetaminophen are needed.

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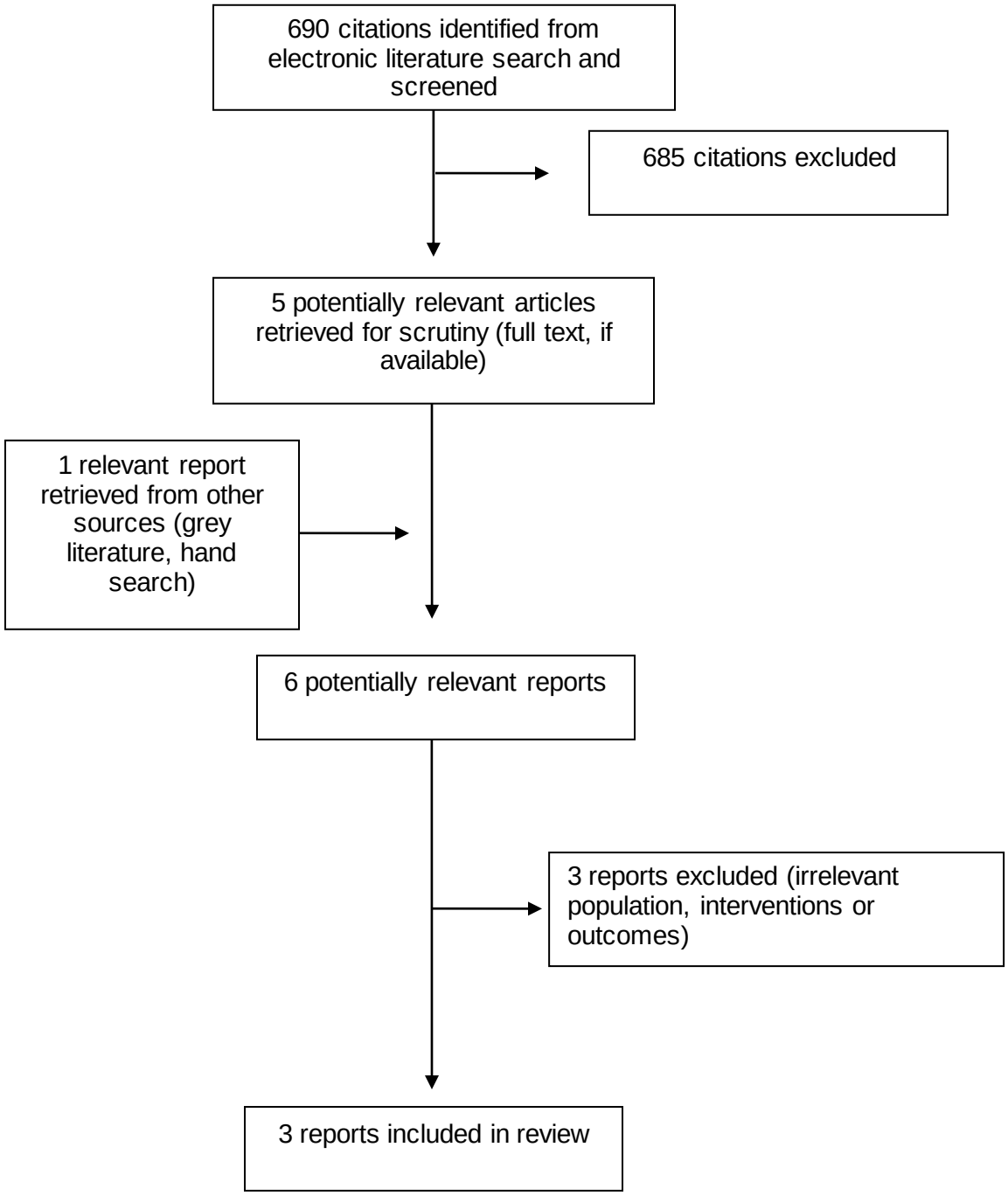
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Systematic Reviews

Table A1: Characteristics of Included Systematic Reviews

First Author, Year, Country	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Studies included Main outcomes
Moore,[12] 2015, UK, Canada	*"Searches were conducted using PubMed and the Cochrane Library (CENTRAL) using the generic form of 'pain' [tiab – restriction to title and abstract only] AND 'ibuprofen' [tiab] or paracetamol' [tiab] AND 'pain condition' [tiab], with filters of human, systematic review and metaanalysis… There was no language restriction, but we included only studies published since 1995 to ensure that information was reasonably up-to-date"* (p 1214)	*"We performed a series of electronic searches for systematic reviews or meta-analyses reporting on the analgesic efficacy of oral ibuprofen alone or oral paracetamol alone compared with placebo"* (p 1214)	*"We excluded reviews that were obviously superseded by subsequent or updated reviews, as in Cochrane reviews"* (p 1214)	One review included for the outcomes on efficacy of different doses of paracetamol Efficacy of paracetamol 1000mg vs paracetamol 600/650 mg in acute post-operative pain (all surgery, dental and non-dental) Efficacy (percent of patients with at least 50% of pain relief over 6h; number-needed-to treat)
Moore,[13] 2015, UK	*"We searched the Cochrane Database of Systematic Reviews Issue 4 on The Cochrane Library for relevant reviews"* (p 5)	*"All Cochrane reviews of randomised controlled trials (RCTs) of single dose oral analgesics for acute postoperative pain in adults (aged 15 years or over)"* (p 4)	*"We limited the overview to medication available in the UK because it is almost impossible to know with certainty what is available in other parts of the world"*(p 4)	Efficacy and safety of paracetamol 975/1000mg vs paracetamol 600/650 mg in acute post-operative pain (all surgery) Efficacy (percent of patients with at least 50% of pain relief over 6h) Safety (percent of patients with at least 1 adverse event; risk ratio)

Appendix 3: Characteristics of Included Clinical Studies

Table A2: Characteristics of Included Clinical Studies

First Author, Year, Country	Study Objectives	Interventions/Comparators	Patients	Main Study Outcomes
Qi,[14] 2012, US	*"The aim of this study was to assess the relative efficacy of acetaminophen 1000 mg versus acetaminophen 650 mg over a 6-hour period in patients experiencing at least moderate postsurgical dental pain"* (p 2247)	Acetaminophen 1000 mg Acetaminophen 650 mg	*"…patients aged 16 to 50 years who experienced at least moderate pain after surgical removal of impacted third molars"* (p 2247) 239 patients received acetaminophen 100 mg single dose 241 patients received acetaminophen 650 mg single dose 60 patients received placebo	Efficacy: Sum of pain intensity and pain relief relative to baseline scores over 6 hours (SPRID6), using the VAS (Visual Analog Scale) Safety: Adverse events

Appendix 4: Summary of Critical Appraisal of Included Study

Table A3: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
Critical appraisal of included systematic reviews (AMSTAR[10])		
Moore,[12] 2015	• a priori design provided • comprehensive literature search performed • conflict of interest stated	• included systematic reviews of randomized controlled trials or non-randomized controlled trials • list of included systematic reviews, and characteristics not provided • list of excluded systematic reviews not provided • unsure if independent systematic reviews selection and data extraction procedure in place • unsure if quality assessment of included systematic reviews provided and used in formulating conclusions • no assessment of publication bias performed • evidence was from single dose; the safety profile needs to be interpreted with caution
Moore,[13] 2015	• a priori design provided • comprehensive literature search performed • included Cochrane reviews of randomized controlled trials • list of included systematic reviews, and characteristics provided • list of excluded systematic reviews provided • independent systematic reviews selection and data extraction procedure in place quality assessment of included systematic reviews provided and used in formulating conclusions • conflict of interest stated	• no assessment of publication bias performed • evidence was from single dose; the safety profile needs to be interpreted with caution
Critical appraisal of included study (Downs and Black[11])		
Qi,[14] 2012	• hypothesis clearly described • patients randomized, blinded • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described • study had sufficient power to detect a clinically important effect	• this is a single-dose study; the safety profile needs to be interpreted with caution

Appendix 5: Main Study Findings and Authors' Conclusions

Table A4: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
Research question 1 (comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the treatment of pain)		
Moore,[12] 2015	Efficacy of paracetamol 1000mg vs paracetamol 600/650 mg in acute post-operative pain (all surgery, dental and non-dental) All surgery Percent of patients with at least 50% of pain relief over 6h Acetaminophen 600/650 mg: 38% Acetaminophen l 1000 mg: 46% Number-needed-to treat, NNT (95% confidence interval CI) Acetaminophen 600/650 mg: 4.6 (3.9 to 5.5) Acetaminophen 1000 mg: 3.6 (3.2 to 4.1) Dental Percent of patients with at least 50% of pain relief over 6h Acetaminophen l 600/650 mg: 35% Acetaminophen 1000 mg: 41% Number-needed-to treat, NNT (95% confidence interval CI) Acetaminophen 600/650 mg: 4.2 (3.6 to 5.2) Acetaminophen 1000 mg: 3.2 (2.9 to 3.6) Other (non-dental) Percent of patients with at least 50% of pain relief over 6h Acetaminophen 600/650 mg: 43% Acetaminophen 1000 mg: 59% Number-needed-to treat, NNT (95% confidence interval CI) Acetaminophen 600/650 mg: 5.6 (4.0 to 9.5) Acetaminophen 1000 mg: 3.7 (3.1 to 4.7)	Not reported for this comparison
Moore,[13] 2015	Efficacy of paracetamol 975/1000mg vs paracetamol 600/650 mg in acute post-operative pain (all surgery) Percent of patients with at least 50% of pain relief over 6h Acetaminophen 600/650 mg: 38% Acetaminophen 975/1000 mg: 46% Number-needed-to treat, NNT (95% confidence interval CI) Acetaminophen 600/650 mg: 4.6 (3.9 to 5.5) Acetaminophen 975/1000 mg: 3.6 (3.2 to 4.1) Safety Percent of patients with at least 1 adverse event Acetaminophen l 600/650 mg: 16% Acetaminophen 975/1000 mg: 18% Risk ratio (95% CI) Acetaminophen 600/650 mg: 1.2 (0.9 to 1.5) Acetaminophen l 975/1000 mg: 1.1 (0.9 to 1.3)	Not reported for this comparison

Table A4: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
Qi,[14] 2012	Efficacy Sum of pain intensity and pain relief relative to baseline scores over 6 hours (SPRID6), using the VAS (Visual Analog Scale) 24% improvement in mean SPRID6 in patients treated with acetaminophen 1000 mg compared with patients treated with acetaminophen 650 mg (529.4 vs 427.3; *P*< 0.001) Both acetaminophen doses statistically had SPRID6 greater than placebo (60.0 with placebo) Safety Acetaminophen 1000 mg: 18.8% of patients reported adverse events Acetaminophen 650 mg: 17.4% of patients Placebo: 21.7% of patients No serious adverse events reported in all patients groups No withdrawals from treatment due to adverse events in all groups Adverse events reported by ≥5% of patients: nausea, vomiting and dizziness	*"Acetaminophen 1000 mg provided clinically meaningful and statistically significantly greater efficacy in treating postsurgical dental pain compared with acetaminophen 650 mg and placebo. The outcomes of this study are limited to the single-dose design of this study"* (p 2247)
Research question 2 (comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the treatment of fever)		
There is no evidence found on the comparative clinical efficacy of 1000 mg acetaminophen compared with 650 mg acetaminophen for the treatment of fever		