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Intravenous Acetaminophen for the Management of Short-Term Post-Operative Pain: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

AE	adverse event
APAP	acetaminophen
CI	confidence interval
IV	intravenous
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
RCT	randomized controlled trial
SR	systematic review
VAS	visual analog scale

Context and Policy Issues

Acute pain in the post-operative setting is common and often sub-optimally managed.[1] Furthermore, this pain is often associated with poor outcomes, including longer hospital stays, delayed mobilization, higher rates of medical complications, and decreased patient satisfaction.[2] There is also a risk of long-term complications from untreated post-operative pain, including worsening functional outcomes and chronic pain syndromes.[2,3]

Monotherapy with opioids has previously been the mainstay of treatment for post-operative pain, however these agents are associated with various adverse events, such as nausea, vomiting, and constipation, which can result in significant discomfort and possibly increase hospital stays.[4] More severe adverse events include respiratory depression and sedation, which can increase risk of respiratory failure, aspiration, decreased mobility, and falls.[1] One study estimated that there was a 3% incidence of prolonged opioid use following major elective surgery.[5] Multimodal analgesia is currently the preferred approach to treating post-operative pain, utilizing different classes of analgesics with different pathways and receptors.[3] Systemic analgesics, such as NSAIDs, acetaminophen, antidepressants, and alpha$_2$ receptor agonists, as well as local anesthetics, can reduce activation of pain receptors and the production or activity of pain-related neurotransmitters.[3] This ultimately results in lower doses of respective agents required to lessen side effects while providing adequate analgesia.[3] Multimodal analgesia is able to improve recovery outcomes after surgery, ensuring rehabilitation while reducing overall costs.[6,7]

Acetaminophen is a widely used analgesic that is a nonopioid option in multimodal analgesia. It is able to easily pass through the blood-brain barrier, and is able to reach high concentration levels in the cerebrospinal fluid.[8] The mechanism by which acetaminophen prevents and reduces pain is yet to be fully elucidated.[9] It is believed to provide analgesic effects by preventing prostaglandin production in the central nervous system and working peripherally to inhibit pain impulses. Given its favourable safety profile, it has become a common household drug and has been available in oral form since 1950.[10] Oral acetaminophen is commonly used as an analgesic several days after surgery since slowed gastric emptying and enteral absorption in the first 24 hours after surgery has limited its use in the early perioperative setting, even when administered rectally.[11-14]

Recently, acetaminophen has been made available in intravenous (IV) form, which has provided an opportunity for it to be used in perioperative and early post-operative period. After IV administration of acetaminophen, a rapid and high plasma concentration has been achieved within five minutes, and pain relief occurs within a few minutes.[15] IV

acetaminophen can theoretically enhance bioavailability and provide an earlier onset of analgesic effect in the immediate postoperative period.[8] Compared to rectal or oral administration, IV acetaminophen produces earlier and higher peak CSF concentration values with less variability.[16]

Given its potential demand for use, particularly for immediate post-operative pain, there is a need to demonstrate whether the addition of IV acetaminophen to the multimodal pain pathway for adult patients requiring post-operative analgesia would be clinically as well as cost-effective. This report was undertaken to examine the current evidence surrounding the clinical and cost-effectiveness of IV acetaminophen in order to inform decision-makers on whether there is value in wider adoption of this product for local use.

Research Questions

1. What is the clinical effectiveness of intravenous acetaminophen for patients with post-operative pain?
2. What is the cost-effectiveness of intravenous acetaminophen for patients with post-operative pain?

Key Findings

Evidence identified from seven systematic reviews was limited in methodological quality and was heterogeneous regarding patient populations, comparators, and time and duration of intravenous acetaminophen administration. One SR found that IV acetaminophen was superior to placebo in the proportion of adult patients undergoing any surgical procedure achieving at least 50% pain relief four or six hours after administration of IV medication. The remaining findings measuring difference in pain scores at various points in the post-operative period were inconsistent, therefore limiting the ability to draw firm conclusions. There was no significant difference in pain scores comparing IV acetaminophen to placebo in adult patients undergoing abdominal surgery.

There was no evidence to show that IV acetaminophen performed better than active comparators such as IV NSAIDs or IV opioids. There was a consistent trend amongst studies showing an overall decrease in opioid consumption with the use of IV acetaminophen; however the magnitude of this decrease is unknown (and thus clinical significance is also unknown). There was no difference found in hospital length of stay when adding IV acetaminophen.

No studies on the cost-effectiveness of IV acetaminophen peri-operatively or immediately post-operatively were identified and the clinical studies mainly focused on short-term outcomes.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Embase, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2013 and August 31, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with post-operative pain in acute care settings
Intervention	IV acetaminophen alone or in combination with other pain medications given in the peri- or post-operative periods for the short-term management of post-operative pain immediately following surgery
Comparator	IV NSAIDs alone or in combination with other pain medications IV opioids alone or in combination with other pain medications Placebo alone or in combination with other pain medications
Outcomes	Q1: Clinical effectiveness i.e. benefit (e.g. opioid-sparing, pain score improvements, length of hospital stay, clinical benefit) or harms (e.g. nausea or vomiting, post-operative constipation, other) Q2: Cost-Effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, economic evaluations

Legend; IV= intravenous; NSAID= non-steroidal anti-inflammatory drugs; Q1= research question 1; Q2= research question 2.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SR) were critically appraised by one reviewer using the AMSTAR 2 tool[17]. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 638 citations were identified in the literature search. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. 583 citations were excluded and 55 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Fifty-two studies were excluded upon full text review. Seven systematic reviews were included in this review. Appendix 1 presents the PRISMA[18] flowchart of the study selection.

References for relevant randomized and non-randomized studies are provided in Appendix 6.

Summary of Study Characteristics

Study Design

Seven systematic reviews (SRs) met the inclusion criteria for this review. [19-25] Five of the seven SRs contained a meta-analysis.[19,20,22,24,25] Four of the seven SRs selected only RCTs for inclusion,[19,21,23,24] one SR selected only prospective studies (either RCTs or cohort studies),[20] and the remaining two SRs selected a combination of RCTs and retrospective cohort studies for inclusion.[22,25] Of the seven SRs, two were published in 2018,[20,22] two were published in 2017,[21,25] one was published in 2016,[24] and two were published in 2013.[19,23] One of the SRs included in this report provided indirect comparisons.[24] The total number of individual randomized and non-randomized studies covered by all included SRs was 123, ranging in publication dates from 1993 to 2017. Overlap of studies included in the SRs is detailed in Appendix 5.

Country of Origin

Authors of two SRs were based in China,[22,25] and one was based in India.[23] The remaining SRs were based in the United States,[19-21,24] one of which was published by the Cochrane Database of Systematic reviews.[24]

Patient Population

All SRs examined adult patients undergoing an operative procedure, and followed these patients into the post-operative period. Four of the seven SRs included only adult patients,[20-22,25] two SRs included studies in adult and pediatric populations,[19,23] and one SR included studies with adults and adolescents from 13 years of age.[24]

The type of surgeries varied across the SRs. Three SRs included patients undergoing orthopedic surgery,[22,23,25] two of which focused only on knee or hip arthroplasty,[22,25] and one including patients undergoing any orthopedic surgery.[23] Two SRs included patients undergoing any operative procedure.[19,24] One SR examined patients undergoing abdominal surgery,[20] and one SR examined patients undergoing cardiac surgery.[21]

Intervention

The intervention of interest was considered by all included SRs to be a broad definition of administering IV acetaminophen as a component of a multimodal approach to pain management. As a result, the dose, frequency and timing of administration varied between SRs.

The dosage of acetaminophen varied widely between SRs as well as individual studies in SRs. In the majority of individual studies, acetaminophen was administered at dosages of 1g for adults and 15 to 30mg/mL for pediatric patients, however there were a few individual studies in two SRs where 2g IV acetaminophen was administered as one-time dose.[19,24] Individual studies most frequently evaluated IV acetaminophen given at regular intervals (often every six hours) post-operatively, however there were some individual studies in which IV acetaminophen was given in single doses, or two doses spaced at least five hours apart.

Four SRs included individual studies using IV propacetamol, a prodrug form of acetaminophen, which is equivalent to acetaminophen at a ratio of 2:1.[21-24] In these cases, propacetamol was often used at a dosage of 2g every six hours, which is equivalent to 1g

acetaminophen every six hours. The remaining three SRs only included IV acetaminophen as an intervention.[19,20,25]

In two SRs, IV acetaminophen was administered in the post-operative period.[20,21] In one of these SRs, only studies in which IV acetaminophen administered for at least 24 hours or at least three doses during the post-operative period were considered,[20] and in the second SR, any study which began administration of IV acetaminophen post-operatively was included, which lasted up to 72 hours or four doses during the post-operative period.[21]

One SR included studies where IV acetaminophen was administered in the peri-operative period, however dosage, administration time and duration were not limited.[22]

The remaining four SRs did not have restrictions of the timing of administration of IV acetaminophen.[19,23-25] In one of these SRs, IV acetaminophen was only given in the peri- and post-operative periods in individual studies.[25] In another of these SRs, the majority of studies administered intervention automatically, no earlier than 30 minutes before the end of surgery or immediately postoperatively,[24] and in the third of these SRs, IV acetaminophen was administered post-operatively, with the exception of one individual study in which IV acetaminophen had been administered peri- or pre-operatively.[23] In the fourth of the included studies, there was a range of individual studies which administered IV acetaminophen in the pre-, peri- and post-operative stages.[19]

Comparators

Two SRs examined the effects of IV acetaminophen compared to placebo.[19,23] and two SRs compared the use of IV acetaminophen to a multimodal analgesia treatment approach without IV acetaminophen.[22,25]

The remaining three SRs included studies contained an active comparator of IV NSAIDs, as well as placebo.[20,21,24] Of these SRs, one also included IV tramadol and oral acetaminophen as comparators[21] and another of these SRs included opioids and local anesthetics as a comparator, in addition to IV NSAIDs.[20]

The NSAIDs used as a comparator in these SRs included: ketoprofen,[20,24] dexketoprofen,[24] diclofenac,[20,24] lornoxicam,[20,24] metamizole,[21,24] dipyrone,[24] meperidine,[20,24] ketorolac,[21,24] and COX-2 inhibitors celecoxib,[24] and parecoxib.[20] The opioids used as a comparator were morphine,[20,21,24] and tramadol[21,24].

Outcomes

All SRs examined differences in pain score and opioid consumption in the post-operative period.[19-25] Regarding difference in pain score, two SRs examined this up to post-operative day 3,[22,25] one SR examined over 24 hours,[20], one SR examined over 12 hours,[20] and three SRs did not specify a length of time, but measured values up to a maximum of 72 hours.[19,21,23] One SR measured mean pain intensity over both four- and six-hours post-intervention, and in turn calculated the mean pain difference between groups.[24] This SR also measured the percentage of patients experiencing at least 50% of maximum pain relief over four or six hours post-intervention.[24]

Regarding difference in opioid consumption, one SR examined this from the operative day to post-operative day 3,[25] two SRs examined this over 24 hours,[20,21] one SR examined this over six hours,[24] and the remaining three SRs did not specify a length of time.[19,22,23]

Additional efficacy outcomes included percentage of patients receiving additional analgesic medication, which was measured in one SR,[24] and length of hospital stay, which was measured in two SRs.[22,25]

Regarding safety outcomes, difference in post-operative nausea and vomiting was measured in four SRs.[19,22,24,25]

A summary of these study characteristics is presented in Appendix 2.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Critical appraisal was conducted using the AMSTAR 2 tool.[17] Of the included SRs, one was considered to be of high quality,[24] four were considered to be of moderate quality,[19,20,22,25] and two were considered to be of low quality.[21,23]

Strengths common to all seven SRs included: establishment of research questions and inclusion criteria *a priori*, use of literature search strategy, provision of a list of included studies, description of important characteristics of included studies, and use of appropriate methods to combine the findings of studies when a meta-analysis was conducted.[19-25] However, grey literature was formally searched in one SR,[20] and only one SR provided a list of excluded studies.[24] Two independent reviewers performed study selection in duplicate for two SRs,[24,25] and performed data extraction in duplicate for five SRs.[20,22-25]

Consideration of the scientific quality of evidence varied across SRs. Quality was assessed in four SRs at the individual study level for included RCTs using the Cochrane Collaboration's tool for assessing risk of bias[20,22,24,25] The Methodological Index for Non-Randomized Studies (MINORS) scale was used by two SRs which included non-randomized studies.[22,25] The quality of evidence for the main outcomes was evaluated using the Recommendations, Assessment, Development and Evaluation (GRADE) tool in the meta-analysis of two SRs.[24,25] One SR did not use a formal assessment to examine methodology of included studies,[19] but did evaluate risk of bias for these studies via categories of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data. Two SRs did not include documentation of scientific quality and did not adequately consider the strengths and limitations of the included studies in formulating conclusions.[21,23]

The likelihood of publication bias was reported to have been assessed in four SRs,[19,20,24,25] however results for this analysis was presented in only two SRs.[20,24] The review author of one SR[19] reported receipt of funding or employment from Cadence Pharmaceuticals which is a subsidiary of Mallinckrodt, the manufacturer of IV acetaminophen.

Appropriate statistical methods were used for all five of the SRs which contained a meta-analysis.[19,20,22,24,25] Statistical heterogeneity was assessed in all five SRs using a Cochrane Q and I^2 statistic and extracted results of studies were weighted.[19,20,22,24,25] In two SRs,[19,20] a random-effects model was applied for meta-analyses to assess outcomes of interest, and in two SRs,[22,25] a random effects model was used for meta-analyses when $I^2 \geq 50\%$ and significant heterogeneity was indicated, otherwise a fixed-effects model was used.

One SR[24] used a fixed-effect model for its statistical analysis, and, due to evidence of heterogeneity in comparisons, used a random-effects model when performing their

sensitivity analysis instead of an original fixed-effect model. In the results section of this study, it was stated that none of the point-estimates for the primary outcome changed in direction, statistically significant analyses remained, changes in effect size were minimal, and 95% confidence intervals were wider with the random-effects model. Of the secondary efficacy outcomes, two relevant group/subgroup analyses changed from demonstrating statistical significance to no longer being statistically significant when a random-effects model was used: pain intensity at six hours (acetaminophen versus NSAIDs), and global evaluation using VAS (acetaminophen or propacetamol versus placebo). In all cases, the point estimates remained similar. Lastly, several AE analyses also changed from demonstrating statistical significance to no longer being statistically significant using the random-effects model. The authors stated that their study conclusions remained sound.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of IV acetaminophen for the Management of Short-Term Post-Operative Pain

Difference in Pain Scores at Operative Day

One SR examined the change in pain scores on operative day in patients taking IV acetaminophen versus IV placebo or normal saline within a multimodal analgesia treatment approach in the peri-operative period.[22] The pooled outcomes of four individual studies showed that there was no significant improvement in pain with the use of IV acetaminophen.

One SR examined the change in pain scores for patients taking IV acetaminophen versus any comparator (IV placebo, IV NSAIDs, or IV opioids) 12 hours after abdominal surgery from the pooled results of six individual studies, with 195 patients in the IV acetaminophen group and 273 patients in the comparator group.[20] There was no difference found between groups for pain scores.

Difference in Pain Scores at Post-operative Day One

Two SRs identified 11 total individual studies which measured change in pain scores at post-operative day one in a total of 1,375 patients undergoing knee or hip arthroplasty, taking IV acetaminophen versus 890 patients taking IV placebo or IV normal saline in addition to a multimodal analgesia treatment approach without IV acetaminophen.[22,25] The pooled outcomes of one SR (841 patients in the IV acetaminophen group and 559 patients in the placebo group) showed no significant improvement in pain with the use of IV acetaminophen.[22] In the second SR (534 patients in the IV acetaminophen group and 331 patients in the IV placebo group), the pooled results demonstrated that pain scores were significantly higher in the control group than in the IV acetaminophen group.[25] One SR found a high degree of heterogeneity in the results,[22] while the other SR did not.[25]

One SR identified 22 individual studies measuring change in pain scores one day after abdominal surgery, comparing patients taking IV acetaminophen to IV placebo, NSAIDs, and opioids.[20] Eight individual studies in this SR compared a total of 331 patients taking IV acetaminophen to a total of 282 patients taking IV placebo, and found no significant improvement with the use of IV acetaminophen. Seven individual studies compared 128 patients taking IV acetaminophen to 207 patients taking IV NSAIDs, and found no significant improvement with the use of IV acetaminophen. Three individual studies

compared 145 patients taking IV acetaminophen to 163 patients taking IV opioids and also found no significant difference in patients taking IV acetaminophen.

Difference in Pain Scores at Post-operative Day Two

Two SRs identified 6 total individual studies measuring change in pain scores at post-operative day 2 in a total of 688 patients taking IV acetaminophen and 438 patients taking IV placebo.[22,25] One SR (534 patients in the IV acetaminophen group and 331 patients in the IV placebo group) found that there was a significant difference in pain scores between groups at this time,[25] while the second SR (225 patients in the IV acetaminophen group and 176 patients in the IV placebo group) found no significant difference in pain scores.[22] There was a high degree of heterogeneity noted in both SRs for these values.

Difference in Pain Scores at Post-operative Day Three

Two SRs identified 5 individual studies measuring change in pain scores at post-operative day 3 in a total 634 patients taking IV acetaminophen and 381 patients taking IV placebo.[22,25] One SR (534 patients in the IV acetaminophen group and 331 patients in the IV placebo group) found a significant difference in pain scores between groups at this time,[25] while the second SR (167 patients in the IV acetaminophen group and 176 patients in the IV placebo group) found no significant difference in pain scores.[22] One SR found a high degree of heterogeneity in the results,[22] while the other SR did not.[25]

Difference in Pain Intensity Scores Post-intervention

One SR measured the change in pain intensity at four and six hours post-intervention, however the data was assessed as being of low or very low quality.[24] Comparisons of IV acetaminophen and placebo did not show a difference at four hours, and demonstrated clinically minor reductions in pain at six hours. Comparisons between IV paracetamol and NSAIDs showed a superiority of NSAIDs at both four and six hours post-intervention, however the difference between groups for these outcomes was deemed to be minor.[24] There was also moderate heterogeneity noted within the data.

Difference in Pain Scores over no specified length of time

Two SRs evaluated individual studies reporting changes in pain scores over no specified length of time.[21,23] In both cases, individual studies were deemed to have a high degree of heterogeneity and therefore results could not be pooled. In one of the SRs, three of the ten individual studies found that there were significantly lower pain scores when IV acetaminophen was compared to placebo when used in addition to a multimodal analgesia treatment approach after cardiac surgery.[21] In the second SR, four of seven individual studies found there to be lower pain scores in the IV acetaminophen group when compared to placebo after any surgery.[23]

Percentage of patients achieving at least 50% pain relief

One SR measured the outcome of the percentage of patients achieving at least 50% pain relief over four and six hours after administration of acetaminophen.[24] This SR found that the minimum reduction in acute pain intensity described by patients as meaningful varied between 30% and 50%, with a larger reductions seen when pain was more severe at baseline. This SR pooled data from five individual studies and found that over four hours, 31% of patients receiving IV acetaminophen had at least 50% pain relief compared to 16% of patients receiving IV placebo. This finding was accompanied with moderate heterogeneity, however were not found to be subject to publication bias. The overall risk

ratio determined for IV acetaminophen versus placebo for an at least 50% improvement in pain relief was 4.8 (95% CI: 2.3 to 10.0), and the derived NNT for one patient to experience an at least 50% improvement in pain relief over four hours was 5 (95% CI: 3.2 to 5.9). Two individual studies in this SR compared IV acetaminophen to IV NSAIDs and found that the percentage of patients experiencing at least 50% pain relief over four hours with an IV NSAID was 60% (97/162) compared to 50% (37/65) of patients taking IV acetaminophen. This difference between groups was not found to be a statistically significant. No studies in this SR compared IV acetaminophen to IV opioids for this outcome.

The percentage of patients achieving at least 50% pain relief at six hours showed a decrease in analgesic effects compared to values at four hours. Ten individual studies provided data, in which 364 patients were treated with IV acetaminophen and 435 were treated with placebo. The percentage of patients experiencing at least 50% pain relief over six hours was 30% (109/364) in the IV acetaminophen group and 10% (42/435) in the placebo group. The relative risk ratio for IV acetaminophen compared to placebo for an at least 50% improvement in pain relief over six hours was found to be 3.7 (95% CI: 2.2 to 6.2) and the derived NNT for one patient to experience an at least 50% improvement in pain relief over six hours was 6 (95% CI 4.6 to 7.1). These results were accompanied with a moderate degree of heterogeneity and found have a high susceptibility to publication bias,[24] Three studies with 212 patients compared IV paracetamol against IV NSAIDs for this outcome. The percentage of patients experiencing at least 50% pain relief over six hours with IV paracetamol was found to be 51% (54/106) compared to 63% (103/163) with IV NSAIDs. This data was also found to be highly susceptible to publication bias, likely due to the low sample size. No individual studies provided data for IV acetaminophen compared to opioids.

Difference in Opioid Consumption

The difference in total opioid consumption was measured in five of the seven included SRs.[20-25]

One SR measured opioid consumption during the periods of four and six hours after IV administration.[24] Six individual studies found that with 70 patients receiving IV acetaminophen, 56 patients receiving IV propacetamol and 129 patients receiving placebo, there was an overall reduction of 1.4 mg (95% CI 1.0 to 1.8) IV morphine equivalents in patients receiving either IV acetaminophen or propacetamol compared to placebo. Thirteen studies reported data from 215 patients taking IV acetaminophen, 201 patients taking propacetamol or both and 361 patients taking placebo, and found that patients taking either IV acetaminophen or propacetamol required 1.9 mg (95% CI: 1.4 to 2.4) less IV morphine equivalents than those receiving placebo. There was a moderate degree of heterogeneity reported between the individual studies. Three studies compared opioid consumption between IV acetaminophen or propacetamol to NSAIDs, with 59 patients receiving IV acetaminophen, 87 receiving propacetamol and 148 receiving an NSAID. Those receiving IV acetaminophen or propacetamol required 0.2 mg (95% CI 0.0 to 0.4) less IV morphine equivalents than those receiving an NSAID at four hours, and there was no statistically significant difference between the groups at six hours post-administration of IV medication. There was no identified heterogeneity between these individual studies.

Opioid consumption at one day after an operative procedure was measured in two SRs,[20,25] and came to conflicting conclusions. One SR pooled data on opioid consumption comparing patients taking IV acetaminophen and placebo from four individual studies and found a significantly lower amount of morphine consumed in the IV acetaminophen group.[25] There

was no morphine equivalent provided to assess the amount, and there was no significant heterogeneity observed in this result. The second SR evaluated 15 individual studies and found that IV acetaminophen was not more effect in reducing opioid consumption than comparator medications.[20] Eight individual studies in this SR compared a total 133 patients taking IV acetaminophen to 283 patients taking placebo; seven individual studies compared 128 patients taking IV acetaminophen to 236 patients taking an IV NSAID, and three individual studies compared a total 145 patients taking IV acetaminophen to a total 163 patients taking IV opioids. There was a high degree of heterogeneity found in the studies using placebo and IV opioids as a comparator, and no heterogeneity found in studies using NSAIDs as a comparator. There was no significant decrease in opioid consumption found for patients taking IV acetaminophen in any of these cases. In fact, IV NSAIDs were found to have the greatest reduction in opioid consumption of all medications, and was found to be statistically significantly lower than IV acetaminophen.

One SR measured opioid consumption at two and three days after a total hip or knee replacement procedure, pooling data from four individual studies.[25] A significantly lower level of opioid consumption was found in a total of 534 patients taking IV acetaminophen compared to a total 331 patients taking placebo at two and three days after the operative day. There was significant heterogeneity noted within the results for post-operative day three, but not in the results for post-operative day two.

Three SRs measured opioid consumption over an unknown measure of time, but up to a maximum of 72 hours post-operatively.[21-23] One SR contained a meta-analysis which pooled data on opioid consumption from ten individual studies.[22] The data compared 957 patients taking IV acetaminophen to 693 patients taking placebo and found that there was a significantly lower amount of opioid consumed in patients taking IV acetaminophen. There was a high degree of heterogeneity observed in the data. The other two SRs did not contain meta-analyses due to reported heterogeneity in the data.[21,23] Of the 12 total individual studies in both SRs measuring opioid consumption in comparing IV acetaminophen to placebo, nine of them found that there was a significant reduction in opioid consumption in the IV acetaminophen group.[21,23]

Length of Hospital Stay

Two SRs compared length of hospital stay in patients undergoing knee and hip arthroplasties and taking IV acetaminophen to those taking placebo.[22,25] The pooled data of both SRs contained similar results in that there was no significant difference in patients taking IV acetaminophen to those taking placebo in length of hospital stay. There was a moderate to high degree of heterogeneity in these results.

Change in Opioid-related Adverse Events

Four SRs evaluated adverse events comparing patients taking IV acetaminophen to placebo,[19,22,24,25] and one SR compared patients taking IV acetaminophen against active comparators.[24] When evaluating nausea, the pooled data from three SRs found a significantly lower incidence of nausea in patients taking IV acetaminophen compared to those taking placebo.[19,24,25] One SR meta-analyzed the data to compare patients taking IV acetaminophen to those taking NSAIDs and found no significant differences between groups.[24] This SR also compared 7% (19/272) patients taking IV acetaminophen to 18% those taking opioids, and found a significantly lower incidence in the IV acetaminophen group.[24] There was a low to moderate degree of heterogeneity identified between individual studies.

Three SRs evaluated incidence of vomiting in patients taking IV acetaminophen to placebo,[19,24,25] and one SR compared those taking IV acetaminophen to those taking active comparators.[24] There was a significantly decreased risk of post-operative vomiting found in patients taking IV acetaminophen compared to placebo in the pooled data of each of the three SRs.[19,24,25] One SR compared the incidence of vomiting between those taking IV acetaminophen and those taking IV NSAIDs through meta-analysis of data.[24] There was no significant difference found between these groups. This same SR compared this outcome in patients on IV acetaminophen against those taking IV opioids, and found that there was a 2% (6/247) incidence of vomiting in patients taking IV acetaminophen compared to 8% (20/248) in those taking IV opioids. There was a significantly lower incidence found in the IV acetaminophen group.

One SR compared the total incidence of adverse events between IV acetaminophen and placebo.[22] This study identified seven individual trials involving a total 11,698 patients taking IV acetaminophen compared against 11 456 patients taking placebo. The pooled results suggested that there was a higher incidence of total adverse events in patients taking IV acetaminophen compared to placebo, however this difference was not significant. This study did not identify the most common adverse events with IV acetaminophen.

Cost-Effectiveness of IV Acetaminophen for the Management of Short-Term Post-Operative Pain

There was no direct evidence identified on the cost-effectiveness of IV acetaminophen for the management of post-operative pain.

Limitations

The quality of evidence in the SRs was impacted by a high degree of heterogeneity in the data reported. Meta-analyses of the pooled data often combined timing of IV acetaminophen administration, different surgical populations, comparator medications, types of controls used, laparascopic versus open surgery, and the timing of pain score measurement. There was also little information provided among the SRs and individual studies surrounding the use of other post-operative measures used in adjunct (ie. topical medications, anxiolytics, medical devices, etc). Lastly, these SRs and their included studies were conducted in a wide range of countries, where the delivery of care, culture surrounding pain reporting and subjectivity of pain may differ, potentially affecting outcomes and generalizability of findings.

Two of the included SRs evaluated studies in pediatric patients as well as adult patients.[19,23] Due to the small numbers of pediatric patients in these SRs, they were difficult to separate for the purposes of this report. Similarly, four of the SRs in this report included smaller individual studies using IV propacetamol, a prodrug form of acetaminophen.[21-24] The inclusion of pediatric patients in some studies as well as the inclusion of IV propacetamol as an intervention may have further contributed to heterogeneity in the data presented.

No economic or healthcare utilization information was identified.

Many of the SRs did not describe which pain scores were employed, whether they were similar in scale between studies, or whether these scales were validated. Furthermore, it was unknown what a minimal clinically important difference in pain scores would be defined as. Similarly, the units of measurement for total opioid consumption were not provided with the exception of one SR,[24] and not measured over a consistent period of time between

studies. There were also a wide range of pain metrics used between the included SRs and at different time points, which impacts the ability to compare results and identify consistencies.

The quality of evidence from the SRs was limited by a small number of studies available for each outcome and the small sample sizes in the included studies. Individual studies were often small-scale, single-centre trials. Most of the SRs stated a need for large, high-quality RCTs. Due to the small number and scale of studies available in the SRs, publication bias was difficult to assess, and carried out in only four of the seven SRs. [19,20,24,25]

There was uncertainty in many of the individual studies included in the SRs related to funding sources. Most individual studies did not clearly state the funding sources used for their analysis, therefore leaving an unknown potential for additional bias.

Individual studies using an NSAID as a comparator, included those such as diclofenac, ketoprofen, dexketoprofen, lornoxicam, metamizole, dipyrone, and meperidine. These medications are used sparingly in Canadian patient populations, and therefore may not be generalizable to NSAIDs used in common practice. In addition, there is a significant side effect profile associated with NSAID medications including gastric ulceration, increased bleeding complications and kidney injuries, which limits its use in many patients.[26]

Conclusions and Implications for Decision or Policy Making

A total of seven systematic reviews relevant to the use of IV acetaminophen for the management of post-operative pain were identified. There was a lack of high-quality evidence found for the comparison of clinical outcomes between patients receiving IV acetaminophen in an operative setting, and a high degree of heterogeneity in the data presented.

Due to this lack of high-quality evidence, it is not possible to draw conclusions with a high level of confidence. One SR deemed to be of high quality demonstrated that IV acetaminophen was statistically superior to placebo in the proportion of patients achieving at least 50% pain relief over four or six hours.[24] There is supportive evidence that IV acetaminophen improved pain scores in adult patients undergoing any operative procedure at various points in the post-operative period when compared against placebo,[21,23,25] however this was not shown in patients undergoing abdominal surgery,[20] and inconsistent evidence was shown in patients undergoing knee and hip arthroplasty,[22,25] and cardiac surgery.[21] The magnitude of this difference is unknown. There was no evidence to show that IV acetaminophen performed better than active comparators such as IV NSAIDs or IV opioids. There was a consistent trend among studies showing an overall decrease in opioid consumption with the use of IV acetaminophen compared to IV placebo; however the magnitude of this decrease is unknown. One SR provided an average of less than 2 mg morphine equivalents after administration of IV acetaminophen, however the clinical significance of this is unknown.[24] There was no evidence to show that IV acetaminophen significantly reduced opioid consumption against active comparators such as IV NSAIDs or IV opioids.

When evaluating safety outcomes, there was a trend towards a reduction in opioid-related adverse events such as nausea and vomiting with the use of IV acetaminophen compared to those taking placebo. One SR found a significantly lower incidence of nausea and vomiting with the use of IV acetaminophen compared to IV opioids, and no significant difference in these outcomes when compared against IV NSAIDs.[24]

Potential economic implications of using IV acetaminophen peri-operatively or immediately post-operatively were difficult to assess, since long-term complications of pain management, such as increased mobility, risk of opioid dependence, rates of medical complications and patient satisfaction, were not measured in these studies. In studies that assessed differences in hospital length of stay, there was no difference found in adding IV acetaminophen to a multimodal pain strategy.

The systematic reviews included in this review represent a portion of the large volume of recent literature available regarding the clinical effectiveness of IV acetaminophen administered in the peri- or post-operative periods. There is a large number of relevant randomized controlled trials (listed in **Error! Reference source not found.**) on various s urgical indications (such as bariatric, gynecological, head and neck, and gastrointestinal) that were not included in the report due to the volume of literature. It is uncertain whether the results of these randomized controlled trials confirm or change overall conclusions.

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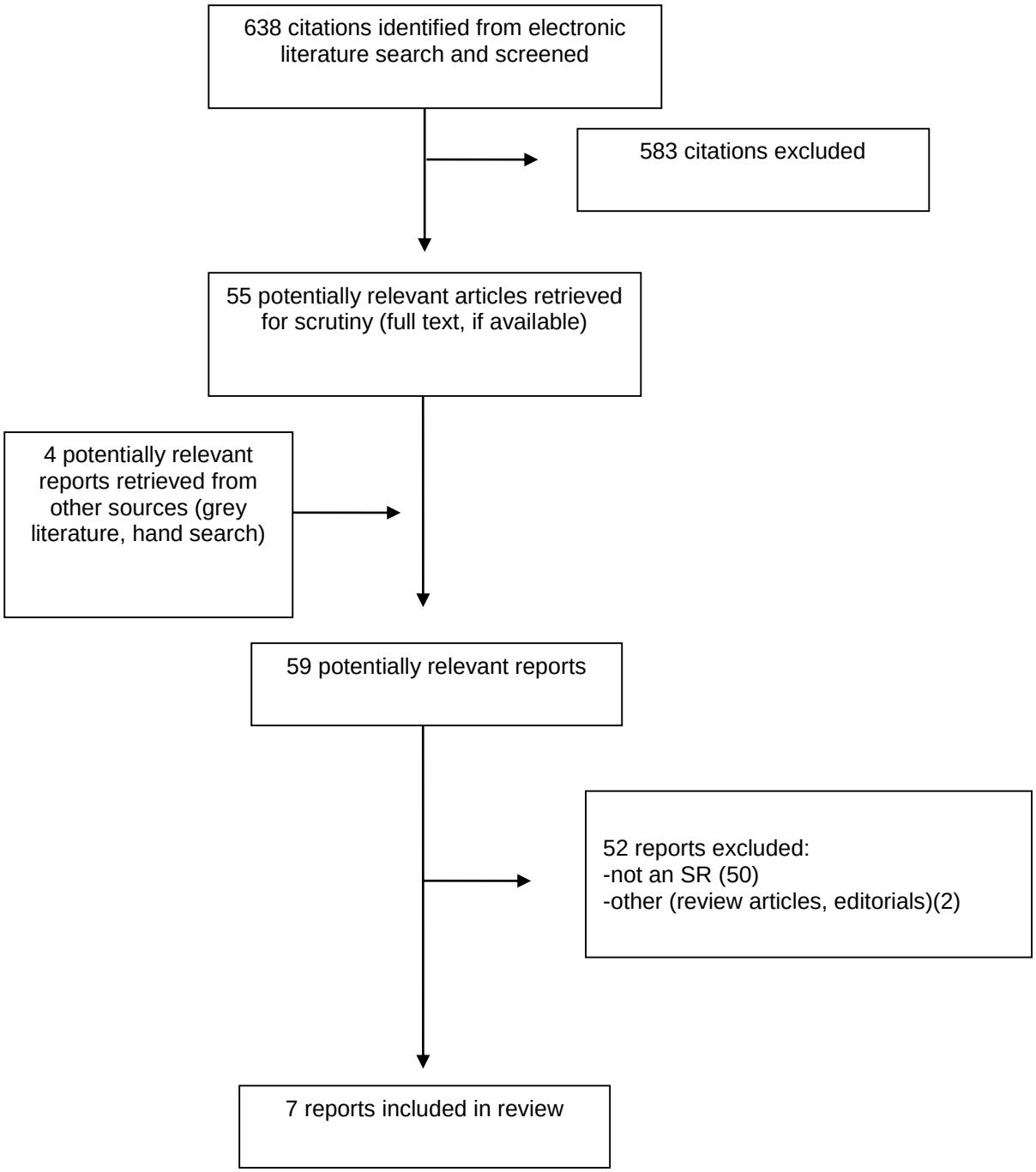
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Blank, 2018[20] **USA**	Randomized controlled trials and prospective cohort studies 17 studies	1,595 adult patients undergoing trans-abdominal surgery (laparascopic, open surgery or both)	IV acetaminophen, IV placebo, IV NSAIDs, IV opioids, local anesthetics	Difference in pain score at 12 and 24 hours post-operative, Total opioid consumption at 24 hours
Guo, 2018[22] **China**	Randomized controlled trials and retrospective cohort studies 11 studies	23,154 adult patients undergoing knee or hip arthroplasty	IV acetaminophen, IV placebo	Difference in pain score at operative day and post-operative days one to three Total opioid consumption Length of hospital stay Total incidence of adverse events
Douzjian, 2017[21] **USA**	Randomized controlled trials 9 studies	586 adult patients undergoing cardiac surgery	IV acetaminophen/ IV propacetamol, IV placebo, IV NSAIDs	Difference in pain score, Total opioid consumption
Yang, 2017[25] **China**	Randomized and non-randomized controlled trials 4 studies	865 adult patients undergoing knee or hip arthroplasty	IV acetaminophen, IV placebo	Difference in pain score at post-operative days one to three; opioid consumption at post-operative days one to three; length of hospital stay; opioid-related adverse effects (nausea, vomiting)
McNicol, 2016[24] **USA**	Randomized, double-blind placebo- or active-controlled single dose clinical trials 75 studies	7,200 adults and adolescent (ages 3 to 13) patients undergoing any operative procedure	IV acetaminophen, IV placebo, IV NSAIDs	Percentage of patients with at least 50% pain relief over four and six hours; difference in pain score at four and six hours post-intervention; time to rescue medication; opioid consumption; percentage of patients experiencing nausea and vomiting
Apfel, 2013[19] **USA**	Randomized, placebo-controlled trials 30 studies	2,364 adult and pediatric patients undergoing any operative procedure	IV acetaminophen, IV placebo	Risk of nausea and vomiting in the post-operative period
Jebaraj, 2013[23] **India**	Prospective randomized controlled trials 8 studies	571 adult and pediatric patients undergoing any orthopedic surgery	IV acetaminophen, IV placebo	Difference in post-operative pain scores, total opioid consumption, opioid-related adverse events (nausea, vomiting)

IV = intravenous; NSAID = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial; USA = United States of America

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[17]

Strengths	Limitations
Blank 2018[20]	
- Research questions, objectives, inclusion criteria, and exclusion criteria were clearly described - A literature search strategy including four named databases was conducted, with key word and search strategy provided - Data extraction was performed in duplicate and data was reviewed by a group, with discrepancies reconciled by discussion until achieving consensus - List of included studies was provided in adequate detail - Risk of bias was assessed in individual studies for allocation concealment, random sequence generation, blinding of outcome assessment, participants and personnel, incomplete outcome data, selective reporting and other bias - Sources of funding for individual studies was provided and an investigation into publication bias was conducted - Authors reported no competing interests	- Was not explicitly stated that review methods were established prior to conduct of the review - Study selection did not appear to be performed in duplicate - List of excluded studies was not provided - High degree of heterogeneity in the majority of analyses and a meta-regression assessed many possible confounders, however none were found to explain the heterogeneity in results - Only three individual studies reported funding sources, potential for additional bias unknown in remainder of studies - NSAID comparators used in individual studies (ie. diclofenac, ketoprofen, and lornoxicam) are not typically prescribed in a Canadian patient population - Only studies published in English were considered
Guo 2018[22]	
- Research questions, objectives, inclusion criteria, and exclusion criteria were clearly described - A literature search strategy including four named databases was conducted, with key word and search strategy provided - Data extraction was performed in duplicate - A list of included studies was provided - Risk of bias was assessed in individual studies for allocation concealment, random sequence generation, blinding of outcome assessment, participants and personnel, incomplete outcome data, selective reporting, and other bias - Authors reported no competing interests	- No justification was provided for the inclusion of RCTs and non-RCTs into this meta-analysis - Study selection did not appear to be performed in duplicate - List of included studies did not provide adequate information regarding outcomes of interest in individual studies - Description of the comparator (“control”) group in individual studies was not provided, may be a source of heterogeneity - List of excluded studies was not provided - Sources of funding for individual studies was not provided - Publication bias was reported to have been visually examined by funnel plots however results were not reported - High degree of heterogeneity between studies - Only examined a population of patients undergoing knee or hip arthroplasty which may impact generalizability to other operative indications - Opioid consumption was not measured over a consistent period of time between individual studies, and a unit of measurement was not provided
Douzjian 2017[21]	
- Research questions and objections were clearly described - Only randomized controlled trials were selected for inclusion as per the study design - A literature search strategy including two named databases was conducted, with key word and search strategy provided - A comprehensive list of included studies was provided - Allocation concealment, blinding, length of follow-up, pre-specified outcomes and power estimates were briefly discussed	- Inclusion and exclusion criteria were not provided, as well as a risk of bias assessment and a list of excluded studies - Details regarding the study selection and data extraction processes were not provided - Sources of funding for individual studies was not provided - Risk of bias for individual studies did not appear to be accounted for in discussion of study results - Heterogeneity in study results was not thoroughly investigated in discussion

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[17]

Strengths	Limitations
	- An investigation into publication bias was not conducted - Funding and potential sources of conflict of interest for this review was not provided
Yang 2017[25]	
- Research questions, objectives, inclusion criteria and exclusion criteria were clearly described - A literature search strategy including four named databases was conducted, with key word and search strategy provided - Study selection and data extraction were performed in duplicate, with discrepancies reconciled by discussion - A comprehensive list of included studies was provided - Risk of bias was assessed in individual studies for allocation concealment, random sequence generation, blinding of outcome assessment, participants and personnel, incomplete outcome data, selective reporting and other bias - Authors reported no competing interests	- List of excluded studies was not provided - Sources of funding for individual studies was not provided - Publication bias was reported to have been examined as a component of the GRADE system however results were not reported - Heterogeneity was adjusted for in the statistical combination of results, however there was a high degree of heterogeneity present in results, with no apparent investigation into sources of heterogeneity, or its impact on review results - Although risk of bias was investigated in individual studies, there was not account for this in evidence synthesis or discussion
McNicol 2016[24]	
- Research questions, objectives, inclusion criteria and exclusion criteria were clearly described - A literature search strategy including four named databases was conducted, with key word and search strategy provided - Study selection and data extraction were performed in duplicate, with discrepancies reconciled by discussion then consultation with a third author for agreement - A list of excluded studies were provided with justification - A comprehensive list of included studies was provided - Risk of bias was assessed in individual studies for allocation concealment, random sequence generation, blinding of outcome assessment, participants and personnel, incomplete outcome data, selective reporting and other bias - Publication bias was assessed in individual studies and its impact on results was discussed - Heterogeneity was clearly presented, and its impact on the results of the review was discussed, as well as an identification of possible sources for heterogeneity - Authors reported no competing interests	- Content experts in the field did not appear to be consulted a priori - Sources of funding for individual studies was recorded however its impact on the result of this review was not explored - A fixed-effect model was used for the statistical analysis in the meta-analyses, which was justified in that the point estimates of all primary analyses only minimally changed when a random-effect model was used, and all statistically significant meta-analyses reportedly remained so - High degree of heterogeneity in the majority of analyses and a meta-regression assessed many possible confounders, such as different types of surgeries included and timing of IV acetaminophen administration within the operative period (pre-operative, peri-operative, post-operative) - Did not consistently provide information about the timing of administration of IV acetaminophen
Apfel 2013[19]	
- Research questions, objectives, inclusion criteria and exclusion criteria were clearly described - A literature search strategy including two named databases was conducted, with key word and search strategy provided - Only randomized-controlled trials were included with justification provided - A list of included studies was provided - Risk of bias was assessed in individual studies for allocation concealment, random sequence generation, blinding of	- No plan for investigating causes of heterogeneity was described a priori - Method for study selection and data extraction was not provided - List of excluded studies was not provided - High degree of heterogeneity in the timing of IV acetaminophen administration between studies - Sources of funding for individual studies was not presented however its impact on the result of this review was explored

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[17]

Strengths	Limitations
outcome assessment, participants and personnel and incomplete outcome data, as well as its impact on results - Heterogeneity was clearly presented, and its impact on the results of the review was discussed, as well as an identification of possible sources for heterogeneity	and was included in sensitivity analyses established a priori - Primary author reported competing interests with industry
Jebaraj 2013[23]	
- Research questions, objectives, inclusion criteria and exclusion criteria were clearly described - A literature search strategy including four named databases was conducted, with key word and search strategy provided - Data extraction was performed in duplicate - A list of included studies was provided - Authors reported no competing interests	- Study selection did not appear to be performed in duplicate - Risk of bias for individual studies was not assessed, and did not appear to be accounted for in discussion of study results - Sources of funding for individual studies was not provided - Heterogeneity in study results was not thoroughly investigated in discussion

GRADE = Recommendations, Assessment, Development and Evaluation system; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug RCT = randomized controlled trial

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Blank, 2018[20]</td></tr>
<tr><td>
<u>IV Acetaminophen versus Any Comparator</u>
- There was no significant difference in pain score found comparing IV acetaminophen to any comparator at 12 hours post-operative (mean difference: -0.25; 95% CI: -0.59 to 0.08; P=0.14)
  ○ Results were associated with a high degree of heterogeneity (Chi^2=78.67, I^2= 91%)
- There was no significant difference in pain score found comparing IV acetaminophen to any comparator at 24 hours post-operative (mean difference: -0.10; 95% CI: -0.33 to 0.14; P= 0.42)
  ○ Results were associated with a high degree of heterogeneity (Chi^2=240.61, I^2= 91%)
- There was no significant difference found comparing IV acetaminophen to any comparator in narcotic consumption at 24 hours post-operative (mean difference: -3.93; 95% CI: -9.12 to 1.25; P=0.14)
  ○ Results were associated with a high degree of heterogeneity (Chi^2=1691.45, I^2= 99%)

<u>IV Acetaminophen versus Non-active Placebo</u>
- There was no significant difference found in pain scores (mean difference: -0.34; 95% CI: -0.69 to 0.01; p=0.06) or total opioid consumption (mean difference: -19.85; 95% CI: -48.42 to 8.73; p=0.17) at 24 hours post-operative between IV acetaminophen and non-active placebo
  ○ Both results were associated with a high degree of heterogeneity (I^2>90%)

<u>IV Acetaminophen versus IV NSAIDs</u>
- There was no significant difference found in pain score at 24 hours post-operative (mean difference: 0.19; 95% CI: -0.04 to 0.42; p=0.11) between IV acetaminophen and IV NSAIDs
  ○ Findings were associated with a moderate degree of heterogeneity (Chi^2=13.95; I^2=57%)
- Narcotic consumption at 24 hours post-operative was significantly lower in the IV NSAID group (mean difference: 11.18; 95% CI: 10.40 to 11.96; P<0.001), no heterogeneity was found in this analysis

<u>IV Acetaminophen versus IV Opioids</u>
- There was no significant difference found in pain scores at 24 hours post-operative between IV acetaminophen and IV opioids (mean difference: -0.34; 95% CI -1.31 to 0.64; P=0.50)
  ○ There was a high degree of heterogeneity in this analysis (Chi^2=9.31; I^2=89%)
- There was no significant difference in narcotic consumption at 24 hours post-operative between IV acetaminophen and IV opioids (mean difference: -2.07; 95% CI: -12.10 to 7.97; P=0.69)
  ○ Results were associated with a high degree of heterogeneity(Chi^2=392.23; I^2=100%)
</td><td>"IV acetaminophen may limit narcotic consumption after laparotomy incisions, and there is an overall benefit for NSAID medications in reducing narcotic consumption after surgery. However, the strength of this finding is limited due to high levels of heterogeneity in the included studies." (page 11)</td></tr>
<tr><td colspan="2">Guo, 2018[22]</td></tr>
<tr><td>
<table>
<tr><th>Outcome</th><th>Standard Mean Difference Sub-total, IV acetaminophen vs IV placebo, (95% CI)</th><th>Heterogeneity</th><th>Test for overall effect</th></tr>
<tr><td>Difference in pain score at operative day</td><td>-0.15 (-0.36, 0.07)</td><td>Chi^2 = 1.93
df = 3 (P = 0.59)
I^2 = 0%</td><td>Z = 1.34 (P = 0.18)</td></tr>
<tr><td>Difference in pain score at POD 1</td><td>0.12 (-0.13, 0.36)</td><td>Tau^2 = 0.07
Chi^2 = 23.58
df = 6 (P = 0.0006)</td><td>Z = 0.94 (P = 0.35)</td></tr>
</table>
</td><td>"Perioperative intravenous acetaminophen use [compared] to multimodal analgesia was associated with significant reduction of total opioid consumption in total hip or knee arthroplasty… The use of IV acetaminophen did not contribute to a decrease in average pain scores after</td></tr>
</table>

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings				Authors' Conclusion
		I^2 = 75%		operation and did not shorten length of hospital stay, and IV acetaminophen did not influence the total occurrence of adverse events." (page 7)
Difference in pain score at POD 2	-0.29 (-0.70, 0.12)	Tau^2 = 0.13 Chi^2 = 11.75 df = 3 (*P* = 0.008) I^2 = 74%	Z = 1.38 (*P* = 0.17)	
Difference in pain score at POD 3	-0.04 (-0.49, 0.41)	Tau^2 = 0.11 Chi^2 = 6.22 df=2 (*P* = 0.04) I^2 = 68%	Z = 0.18 (*P* = 0.85)	
Difference in total opioid consumption	-0.66 (-1.13, -0.20)	Tau^2 = 0.51 Chi^2 = 154.61 df = 9 (*P* < 0.00001) I^2 = 94%	Z = 2.78 (*P* = 0.005)	
Difference in post-operative length of stay in hospital	-0.05 (-0.26, 0.15)	Tau^2 = 0.03 Chi^2 = 12.57 df=4 (*P* = 0.01) I^2 = 68%	Z = 0.49 (*P* = 0.62)	
Difference in total occurrence of adverse events	**0.87 (0.57, 1.33)**	Tau^2 = 0.19 Chi^2 = 24.73 df = 6 (*P* = 0.0004) I^2 = 76%	Z = 0.64 (*P* = 0.52)	

Douzjian, 2017[21]

Key Findings in Included Studies

- Seven RCTs (between 1999 and 2010) in this systematic review were found to be relevant to this report
- Two of the RCTs compared IV acetaminophen (or IV propacetamol) to an active comparator (ketorolac in two RCTs, tramadol in one RCt and metamizol in one RCT)
    - IV acetaminophen (or IV propacetamol) was found to be the least effective analgesic when measured against active comparators with respect to patient pain scores
- Five of the RCTs compared IV acetaminophen (or IV propacetamol) to placebo
    - Three of these RCTs found IV acetaminophen to have lower pain scores than placebo (one RCT measured pain scores at six and twelve hours post-operative, one RCT measured pain scores at the time of extubation, and one RCT did not give a time of measurement); the other two RCTs did not see a significant difference in pain scores
    - Four of these RCTs found a reduction in opioid consumption in patients taking IV acetaminophen, and one RCT did not see a significant change against placebo
    - Three of the five RCTs measured a difference in nausea and vomiting between IV acetaminophen and placebo; two of which did not find a significant difference, and one found a lower incidence of nausea with IV acetaminophen but not vomiting

"[IV acetaminophen] does not necessarily improve postoperative pain scores compared with the oral or rectal route… Clinical trials in the cardiac surgery population have not reliably or consistently demonstrated benefit when IV acetaminophen was added to a background opioid therapy. As such, with minimal clinical benefit, the routine administration of IV acetaminophen to all adult cardiac surgery patients is not justified based on data published to date." (page 7)

Yang, 2017[25]

Opioid Consumption and Pain Score Outcomes

Outcome	Results			Heterogeneity		
	WMD	95% CI	*P*-value	I^2 %	Chi^2	P
Difference in Pain Scores at POD1	-0.954	-1.204, -0.703	0.000	0%	2.51	0.474

"Additional IV acetaminophen to multimodal analgesia could significantly reduce pain and opioid consumption

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings							Authors' Conclusion
Pain Scores at POD2	-1.072	-2.072, -0.073	0.000	86.2%	21.80	0.000	after total joint arthroplasty with fewer adverse effects. Higher quality RCTs are required for further research" (page 11)
Pain Scores at POD3	-0.883	-1.142, -0.624	0.000	37.4%	4.79	0.188	
Opioid Consumption POD1	-3.144	-4.142, -2.146	0.000	0%	0.95	0.813	
Opioid Consumption POD2	-5.665	-7.383, -3.947	0.000	0%	0.62	0.892	
Opioid Consumption POD3	-3.563	-6.136, -0.991	0.007	65.9%	8.81	0.032	
Length of hospital stay	0.095	-0.069, 0.260	0.256	NR	NR	NR	

Safety Outcomes

Outcome	Results			Heterogeneity		
	RD	95% CI	*P*-value	I^2 %	Chi^2	P
Nausea	-0.101	-0.146, -0.057	0.000	0%	0.28	0.963
Vomiting	-0.082	-0.123, -0.042	0.000	0%	0.70	0.873

McNicol, 2016[24]

Outcome	Comparison	Risk Ratio (95% CI)	Heterogeneity	Test for overall effect	"This review provides high-quality evidence that a single dose of either IV acetaminophen or IV propacetamol provides around four hours of effective analgesia for about 36% of patients with acute postoperative pain. Low to very low quality evidence demonstrates that both formulations are associated with few adverse events, although patients receiving IV propacetamol have a higher incidence of pain on infusion than both placebo and IV acetaminophen." (page 2)
Percentage of patients with at least 50% pain relief over four hours post-administration	IV acetaminophen vs placebo	4.80 (2.30 to 10.00) for IV acetaminophen	Chi^2 = 10.56 df = 4 (*P* = 0.03) I^2 = 62%	Z = 4.18 (*P* = 0.000029)	
	IV acetaminophen/ IV propacetamol vs placebo	2.53 (2.01 to 3.19) for IV acetaminophen	Chi^2 = 24.43 df = 12 (*P* = 0.02) I^2 = 51%	Z = 7.89 (*P* <0.00001)	
	IV acetaminophen vs NSAIDs	0.90 (0.72 to 1.13)	Chi^2 = 0.04 df = 1 (*P* = 0.84) I^2 = 0%	Z = 0.90 (*P* =0.37)	
	IV acetaminophen/ IV propacetamol vs NSAIDs	1.01 (0.86 to 1.18)	Chi^2 = 8.08 df = 4 (*P* = 0.09) I^2 = 51%	Z = 0.07 (*P* =0.94)	
Percentage of patients with at least 50% pain relief over six hours post-administration	IV acetaminophen vs placebo	3.65 (2.15 to 6.21) for IV acetaminophen	Chi^2 = 7.75 df = 5 (*P* = 0.17) I^2 = 36%	Z = 4.78 (*P* <0.0001)	
	IV acetaminophen/ IV propacetamol vs placebo	2.86 (2.10 to 3.91)	Chi^2 = 17.39 df = 10 (*P* = 0.07) I^2 = 43%	Z = 6.62 (*P* < 0.0001)	
	IV acetaminophen vs NSAIDs	0.82 (0.66 to 1.02)	Chi^2 = 0.41 df = 2(*P* = 0.82) I^2 = 0%	Z = 1.79 (*P* = 0.073)	
	IV acetaminophen/ IV propacetamol vs NSAIDs	0.79 (0.66 to 0.95) for IV NSAIDs	Chi^2 = 0.75 df = 4 (*P* = 0.95) I^2 = 0%	Z = 2.56 (*P* = 0.01)	
Pain intensity at four hours post-administration	IV acetaminophen vs placebo	-1.21 (-3.73 to 1.31)	Chi^2 = 2.14 df = 5 (*P* = 0.83) I^2 = 0%	Z = 0.94 (*P* = 0.35)	
	IV acetaminophen vs NSAIDs	5.02 (3.18 to 6.86) for IV NSAIDs	Chi^2= 11.82 df = 5 (*P* = 0.04) I^2 = 58%	Z = 5.34 (*P* < 0.0001)	
Pain intensity at six hours post-	IV acetaminophen vs placebo	-7.48 (-8.98 to -5.97) for IV acetaminophen	Chi^2= 105.72 df = 11 (*P* < 0.00001)	Z = 9.75 (*P* < 0.00001)	

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings					Authors' Conclusion
administration			I^2 = 90%		
	IV acetaminophen vs NSAIDs	2.95 (1.18 to 4.72) for IV NSAIDs	Chi^2= 17.51 df = 8 (*P* = 0.03) I^2 = 54%	Z = 3.27 (*P* = 0.0011)	
	IV acetaminophen vs IV opioids	3.00 (-1.57 to 7.57)	N/A	Z = 1.29 (*P* = 0.20)	
Opioid Consumption over four hours	IV acetaminophen vs placebo	-1.33 (-1.75 to -0.91) for IV acetaminophen	Chi^2= 6.73 df = 3 (*P* = 0.08) I^2 = 55%	Z = 6.23 (*P* < 0.00001)	
	IV acetaminophen/ IV propacetamol vs placebo	-1.42 (-1.81 to -1.03) for IV acetaminophen/ IV propacetamol	Chi^2= 8.23 df = 5 (*P* = 0.14) I^2 = 39%	Z = 7.13 (*P* < 0.00001)	
	IV acetaminophen/ IV propacetamol vs NSAIDs	-0.19 (-0.37 to -0.02)	Chi^2= 0.70 df = 2 (*P* = 0.70) I^2 = 0%	Z = 2.14 (*P* = 0.033)	
Opioid consumption over six hours	IV acetaminophen vs placebo	-1.83 (-2.35 to -1.31)for IV acetaminophen	Chi^2 = 24.05 df = 7 (*P* = 0.001) I^2 = 71%	Z = 6.90 (*P* < 0.00001)	
	IV acetaminophen/ IV propacetamol vs placebo	-1.92 (-2.41 to -1.42) for IV acetaminophen	Chi^2 = 35.18 df = 13 (*P* < 0.00001) I^2 = 63%	Z = 7.62 (*P* < 0.00001)	
	IV acetaminophen vs NSAIDs	-0.81 (-0.87 to 2.49)	Chi^2 = 5.68 df = 2 (*P* = 0.06) I^2 = 65%	Z = 0.94 (*P* = 0.35)	
	IV acetaminophen/ IV propacetamol vs NSAIDs	-0.12 (-0.37 to 0.12)	Chi^2 = 28.60 df = 7 (*P* = 0.00017) I^2 = 76%	Z = 0.97 (*P* = 0.00017)	
Patients experiencing nausea	IV acetaminophen/ IV propacetamol vs placebo	0.84 (0.73 to 0.98) for IV acetaminophen/ IV propacetamol	Chi^2 = 29.61 df=15 (*P* = 0.01) I^2 = 49%	Z = 2.26 (*P* = 0.024)	
Patients experiencing vomiting	IV acetaminophen/ IV propacetamol vs placebo	0.70 (0.57 to 0.87) for IV acetaminophen/ IV propacetamol	Chi^2 = 23.59 df = 15 (*P* = 0.07) I^2 = 36%	Z = 3.28 (*P* = 0.0010)	
Apfel, 2013[19]					
Post-operative Nausea and Vomiting - IV acetaminophen was associated with a relative risk (95% CI) of 0.73 (0.60, 0.88) for nausea and 0.63 (0.45, 0.88) for vomiting, but with significant heterogeneity for nausea (P = 0.02) and vomiting (P=0.006) - NNT for IV acetaminophen was 12.3 (7.6 to 32.3) for nausea and 14.2 (8.3-50.8) for vomiting - Sensitivity analyses revealed that IV acetaminophen reduced nausea (0.63, 0.54-0.75) and vomiting (0.42, 0.31-0.56) in investigator-initiated trials, but did not reduce nausea (0.42, 0.31-0.56) and increased vomiting (1.41, 1.02-1.96) in industry-sponsored clinical trials - IV acetaminophen was generally started prophylactically in investigator-initiated trials, while it was generally given the day before surgery in industry-sponsored registration trials					"Prophylactic IV acetaminophen doses reduce post-operative nausea and vomiting with an effect size that compares well with data known from other antiemetics. [Results] suggest that the antiemetic effect of IV acetaminophen

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
- Further sensitivity analyses revealed that prophylactically administered IV acetaminophen reduced nausea and vomiting irrespective of whether it was started before surgery, intra-operatively or immediately after surgery	is not mediated through the reduction of post-operative opioid consumption, but through direct mechanisms or through reduction of post-surgical pain." (page 10)

Comparison	IV Acetaminophen	Control	Risk Ratio (95% CI)	*P*-value effect	*P*-value hetero-geneity	*P*-value Egger's Test
Nausea	281/1122	351/1097	0.73 (0.60, 0.88)	0.001	0.02	0.07
Vomiting	125/977	178/954	0.63 (0.45, 0.88)	0.008	0.006	0.20

Opioid Consumption and Pain Score Outcomes

- Reduction of post-operative opioids (average reductions were about 9 mg of morphine equivalents) did not contribute to the antiemetic effect of prophylactic IV acetaminophen (OR 0.89, 95% 0.64-1.22) for 10 mg of morphine equivalents (***P***=0.45)
- Reduction in post-operative pain (average reduction was about 0.9 points) was associated with a significant reduction in post-operative nausea (OR 0.66, 95% CI 0.47-0.93) per 1 point (P=0.02)
- Egger's regression tests did not reveal any evidence of publication bias for any of the studied outcomes (***P*** > 0.05 for all outcomes)

Jebaraj, 2013[23]

Key Outcomes in Included Studies

Study	Treatment groups	Duration and Timing	Outcome Measures	Analgesic Outcome	Opioid Consumption
Khalili 2013	15mg/kg IV APAP	Preventive group: before skin closure Preemptive group: 30min before surgery	Pain (VRS) 5 mins pre-op; 6, 12, 18 and 24h post-op; 24h meperidine consumption	Lower pain score in both preemptive and preventive APAP groups at 6h	Opioid consumption lowest in preemptive APAP group
Hiller 2012	30mg/kg IV APAP for 15m; max dose 1.5g	End of surgery and twice thereafter at 8h intervals	VAS Score PCA opioid requirements	VAS score lower in APAP group (39%) compared to placebo (72%) (*P* < 0.05)	No significant difference in opioid consumption during 24h post-operative period
Hynes 2006	2 g IV Prop-acetamol IV Placebo	Two doses 5h apart	Pain relief Use of rescue analgesia	Significantly better pain relief with IV APAP	Significantly higher use of rescue analgesia at 5h and 10h in placebo group
Sinatra 2005	1 g IV APAP2 g IV prop-acetamol IV Placebo	Single and repeated doses, post-operative	Pain relief (0-5) Morphine usage (PCA)	Better pain relief when compared to placebo group	Median time to first morphine rescue longer, reduced morphine consumption over 24h period in IV APAP group
Hern-andez-	2 g IV prop-	Repeated doses, post-	Pain intensity (VAS, VRS)	Similar pain relief at most	Opioid consumption 46%

"IV acetaminophen is a safe and effective component of multimodal analgesic regimen, and it reduces postoperative opioid consumption after orthopedic surgery, but at present there is insufficient data to decide whether [IV acetaminophen] reduces opioid-related adverse effects." (page 5)

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings						Authors' Conclusion
Palazon 2001	acetamol IV Placebo	operative	Morphine usage (PCA)	time points	lower in IV APAP group	
Delbos 1995	2 g IV Prop-acetamol IV Placebo	Repeated doses, post-operative	Pain intensity (VAS, VRS) Morphine usage (PCA)	No difference in pain score	At 24h, opioid consumption was significantly lower with propacetamol	
Peduto 1998	2g IV prop-acetamol IV Placebo	Repeated doses, post-operative	Pain intensity (VAS, VRS) Morphine usage (PCA)	No difference in pain intensity	Reduction in PCA opioid consumption	
Granry 1997	30 mg/kg prop-acetamol	Single injection	Visual and verbal pain scale	Up to 6h, visual and verbal pain scores significantly lower in propacetamol group		

Adapted from Intravenous Paracetamol Reduces Postoperative Opioid Consumption after Orthopedic Surgery: A Systematic Review of Clinical Trials, Jebaraj et al. 2013. Available from: https://www.hindawi.com/journals/prt/2013/402510/ Creative commons license: https://creativecommons.org/licenses/by/3.0/

APAP = acetaminophen; CABG = coronary artery bypass graft; CI = confidence interval; h = hour; IV = intravenous; kg = kilograms; mg = milligrams; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; PCA = patient controlled analgesia; PO = by mouth; POD = post-operative day; Q6H = every 6 hours; PRN = as needed; RR = risk ratio; VAS = visual analog scale

Appendix 5: Overlap between Included Systematic Reviews

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Author and Date	Systematic Review Citation						
	Blank 2018[20]	Guo 2018[22]	Douzjian 2017[21]	Yang 2017[25]	McNicol 2016[24]	Apfel 2013[19]	Jebaraj 2013[23]
Abdulla 2012a	X				X		
Abdulla 2012b	X				X		
Abrun 2003					X		
Akarsu 2010					X		
Akil 2014					X		
Alhashemi 2006	X						
Alimian 2014	X						
Apfel C 2015		X					
Arici 2009					X	X	
Arslan 2011					X	X	
Arslan 2013					X		
Atallah 2010			X				
Atef 2008					X	X	
Avellaneda 2000			X				
Beaussier 2005					X		
Boccara 2005	X						
Brodner 2011					X	X	
Cakan 2009					X	X	
Camu F 2017		X					
Candiotti 2008						X	
Cattabriga 2007			X			X	
Chen 2011					X		
Ciummo F 2015		X					
Cok 2011						X	
Corness 2010							
Dejonckheere 2001					X		
Delbos 1995					X		X
Eremenko 2009			X		X		
Emir 2010						X	
Fadly 2006						X	

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Author and Date	Systematic Review Citation						
	Blank 2018[20]	Guo 2018[22]	Douzjian 2017[21]	Yang 2017[25]	McNicol 2016[24]	Apfel 2013[19]	Jebaraj 2013[23]
Faiz 2014					X		
Farkas 1992					X		
Fletcher 1997					X		
Gallipani A 2017		X		X			
Gimbel 2008						X	
Gokten 2011						X	
Granry 1997							X
Grundmann 2006						X	
Gupta A 2016		X		X			
Hahn 2003					X		
Hernandez-Palazon 2001							X
Hiller 2012					X		X
Hong 2010						X	
Hynes 2006					X		X
Inal 2006					X		
Jahr 2012 Study 2, 65-					X		
Jahr 2012 Study 2, 65+					X		
Jahr 2012 Study 3, 65-					X		
Jahr 2012 Study 3, 65+					X		
Jarde 1997					X		
Jokela 2010	X					X	
Juhl 2006					X		
Kamath 2014	X				X		
Kampe 2006					X		
Kara 2010					X		
Karaman 2010					X		
Kelly JS 2014		X					
Kemppainen 2006					X		

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Author and Date	Systematic Review Citation						
	Blank 2018[20]	Guo 2018[22]	Douzjian 2017[21]	Yang 2017[25]	McNicol 2016[24]	Apfel 2013[19]	Jebaraj 2013[23]
Khajavi 2007					X		
Khalil 2005			X				
Khalili 2013					X		X
Khan 2007					X		
Kilicaslan 2010					X	X	
Koppert 2006					X		
Korkmaz 2010					X		
Lahtinen 2002			X		X		
Landwehr 2005					X		
Lee 2010					X	X	
Leykin 2008					X		
Looke TD 2013		X					
Ma 2003					X		
Maghsoudi 2014					X		
Marty 2005					X		
Memis 2010	X					X	
Mimoz 2001	X				X		
Minkowitz 2008						X	
Mitra 2012					X		
Moller 2005a					X		
Moller 2005b					X		
Moon 2011						X	
Mowafi 2012	X						
Murata-Ooiwa M 2017		X		X			
Ohnesorge 2009					X	X	
Omar 2011					X		
Oncul 2011					X		
O'Neal JB 2017		X		X			
Oreskovic 2014					X		
Paech 2014					X		
Pal 2014	X						

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Author and Date	Systematic Review Citation						
	Blank 2018[20]	Guo 2018[22]	Douzjian 2017[21]	Yang 2017[25]	McNicol 2016[24]	Apfel 2013[19]	Jebaraj 2013[23]
Peduto 1998					X		X
Pettersson 2005			X				
Pettersson 2006			X				
Platzer 2011						X	
Ranucci 1999			X				
Salihoglu 2009						X	
Salonen 2009					X		
Sanyal 2014					X		
Shimia 2014					X		
Siddik 2001					X	X	
Sinatra 2005					X		X
Singla NK 2014 Study 1		X					
Singla NK 2014 Study 2		X					
Strode 2016	X						
Sumer 2014	X						
Swaika 2013	X						
Tiippana 2008					X		
Togrul 2011					X		
Topal 2009						X	
Toygar 2008						X	
Tunali 2013					X		
Tuncel 2012					X		
Tuncel 2015	X						
Unal 2013					X		
Unal 2015	X						
Upadya 2015	X						
Uvarov 2008						X	
Van Aken 2004					X		
Varrassi 1999					X		
Viscusi 2008						X	

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Author and Date	Systematic Review Citation						
	Blank 2018[20]	Guo 2018[22]	Douzjian 2017[21]	Yang 2017[25]	McNicol 2016[24]	Apfel 2013[19]	Jebaraj 2013[23]
Vuilleumier 1998					X		
Wininger 2010	X				X	X	
Zhou TJ 2001		X			X		

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