Immediate-Rescue and Related Designs for Analgesic Trials in Newborns and Infants

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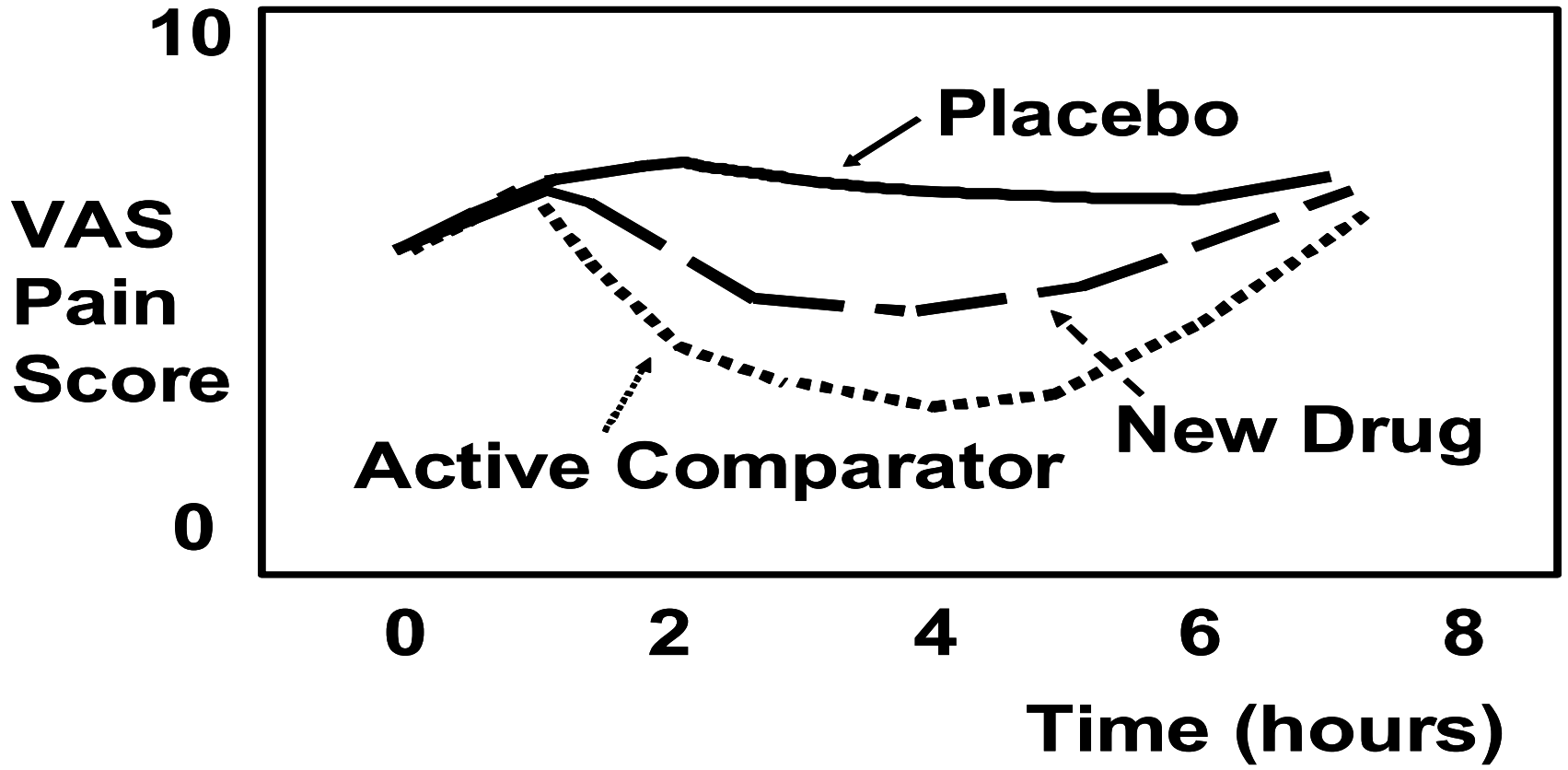
Background and Questions

- What are immediate-rescue designs, how do they differ from traditional analgesic trials?
- How have immediate-rescue designs performed to date?
  - in the entire pediatric age range
  - in neonate – age 2
- Are there ways to improve on these designs?

Background

- Pediatric analgesic trials historically have had difficulties with low enrollments, failed trials.
- 2010 FDA consensus workshop
- 2012 Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. Published in *Pediatrics, 2012 129: 354-64*
- Recommendation to consider immediate-rescue pragmatic designs
- Analgesic-sparing, especially opioid-sparing, as a surrogate efficacy measure instead of pain intensity scores.

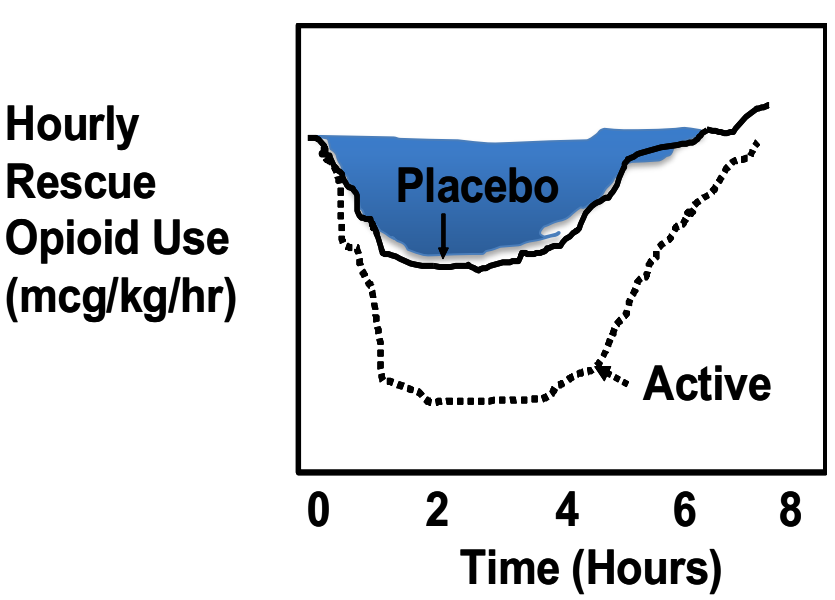
Traditional Single-Dose Analgesic Trial Design

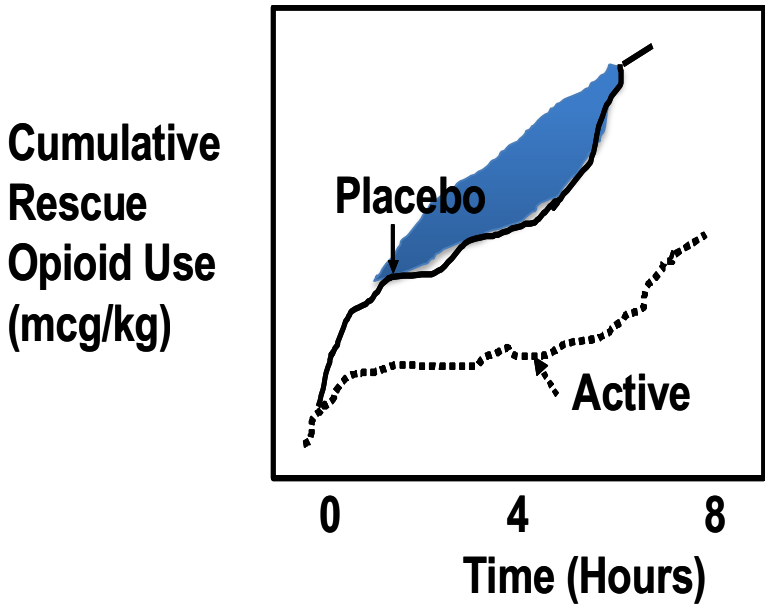


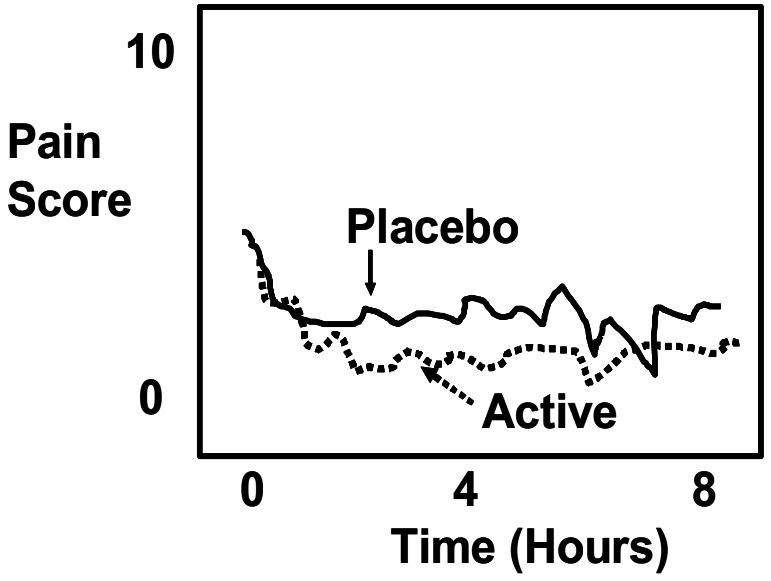
Analgesic-Sparing as a Surrogate Measure of Analgesic Efficacy

- Double-Blind, Parallel-Placebo
- Group A gets active drug
- Group B gets placebo
- Both groups get immediate access to rescue analgesia.
  - For postoperative patients, this could be a PCA or NCA with an opioid.

Immediate-Rescue Design Using PCA/NCA







Questions for 2021 Workshop

- How have immediate-rescue designs been implemented for neonate-age 2 analgesic trials before and after 2015?
- Are there uniquely different challenges for these trials in neonate-age 2 trials compared to trials throughout pediatrics?
- Initial phase of a new systematic review for neonate-age 2 trials
- New challenges imposed by practice changes from 2009 - 2021

Immediate Rescue Designs in Pediatric Analgesic Trials

A Systematic Review and Meta-analysis

Joe Kossowsky, Ph.D., Carolina Donado, M.D., Charles B. Berde, M.D., Ph.D.

ABSTRACT

Background: Designing analgesic clinical trials in pediatrics requires a balance between scientific, ethical, and practical concerns. A previous consensus group recommended immediate rescue designs using opioid sparing as a surrogate measure of analgesic efficacy. The authors summarize the performance of rescue analgesic designs in pediatric trials of four commonly used classes of analgesics: opioids, nonsteroidal antiinflammatory drugs, acetaminophen, and local anesthetics.

Methods: MEDLINE, Embase, CINAHL, The Cochrane Library, and Web of science were searched in April 2013. The 85 studies selected were randomized or controlled clinical trials using immediate rescue paradigms in postoperative pain settings. A random-effects meta-analysis was used to synthesize predefined outcomes using Hedges' g. Difference between the means of the treatment arms were also expressed as a percentage of the corresponding value in the placebo group (placebo-treatment/placebo). Distributions of pain scores in study and control groups and relationships between opioid sparing and pain scores were examined.

Results: For each of the four study drug classes, significant opioid sparing was demonstrated in a majority of studies by one or more of the following endpoints: (1) total dose (milligram per kilogram per hour), (2) percentage of children requiring rescue medication, and (3) time to first rescue medication (minutes). Pain scores averaged 2.4/10 in study groups, 3.4/10 in control groups.

Conclusions: Opioid sparing is a feasible pragmatic endpoint for pediatric pain analgesic trials. This review serves to guide future research in pediatric analgesia trials, which could test whether some specific design features may improve assay sensitivity while minimizing the risk of unrelieved pain.

(ANESTHESIOLOGY 2015; 122:150-71)

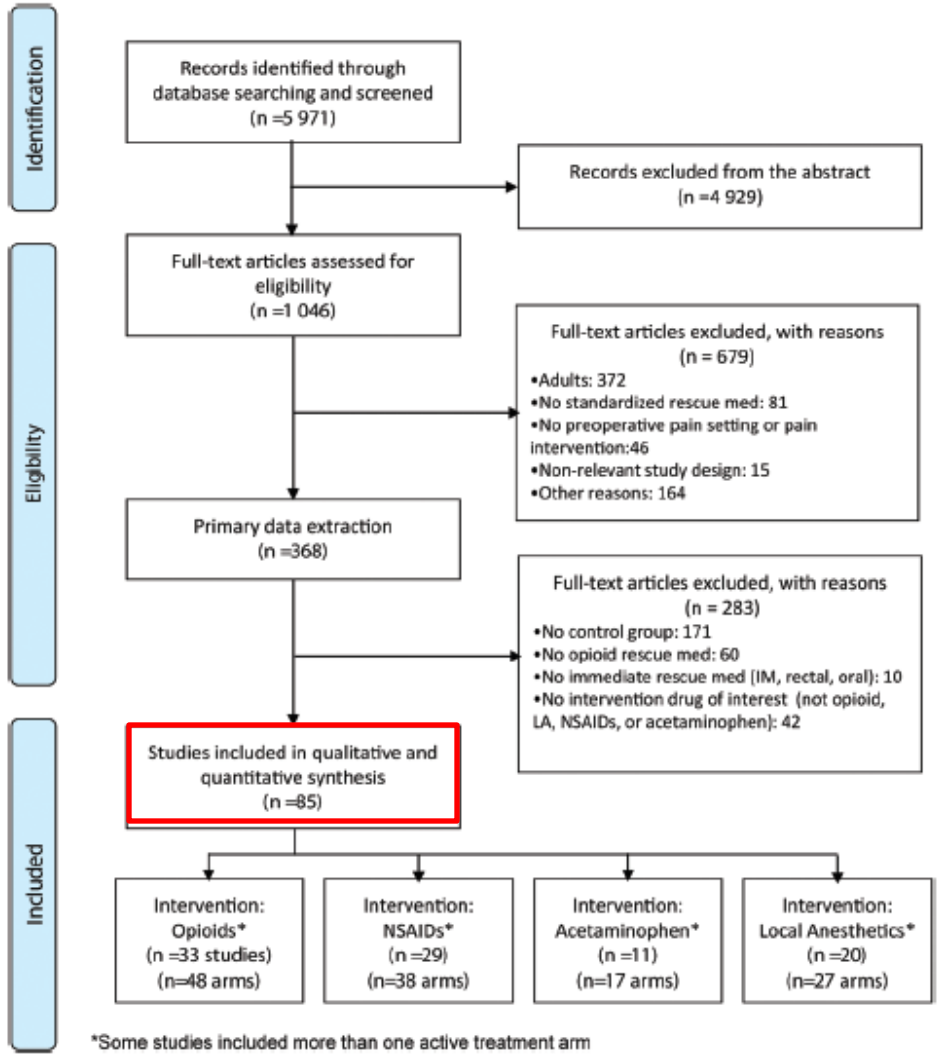


Fig. 2. Flow chart of literature search with summary of excluded and included studies. IM = intramuscular; LA = local anesthetic; NSAIDs = nonsteroidal antiinflammatory drugs.

Selection Criteria

1. Randomized or controlled clinical trial
2. Children and adolescents aged ≤18 yr
3. Use of immediate rescue paradigms
4. Assessed rescue medication and/or pain scores in postoperative pain setting

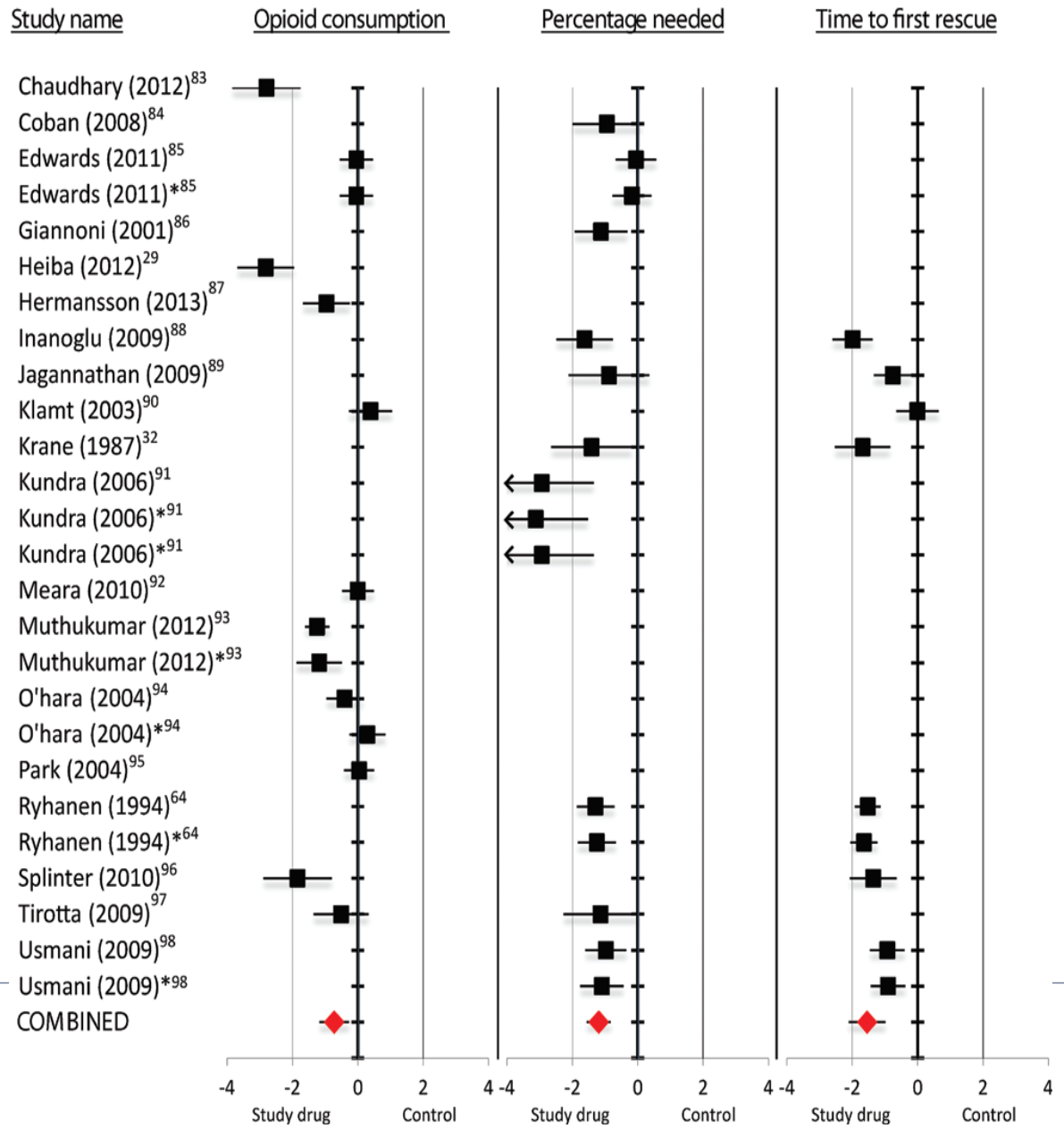
We included articles only if:

1. Included placebo or control groups
2. Used IV opioids as rescue medication
3. Used opioids, NSAIDs, acetaminophen, or local anesthetics as the "study drug,"

We chose to evaluate the following three analgesic sparing outcomes:

1. Rescue opioid usage (mg/kg/hr)
2. Percentage of subjects requiring rescue medication
3. Time to first rescue medication (mins)

Local Anesthetics as Study Drug



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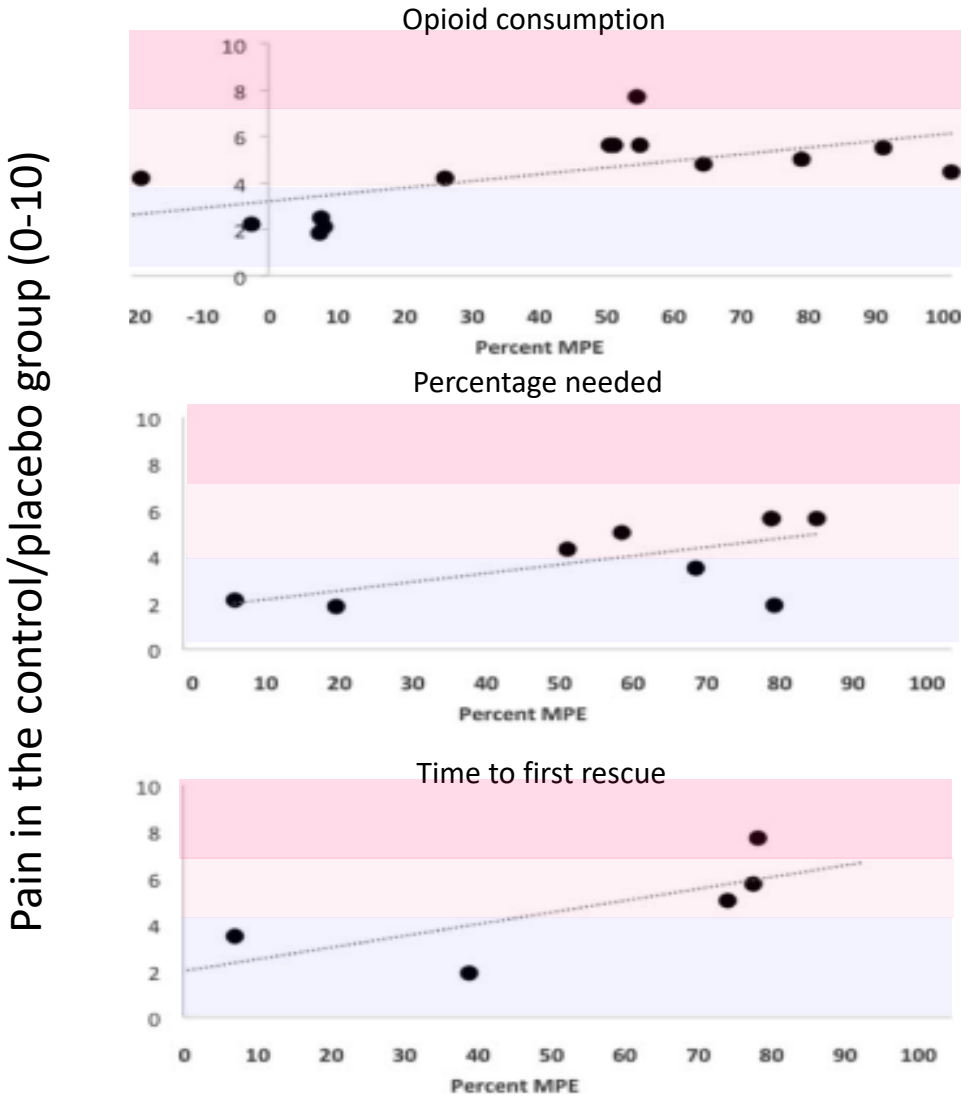
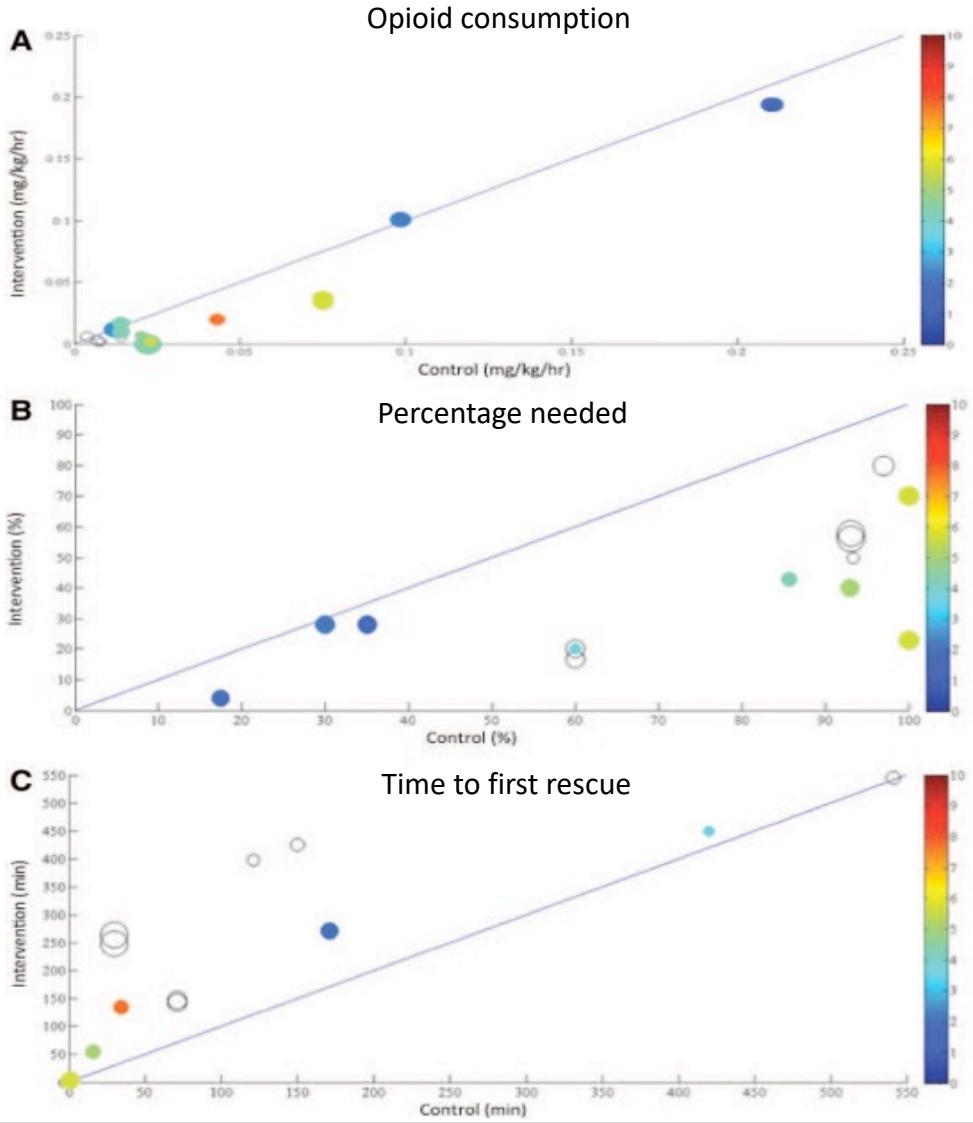
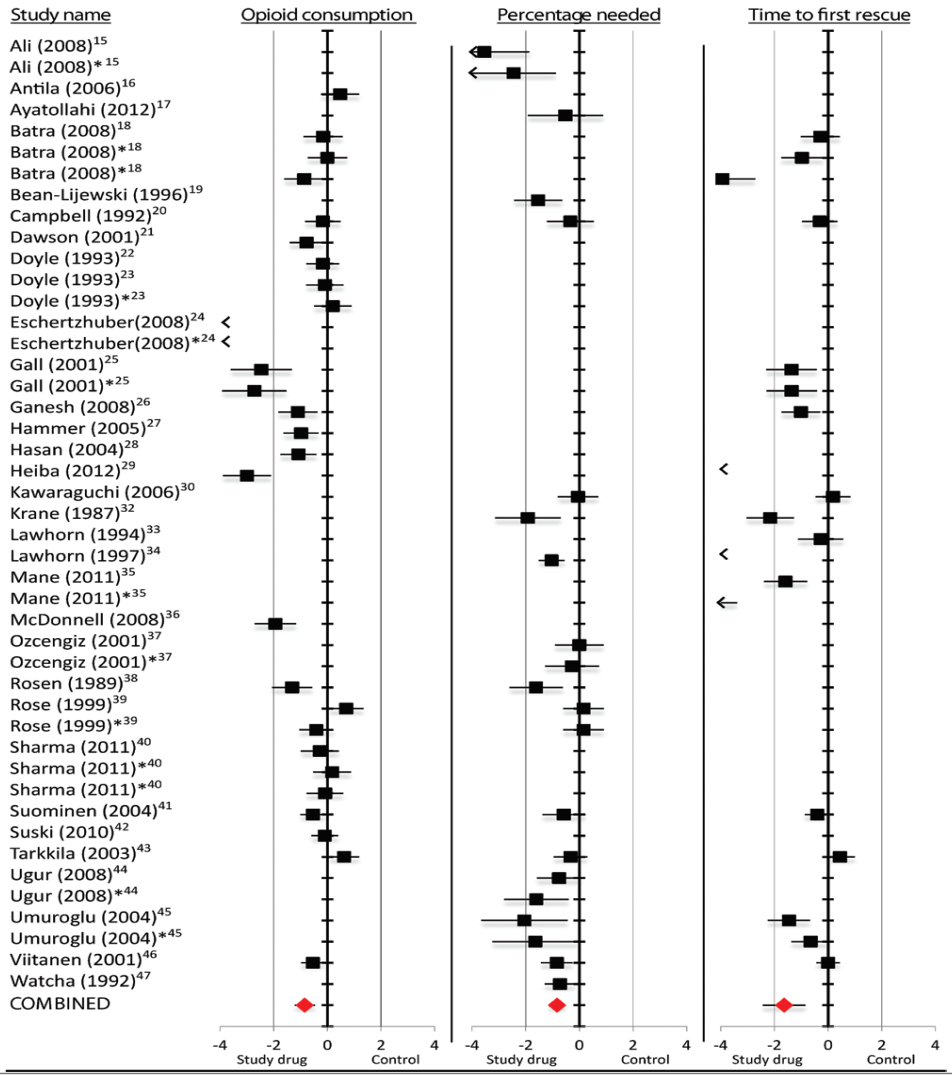
Local Anesthetics as Study Drug

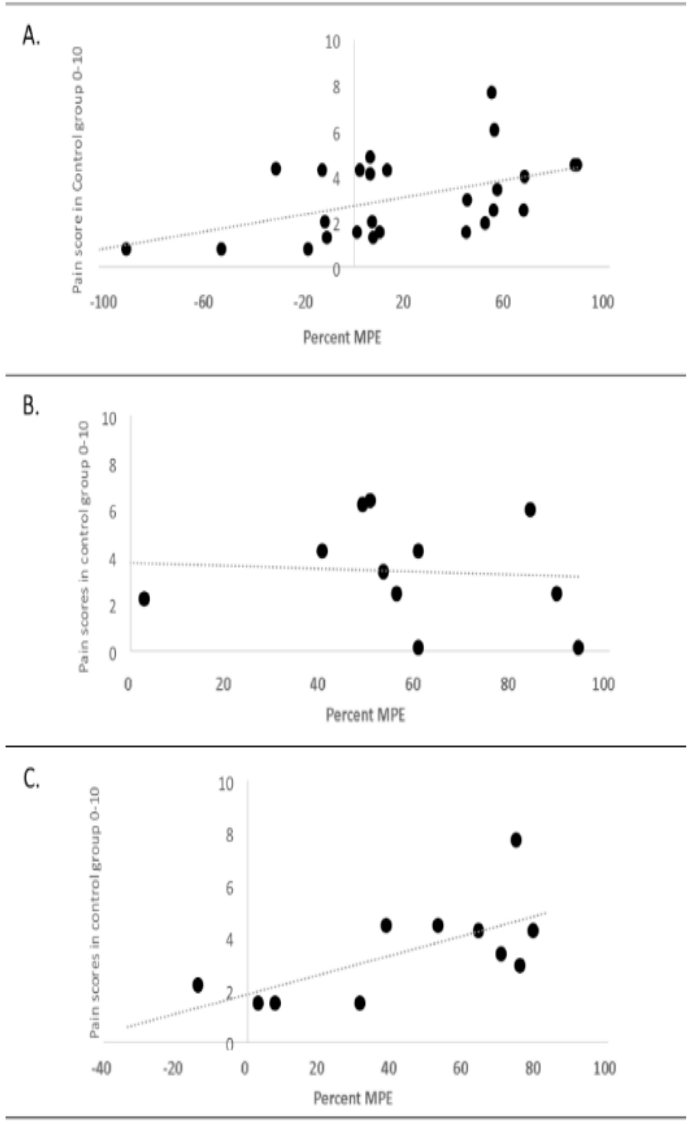


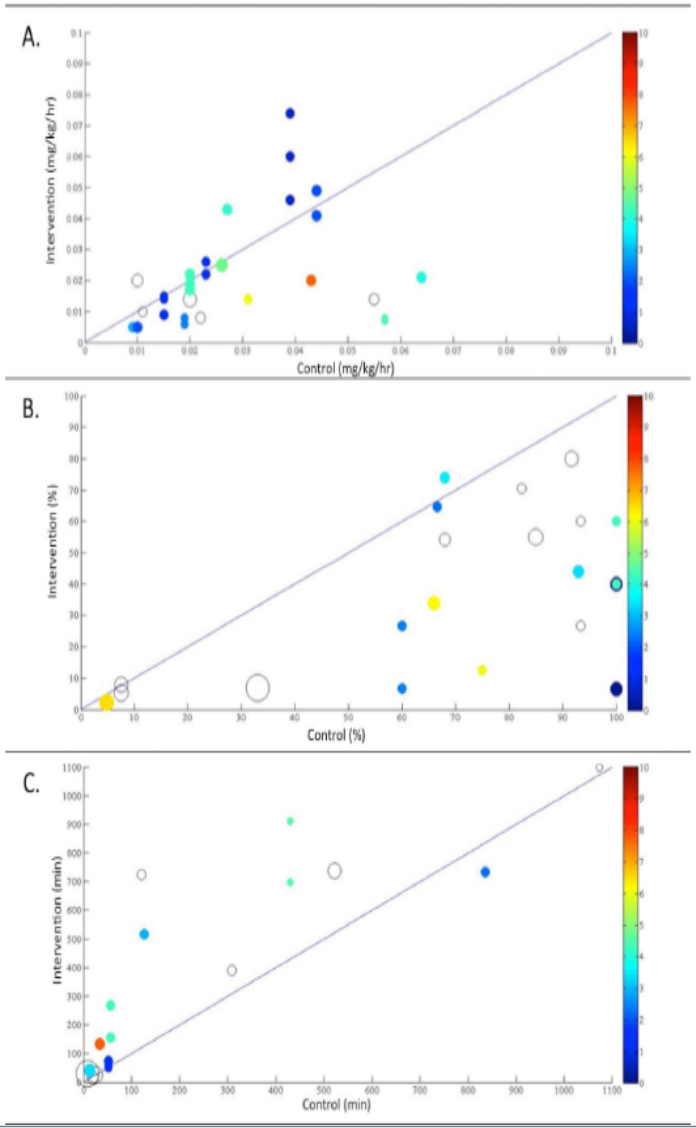


Maximum possible effect
(placebo –study/placebo)

Opioid as Study Drug







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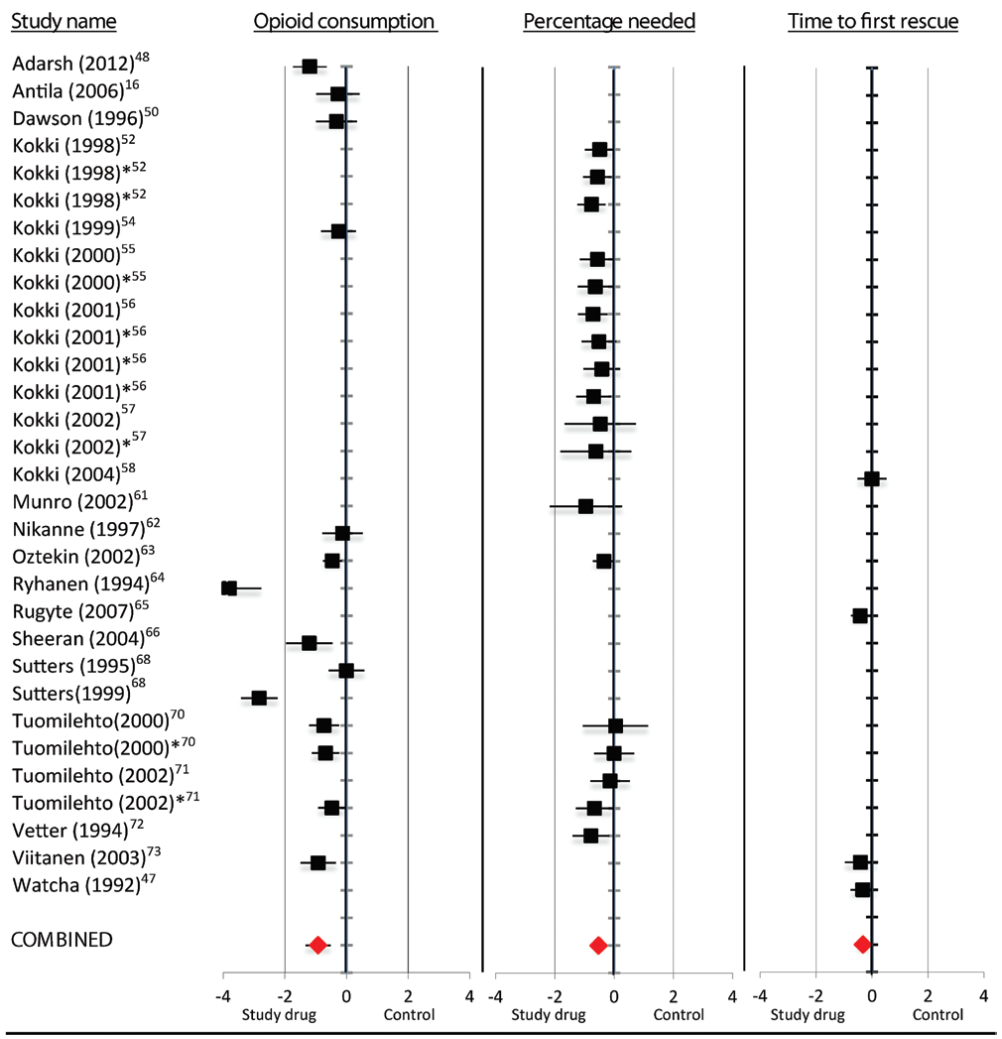
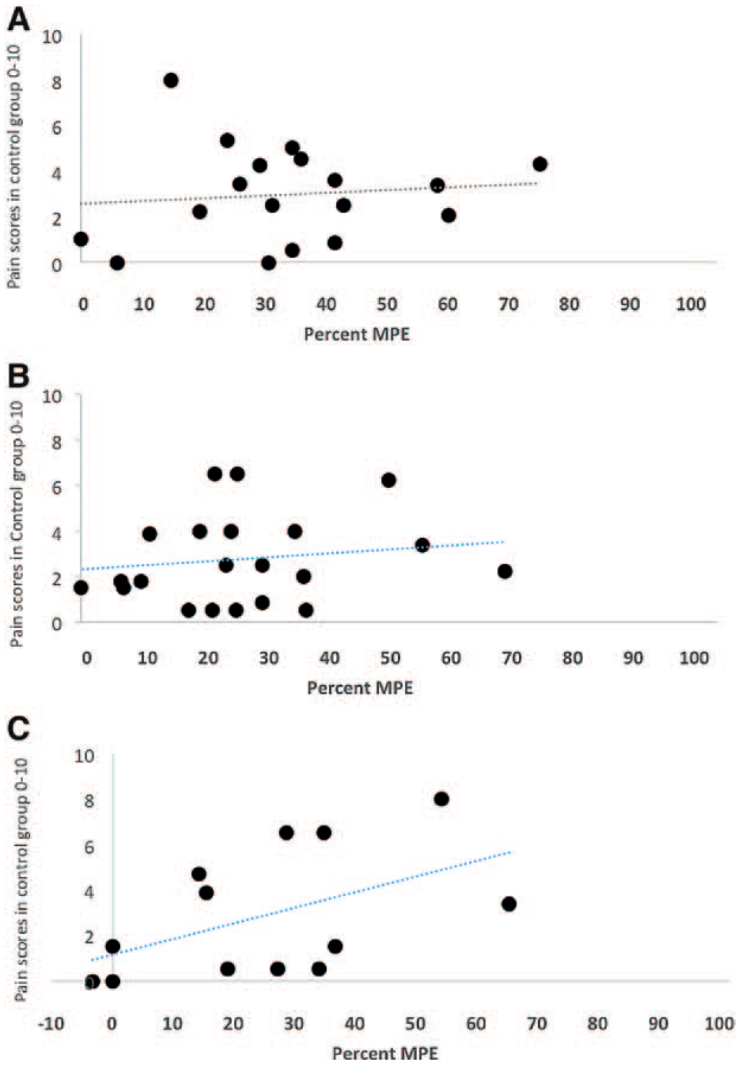
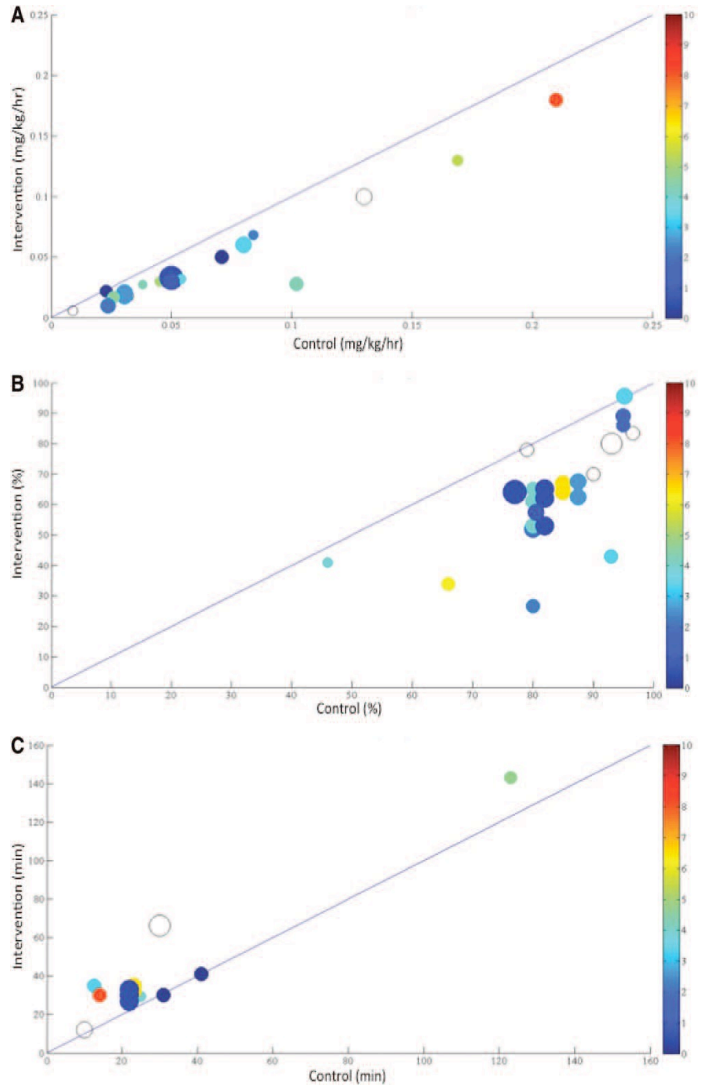
NSAIDs as Study Drug







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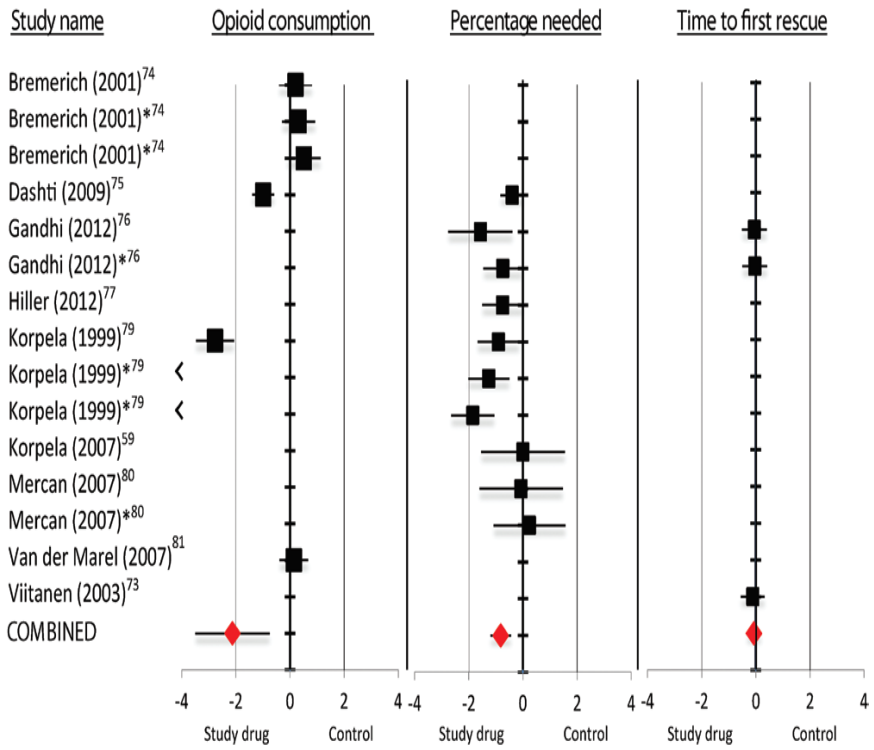
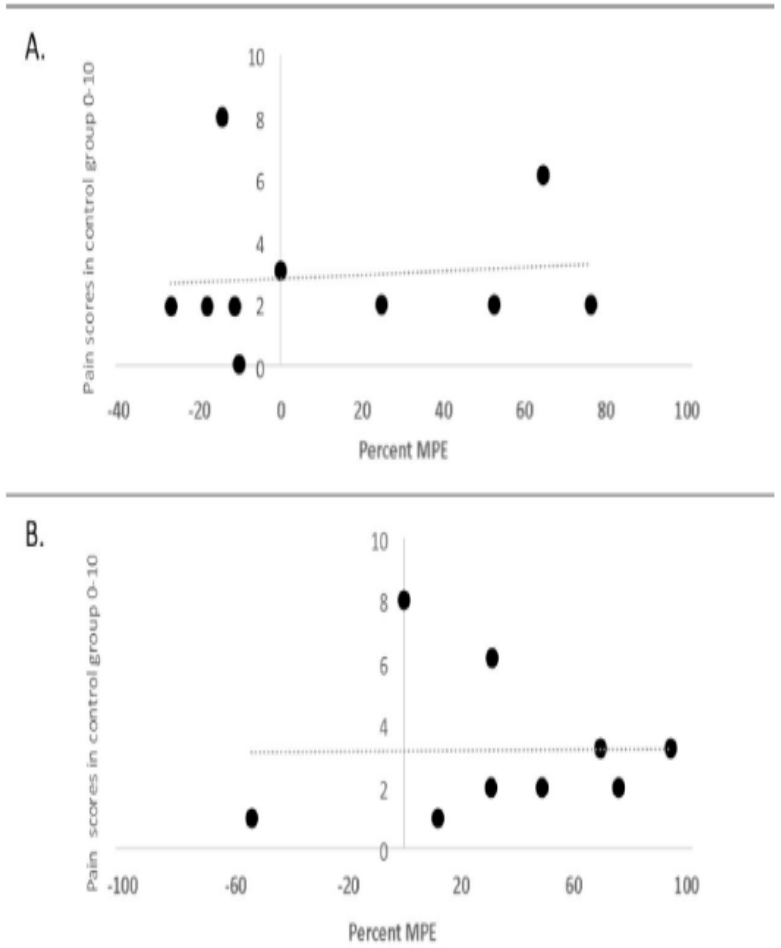
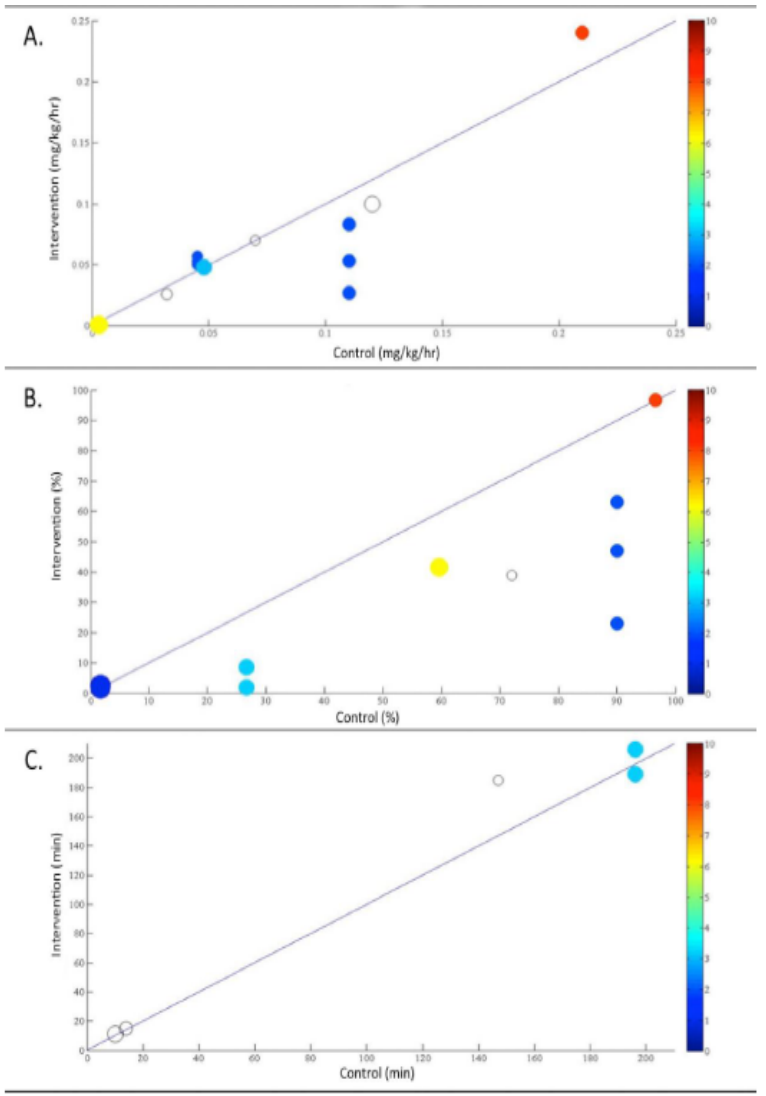
Acetaminophen as Study Drug







Take home points from 2015 paper

- Immediate rescue analgesic trials show reasonable assay sensitivity and tolerably low burden (low-moderate pain scores) for children after surgery.
- High variations in the design methodologies
  - End points selected
  - Rescue medication
  - Observation time

Immediate Rescue Designs in Neonate-Age 2 Analgesic Trials:

- Replicate the previous work
  - Update search from 2013 to date
  - Focus on neonates to <2 years of age
- Similar Inclusion criteria




Immediate Rescue Designs in Neonate-Age 2 Analgesic Trials:

- Expanded to included head-to-head /add-on comparisons

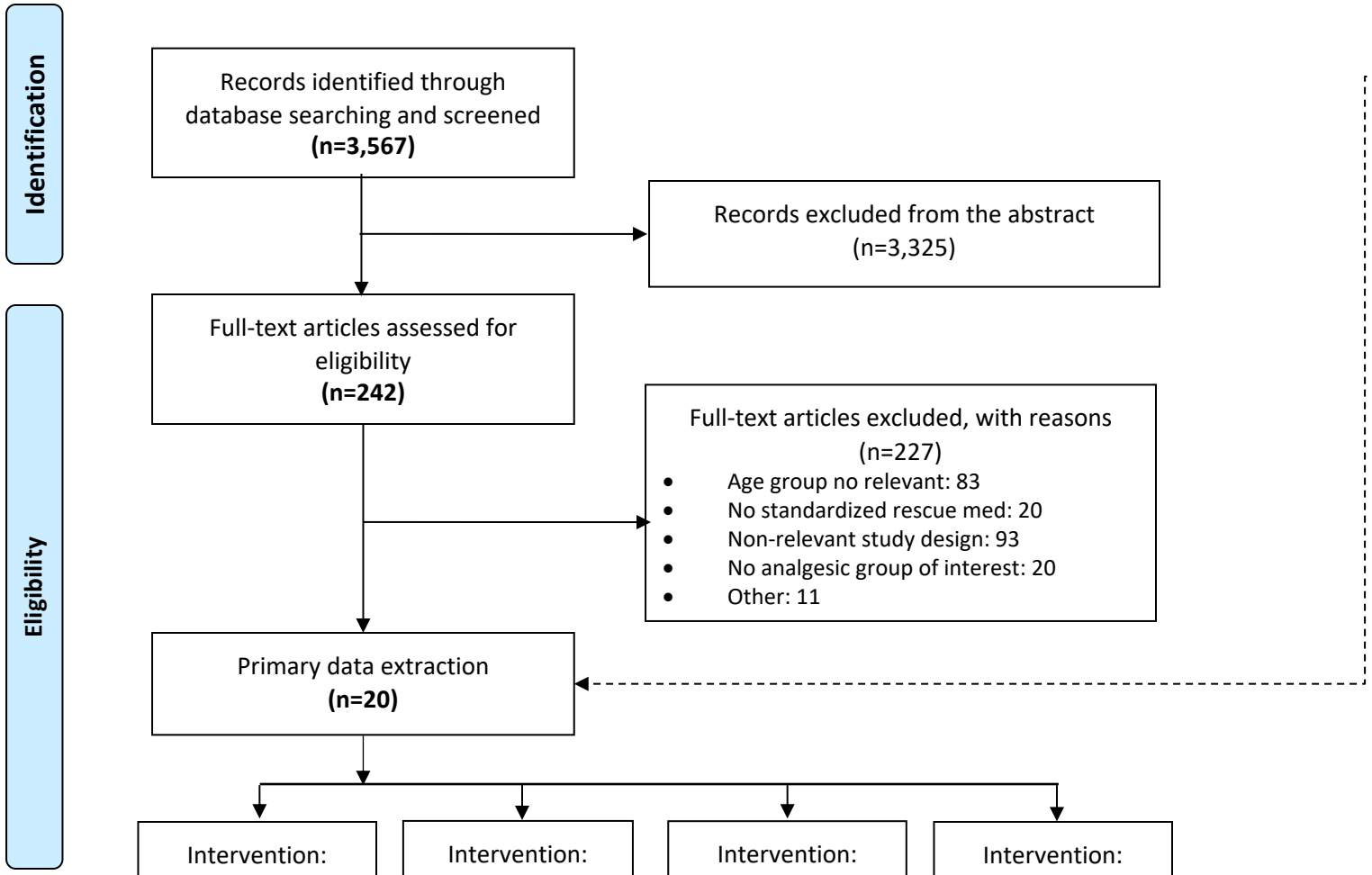
Placebo control:
Group 1 -> Active Med A
Group 2 -> Placebo

Add-on:
Group 1 -> Active Med A
Group 2 -> Active Med A + Active med B

Head –to-Head:
Group 1 -> Active Med A
Group 2 -> Active Med B

Immediate rescue available to all groups

- Use of Network Meta-Analysis to compare the clinical effectiveness of these three types of studies



5 from 2015 paper

45% (n=9) are head-to-head studies

Trends in Pediatric Postoperative Care from 2009 – 2021: Challenges for Analgesic Trials

- Enhance Recovery After Surgery (ERAS) Protocols, Treatment Bundles
- Greater emphasis on minimizing opioid exposure, reduced use of opioid infusions, lower starting opioid infusion rates
- Rapidly increasing use of regional anesthesia, especially with ultrasound guided peripheral/plexus blocks and catheters
- Widespread practice of scheduled acetaminophen and NSAID as basal analgesic regimen

Conclusions

- Immediate rescue designs and add-on designs have some favorable pragmatic advantages for neonatal-age 2 trials, and they are being used widely for analgesic trials.
- Current trends in care, including round-the-clock use of acetaminophen-NSAID combinations, wide use of regional anesthesia, and greater avoidance of opioids have implications for design of neonatal-pediatric trials.
- With wider use of **add-on** and **head-to-head** trials in neonatal – age 2 trials, is there a role for **network meta-analysis** for judging clinical effectiveness?

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