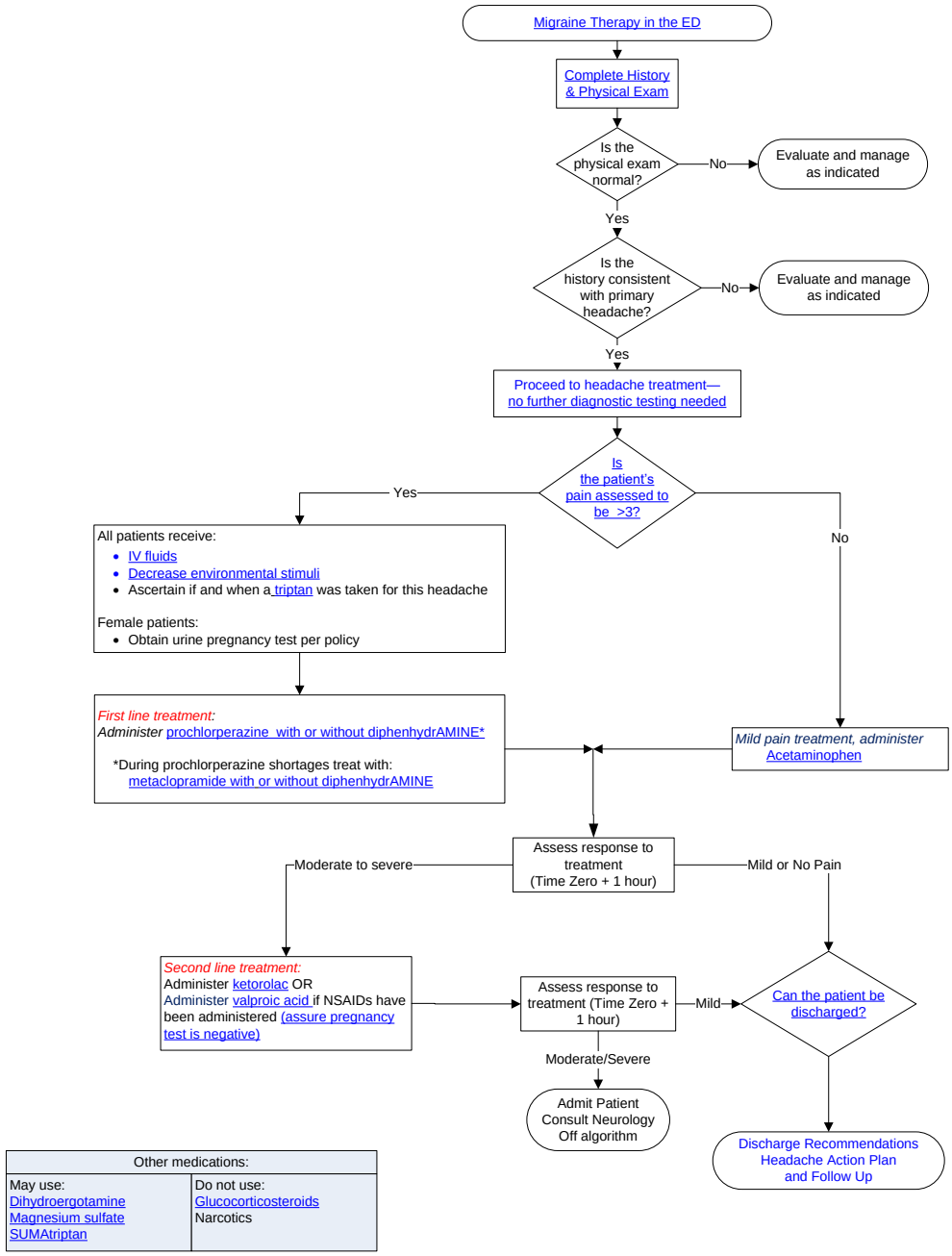
Children's Mercy Hospitals and Clinics
Evidence Based Practice Clinical Practice Guide

Migraine in the ED/UCC



Definition: Acute migraine is a primary headache disorder. It is periodic in nature. Migraine headache is usually unilateral and throbbing in nature. Nausea, vomiting, photophobia, phonophobia, and abdominal pain are symptoms associated with migraine. Some patients may experience an aura before or during headache symptoms (HIS Classification of MigrFsupporaine, retrieved 2014).

Epidemiology: Migraine headaches are a common complaint in children. The frequency of migraine occurrence increases through adolescence. The means onset of migraine is 7.2 years for males and 10.9 years for females (Lewis et al., 2014). The prevalence of migraine headache increases with age:

Age	Migraine Prevalence
3-7 years	3%
4-11 years	4-11%
11-15 years	8-23%

Objective of Guideline: The objective of the CPG is to standardize the care of children seen in the Emergency Department with a chief complaint of a migraine.

Target Users: Emergency Department/Urgent Care Center physicians, General Pediatricians, Pediatric Nurse Practitioners, and Hospitalists

Guideline Inclusion Criteria:

Children > 8 years and < /= 21 years of age
Normal physical exam
History consistent with primary headache

Guideline Exclusion Criteria:

Signs of secondary headache, such as focal neurological changes
Hypertension
Trauma

Clinical Questions Answered by Guideline:

1. In children who present to the ED with a refractory migraine headache, does getting a computed tomography (CT) scan versus not getting a CT scan change the management in the ED (see Appendix A)?
2. In the pediatric patient diagnosed with a refractory migraine, is prochlorperazine an effective treatment compared to ketorolac, metoclopramide, sodium valproate, IV magnesium (see Appendix B)?
3. In the pediatric patient diagnosed with acute migraine is valproic acid an effective treatment (see Appendix C)?
4. In the pediatric patient diagnosed with a refractory migraine, is DHE effective in the treatment of refractory migraine (see Appendix D)?
5. In patients with migraine, does treatment with intravenous magnesium sulfate alleviate headache (see Appendix E)?

Additional Critically Appraised Topics (CATs) were prepared:

- Corticosteroids for refractory migraine in the pediatric ED (see Appendix F
- Ketorolac for refractory migraine in the pediatric ED (see Appendix G)
- Metoclopramide for refractory migraine in the pediatric ED (see Appendix H)
- Sumatriptan for refractory migraine in the pediatric ED (see Appendix I)

Practice Recommendations:

1. *History and Physical Exam*

The patient with headache will typically present with:

- Headache attack lasting 1-72 hours
- Headache has at least two of the following four features:
  - Either bilateral or unilateral (frontal/temporal) location
  - Pulsating quality
  - Moderate to severe intensity
  - Aggravated by routine physical activities
- At least one of the following accompany the headache:
  - Nausea and vomiting
  - Photophobia and phonophobia (Lewis et al., 2004)
- Differential diagnosis
  - Tension headache
  - Cluster headache

2. *Diagnostic evaluation*

Assess the patient's pain using age appropriate pain scales. FACES pain scale is appropriate for children 3 years and older, and the Visual Analog Scale is appropriate for children 6 years and older. Migraine is diagnosed by detailed history and physical, we recommend against neuroimaging (see Appendix A for the complete CAT).

3. *Treatment:*

Mild Pain- For children who rate their pain mild, and do not meet the exclusion criteria of the Analgesia Standing Order (for CM users, the policy is found at: http://scope/policies/837), either acetaminophen or ibuprofen may be administered and discharge should include the Headache Relief Guide.

Moderate to Severe Pain- For children who rate their pain as moderate to severe, CATs have been synthesized for each of the potential medications.

- First line
  - Prochlorperazine – see Appendix B for the complete CAT
- Back up first line
  - Metoclopramide – see Appendix H for the complete CAT
- Second line
  - Ketorolac– see Appendix G for the complete CAT
  - Valproic acid– see Appendix C for the complete CAT
- May be used (in alphabetical order)
  - Dihydroergotamine– see Appendix D for the complete CAT
  - Magnesium Sulfate (IV) – see Appendix E for the complete CAT
  - Sumatriptan– see Appendix I for the complete CAT
- Not recommended
  - Glucocorticosteroids– see Appendix F for the complete CAT
  - Narcotics

Outcome Measures:

Global:

PowerPlan Usage
Use of Migraine Action Plan –
LOS

Diagnostics

Radiology

CT

Medications

If Pain Score < 3
- Acetaminophen- if given via the Analgesic Standing Order
- Ibuprofen -if given via the Analgesic Standing Order
- Naproxen -if given via the Analgesic Standing Order

If Pain score >/= 3

Preferred first line treatment
- Prochlorperazine-
- Diphenhydramine

Preferred treatment (when prochlorperazine is not available)
- Metoclopramide

Second choice treatments
- Valproic acid
- Ketorolac
- Dihydroergotamine
- Magnesium sulfate IV
- Sumatriptan

Not recommended
- Narcotics
- Glucocorticosteroids

Potential Cost Implications:

The goal of the Migraine CPG is to reduce the cost by decreasing unnecessary interventions for this population.

Potential Organizational Barriers:
Staff education and parental expectations

Supporting tools:

PowerPlan:
Unique Plan Description: EDP Migraine CPG EKM
Plan Selection Display: EDP Migraine CPG
PlanType: ED/UCC
Version: 5
Begin Effective Date: 06/09/2016 06:33
End Effective Date: Current
Available at all facilities

EDP Migraine CPG EKM
Vital Signs/Monitoring

☐ Vital signs

☐ CR monitor

Frequency: Continuous, RN to change limits Yes, Upper HR limit 185, Lower HR limit 95, Upper RR limit 70, Lower RR limit 20, Cardiorespiratory Leads 3 [Less Than 6 month(s)] (DEF)*

Frequency: Continuous, RN to change limits Yes, Upper HR limit 180, Lower HR limit 85, Upper RR limit 60, Lower RR limit 15, Cardiorespiratory Leads 3 [6 - 36 month(s)]

Frequency: Continuous, RN to change limits Yes, Upper HR limit 150, Lower HR limit 60, Upper RR limit 50, Lower RR limit 12, Cardiorespiratory Leads 3 [3 - 11 year(s)]

Frequency: Continuous, RN to change limits Yes, Upper HR limit 140, Lower HR limit 20, Upper RR limit 35, Lower RR limit 10, Cardiorespiratory Leads 3 [Greater Than or Equal To 11 year(s)]

Frequency: Continuous, RN to change limits Yes, Upper HR limit 200, Lower HR limit 100, Upper RR limit 70, Lower RR limit 20, Cardiorespiratory Leads 5, Cyanotic Cardiac

☐ Temperature

☐ BP

Upper Systolic Limit: 110, Lower Systolic Limit: 60, Upper Diastolic Limit: 60, Lower Diastolic Limit: 30, Upper MAP Limit: 75, Lower MAP Limit: 40 [6 - 24 month(s)] (DEF)*

Upper Systolic Limit: 120, Lower Systolic Limit: 70, Upper Diastolic Limit: 80, Lower Diastolic Limit: 30, Upper MAP Limit: 90, Lower MAP Limit: 45 [3 - 10 year(s)]

Upper Systolic Limit: 140, Lower Systolic Limit: 80, Upper Diastolic Limit: 90, Lower Diastolic Limit: 40, Upper MAP Limit: 105, Lower MAP Limit: 50 [Greater Than or Equal To 11 year(s)]

Upper Systolic Limit: 95, Lower Systolic Limit: 55, Upper Diastolic Limit: 60, Lower Diastolic Limit: 35, Upper MAP Limit: 70, Lower MAP Limit: 40 [Less Than 6 month(s)]

☐ Pain assessment

Nutrition/Diet

☐ NPO diet

Nursing

☑ Minimize Environmental Stimulation

Provide a quiet low lit room, minimize television, telephone, and visitation.

☐ Gown patient

Consults/Therapy

☐ Consult to Child Life

T;N, Urgent

☐ Consult to Neurology

Laboratory

☐ Urine pregnancy test POC

Radiology

Only needed with atypical migraine, headache associated with seizure, or abnormal

neurological examination.(NOTE)*

☐ CT Head or Brain w/o Contrast

Continuous Medications/Fluids

☐ IV placement

☐ NS fluid bolus

☐ D5W 1/2NS

☐ D5NS

Medications

Oral medications are reserved for headache pain scores less than or equal to 3. Refer to Pain Management Policy P-15.(NOTE)*

☐ acetaminophen

15 mg/kg, PO, 1 time only

Comments: Max Dose: 1 Gm/ dose

☐ ibuprofen

10 mg/kg, PO, 1 time only

Comments: Max Dose: 800 mg/ dose

☐ ondansetron 4 mg/5 mL oral solution

2 mg, PO, 1 time only, dosing for pts 8 kg to 15 kg. (DEF)*

4 mg, PO, 1 time only, dosing for pts 15.1 kg to 30 kg.

8 mg, PO, 1 time only, dosing for pts >30 kg.

☐ ondansetron 4 mg oral tablet

4 mg, PO, 1 time only, dosing for pts 15.1 kg to 30 kg

☐ ondansetron 4 mg oral tablet, disintegrating

2 mg, PO, 1 time only (DEF)*

Comments: Place tablet on tongue and let disintegrate.

4 mg, PO, 1 time only

Comments: Place tablet on tongue and let disintegrate.

☐ ondansetron 8 mg oral tablet

8 mg, PO, 1 time only, dosing for pts >30 kg

☐ ondansetron 8 mg oral tablet, disintegrating

8 mg, PO, 1 time only

Comments: Place tablet on tongue and let disintegrate.

First Line Medications

For a pain score equal to or greater than 4. First treatment - use med(s) prochlorperazine and diphenhydramine.(NOTE)*

☐ prochlorperazine

0.15 mg/kg, IV Push, 1 time only, Nausea/Vomiting, Not for use in patients < 2 years old. (DEF)*

Comments: Maximum dose: 10 mg/dose

0.1 mg/kg, PO, 1 time only, Not for use in patients < 2 years old.

Comments: Maximum dose: 10 mg/dose

☐ diphenhydrAMINE

1 mg/kg, IV Push, 1 time only [Less Than 50 kg] (DEF)*

Comments: Maximum dose: 50 mg/dose

25 mg, IV Push, 1 time only

50 mg, IV Push, 1 time only [Greater Than or Equal To 50 kg]

☐ metoclopramide

0.1 mg/kg, IV, 1 time only (DEF)*

Comments: Maximum dose: 10 mg/dose. Should only be given if prochlorperazine is not available.

5 mg, IV, 1 time only

10 mg, IV, 1 time only

Second Line Medications

☐ ketorolac injectable

0.5 mg/kg, IV Push, 1 time only (DEF)*

Comments: Maximum Dose: 30 mg/dose. Ketorolac should only be used if it has been 6 hours since last Ibuprofen or 12 hours since last Naproxen dose was given.

15 mg, IV Push, 1 time only

Comments: Ketorolac should only be used if it has been 6 hours since last Ibuprofen or 12 hours since last Naproxen dose was given.

30 mg, IV Push, 1 time only

Comments: Ketorolac should only be used if it has been 6 hours since last Ibuprofen or 12 hours since last Naproxen dose was given.

☐ valproic acid

20 mg/kg, IV, 1 time only

Comments: Maximum dose: 1000 mg/dose

Other Medications

☐ magnesium sulfate

25 mg/kg, IV, 1 time only (DEF)*

Comments: Maximum dose: 2000 mg/dose

50 mg/kg, IV, 1 time only

Comments: Maximum dose: 2000 mg/dose

1,000 mg, IV, 1 time only

2,000 mg, IV, 1 time only

☐ SUMAtriptan

0.06 mg/kg, Subcutaneous, 1 time only

Comments: Max Dose : 6 mg. Do not use if being admitted

☐ ondansetron injectable

2 mg, IV, 1 time only, dosing for pts 8 kg to 15 kg (DEF)*

4 mg, IV, 1 time only, dosing for pts 15.1 kg to 30 kg

8 mg, IV, 1 time only, dosing for pts >30 kg

☐ Dihydroergotamine intermittent infusion

0.5 mg, IV, infuse over 30 minute(s), 1 time only, 1 dose(s)

*Comments: Infuse over at least 30 minutes. Maximum total dose: 1 mg. Consult Neurology prior to giving this medication and for dosing schedule for additional doses. Contraindicated if triptan given within last 24 hours. Administer second (increased) dose after 4 hours for a total of 2 doses of dihydroergotamine today. **Pharmacy: Dilute in 50 mls of NS. Use IV set - dihydroergotamine in NS*

Topicals

☐ J-Tip with buffered lidocaine 1%

☐ AneCream 4% topical cream

Discharge

Please use this link as a resource when developing a migraine discharge plan. Provider link is in the upper left corner.(NOTE)*

***Report Legend:**

DEF - This order sentence is the default for the selected order
GOAL - This component is a goal
IND - This component is an indicator
INT - This component is an intervention
IVS - This component is an IV Set
NOTE - This component is a note
Rx - This component is a prescription
SUB - This component is a sub phase

Guideline Preparation: This guideline was prepared by The Office of Evidence Based Practice (EBP) in collaboration with content experts at Children's Mercy Kansas City. Development of this guideline supports the Department of Clinical Effectiveness's initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified the conflict will be disclosed next to the team members name.

Team Members:

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- Jacqueline Bartlett, PhD, RN, EBP Director
- Jarrod Dusin, MS, RD, LD, CNSC, EBP Program Manager
- Nancy Allen, MS, MLS, RD, LD, EBP Program Manager

Guideline development funded by: No external funding was obtained

Development Process:

The review summary documents the following steps:

1. Review of existing internal and external guidelines and standards
   a. Internal guidelines: Migraine in the ED (2010)
   b. External guidelines: AAN Practice Parameter (D. W. Lewis et al., 2002)
      AAN Practice Parameter (D. Lewis et al., 2004)
2. Review preparation
   a. PICOT questions established
   b. Team leaders confirmed search terms used
3. Databases searched
   a. AHRQ National Guideline Clearinghouse
   b. Medline
   c. Cochrane
   d. CINAHL
4. Critically analyze the evidence
   a. Guidelines
      i. AGREE II (Brouwers et al., 2010) criteria were used to analyze published clinical guidelines
   b. Literature
      i. Review Manager 5.3 (Higgins & Green, 2011)tools were used to analyze the literature (e.g. study limitations, consistency of results, directness of evidence, precision and reporting bias)
      ii. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Schünemann H, 2016) criteria evaluated the literature based on:
         1. The balance between desirable and undesirable effects
         2. Patient values and preferences
         3. Resource utilization

         The table below defines how the quality of the evidence is rated and how the recommendation is established based on the type of evidence:

Quality	Type of Evidence

High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies.
Moderate	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies.
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence.
Very Low	Evidence for at least 1 of the critical outcomes from unsystematic clinical observations or very indirect evidence.
Recommendation	Type of Evidence
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects

5. Recommendations for the guideline were developed by a consensus process incorporating the three principles of EBP (current literature, content experts, and patient and family preference [when possible])

Approval Process: Guidelines are reviewed and approved by <insert external expert reviewer>, Content Expert Team, the Office of EBP, and other appropriate hospital committees as deemed suitable for the guidelines intended use. Guidelines are reviewed and updated as necessary every 3 years within the Office of EBP at CMH&C. Content expert teams will be involved with every review and update.

Disclaimer:
The content experts and the Office of EBP are aware of the controversies surrounding the treatment of refractory migraine in the ED/UCC. When evidence is lacking or inconclusive, options in care are provided in the guideline and the power plans that accompany the guideline.

These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time.

It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.

Appendix A

Neuroimaging for Refractory Migraine in the ED

Specific Care Question :
Does a head CT scan compared to no head CT scan change the management of a child with migraine?

Question Originator:
Migraine Management in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on moderate quality evidence, the Migraine in the ED CPG team makes a strong recommendation against obtaining a CT scan for a refractory migraine. The Practice Parameter of the American Academy of Neurology (AAN) (Lewis & Dorbad, 2000) is the basis of our recommendation. We concur with AAN and recommend against obtaining a CT scan on a routine basis in children with recurrent headaches and normal neurological exam. However, exceptions are made for children with abnormal neurological exams and children with recent onset of severe pain, or change in the type of headache.

Synthesis:
Lewis & Dorbad, (2000) published a Practice Parameter for the evaluation of children and adolescents with recurrent headaches. The AGREE II (Brouwers et al., 2010) tool was used to assess the methodological vigor and transparency of the Practice Parameter. The Practice Parameter was assigned a score of 5 (range: 1-7; higher is better).
The major weaknesses of the AAN Practice Parameter are

1. Limited stakeholder involvement
2. Process of developing the Practice Parameter is not clearly described
3. Role of competing interests are not clearly described

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Nancy H Allen, MS, MLS, RD, LD

Search Strategy and Results:
("Migraine Disorders"[Mesh] AND "Tomography, X-Ray Computed"[Mesh]) AND "Pediatrics"[Mesh]

Studies included in this review: No studies were identified
(Lewis & Dorbad, 2000)

Method Used for Appraisal and Synthesis:
The AGREE II (Brouwers et al., 2010) was used to assess the methods of the development of the included guideline(s).

Updated October 28 2015, Jan 26, 2016, March 4 2016, March 8 2016

Appendix B

Prochlorperazine for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with a refractory migraine, is prochlorperazine an effective treatment compared to ketorolac, metoclopramide, sodium valproate, IV magnesium?

Question Originator:

Migraine in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on low quality evidence, the Migraine in the ED CPG team conditionally recommends the use of prochlorperazine with or without diphenhydramine for the treatment of refractory migraine in the ED. The included studies are methodologically strong. However, the evidence is downgraded for inconsistency because definitions for (a) treatment success, (b) time to administer rescue medications, and (c) categorization of adverse events vary among the studies. Finally, the evidence is downgraded for imprecision, due to the small number of subjects with the desired outcome (See Figure 1).

Literature (see Table 1) supporting this recommendation:

Eleven RCTs were used to support this recommendation. Prochlorperazine was compared to other medications (ketorolac, metoclopramide, magnesium sulfate, promethazine, and chlorpromazine) on the outcome, Treatment success one to two hours after treatment. (Brouseau, 2004, Coppola, 1995, Ginder, 2000. Callan, 2007, and Kanis 2013) (see Figure 2). For the comparison of prochlorperazine vs. metoclopramide, there was no difference in the change in pain intensity measured at 2 hours after medication administration. (Friedman, et al., 2008) When compared to magnesium sulfate, there was no difference between the treatment groups (Ginder, 2000). However, the sample sizes are exceedingly small (range 36-349 subjects). The included studies defined "treatment success" in various manners. Therefore, there is inconsistency among the studies. (See Figures 2-5)

Dose: Prochlorperazine 0.15 mG/kg (max 10 mG), administer via IV, 1 mG/min.

EBP team member responsible for reviewing, synthesizing, and developing this literature:

Evidence Based Scholars

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Search Strategy and Results:

PubMed Search: ("Prochlorperazine"[Mesh] OR "Diphenhydramine"[Mesh] OR "Sumatriptan"[Mesh] OR "Tryptamines"[Mesh]) AND "Migraine Disorders"[Mesh] AND ("2007/06/01"[PDat] : "2012/05/29"[PDat] NOT (Case Reports[ptyp] OR Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp]) AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

EMBASE

No. **Query**	**Results**
#27 **#25** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND [embase]/lim NOT [medline]/lim	**1**
#26 **#25** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk)	**21**
#25 **#7** AND **#24**	**28**
#24 **'prochlorperazine'**/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**48**
#23	**0**

prochloperazine AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**1**
#22 **#7** AND **#21**	**4**
#21 **'compazine'**/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**4**
#20 **'compazine'**/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**0**
#19 **procholperzine** AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**2**
#18 **#7** AND [embase]/lim NOT [medline]/lim AND **'antihistaminic agent'**/de	**15**
#17 **#7** AND [embase]/lim NOT [medline]/lim AND **'steroid'**/de	**966**
#16 **#7** AND [embase]/lim NOT [medline]/lim	**7**
#15 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de AND [embase]/lim NOT [medline]/lim	**12**
#14 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'valproic acid'**/de AND [embase]/lim NOT [medline]/lim	**72**
#13 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'valproic acid'**/de	

37

#12
#7 AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de

23

#11
#7 AND (**'controlled study'**/de OR **'major clinical study'**/de) AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de

1

#10
'tryptamine'/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py

1

#9
'tryptamine'/exp AND **derivative** AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py

233

#8
#7 AND (**'controlled study'**/de OR **'major clinical study'**/de) AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk)

1,743

#7
'migraine'/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py

17,409

#6

'migraine'/exp OR **migraine** AND [2009-2014]/py

Studies included in this review:
Brousseau, Duffy, Anderson, & Linakis, 2004
Callan, Kostic, Bachrach, & Rieg, 2008
Collins et al., 2001
Coppola, Yealy, & Leibold, 1995
Friedman et al., 2014
Ginder, Oatman, & Pollack, 2000
Jones, Pack, & Chun, 1996

Kanis & Timm, 2014
Tanen, Miller, French, & Riffenburgh, 2003
Trottier, Bailey, Dauphin-Pierre, & Gravel, 2010

Excluded Studies and Reason for Exclusion:

Study	Reason for exclusion
Trottier 2013	Reports on the sensitivity of a migraine questionnaire to diagnose migraine Does not answer our questions.
Weaver 2003a	EXCLUDE: Study done in adults, but the study medication droperidol has a FDA "black box" warning regarding QT prolongation and torsade de pointes

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) (Higgins & Green, 2011).

Updated June 9 2015, June 24 2015,March 7 2016

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Table 1

Characteristics of included studies:

Brousseau 2004

Methods	Double-blind RCT
Participants	62 children presenting to ED with migraine **Setting**: Two pediatric emergency departments (EDs) **Subjects randomized**: 62 randomized **Subjects completed** 62 **Gender:** 42% male; mean age of enrolled subjects was 13.7 years (range 7.25-18 years) **Inclusion Criteria:** age range 5-18 years. Meeting the Prensky and Sommer criteria for migraine. **Exclusion Criteria:** any contraindication to the use of prochlorperazine or ketorolac, children unable to complete the Nine Faces Pain Scale. **Power Analysis**: was performed, the goal sample size was 49 subjects per group. Power was not met.
Interventions	Children were enrolled after the decision was made to treat with an IV medication. All children received a fluid bolus of 10 ml/kg of NS over 30 minutes. Treatment group: IV prochlorperazine (0.15 mG/kg: maximum 10 mG) over a 10 minute period N= 33 randomized Control IV ketorolac (0.5 mG/kg, maximum 30 mG) N= 29 randomized After 60 minutes those who did not respond to the first treatment were treated with the other medication, and the Nine Faces Pain Scale was re-administered 60 minutes thereafter.
Outcomes	Nine Faces Pain Scale to determine treatment success- greater to or equal to 50% reduction in pain score within 60 minutes of treatment.
Notes	Only the results from the first 60 minutes are included here.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Block randomization in the hospital pharmacy

Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Medication was supplied to the ED in such a way that the treating nurse, physician, and patient were all blinded to the medication given. The code for the blinding was maintained in the pharmacy and was not available to any investigator until the completion of the study.
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	Number or subjects per group should have been 49. Only 62 subjects were enrolled, 30 in the treatment group and 29 in the control group. Power was not met.
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	This study was stopped at the 50% enrollment because "interim analysis disclosed a clear difference between the 2 treatments"

Callan 2007

Methods	Prospective, double-blinded, randomized controlled trial
Participants	**Setting:** Department of Emergency Medicine, Naval Hospital in Okinawa, Japan and Department of Emergency Medicine, Naval Medical Center in Portsmouth, Virginia. **Randomized:** a standardized order sheet was utilized to prevent foreknowledge or the ability to alter subject assignment. Computer-generated random numbers table was used to randomize each subject to receive a 2-mL solution containing either promethazine (25 mG) or prochlorperazine (10 mG) intravenously, over a 2 minute period followed by a 10-mL flush or normal saline. Drug prep and subject randomization were performed by a research pharmacist before patient enrollment. A total of 70 subjects were enrolled: 35 received promethazine and 35 received prochlorperazine. **Completed:** 66 patients completed all portions of the study which included follow-up. Three subjects dropped out before study completion and 1 was subsequently diagnosed with aseptic meningitis the following day. Those patients lost to follow-up were distributed evenly between both groups and included in an 'intention to treat' analysis. **Gender:** 77% of subjects receiving Prochlorperazine were female and 85% of subjects receiving promethazine were female.

	Inclusion criteria: Patients between ages of 18 and 65 and who did not meet the exclusion criteria and who presented with a benign headache. **Exclusion criteria:** Patients with prior involvement in this study, were pregnant, had a temperature > 38.5 degrees C (100.5 deg F), had a diastolic blood pressure > 104 mm Hg, had a history of non-skin cancer, described their current headache as atypical in character or location from their usual headaches, had altered mental status, had the "worst headache of their life, " had neurological symptoms, had a history of trauma, had thunderclap onset, had meningeal signs, or had a headache post lumbar puncture. Additionally, patients were excluded if they had a known allergy to the study drugs, or reported use of ergot amines, anti-emetics, anti-psychotics, or sedatives in the previous 24h. **Power analysis:** Thirty-two patients were needed in each group to find a 25-mm difference between the group mean on the 100-mm visual analog scale(VAS) at 60 minutes, with a power of 0.80 and an alpha of 0.05.
Interventions	**Treatment group:** 35 patients received 2-mL solution of 10mG prochlorperazine **Control group:** 35 patients received 2-mL solution of 25mG promethazine
Outcomes	Headache reduction: **At 30 minutes** post IV of medication, 69% in the prochlorperazine group and 39% in the promethazine group had a reduction in visual analog score (VAS) of >25mm **At 60 minutes** post IV of medication, 91% in the prochlorperazine group and 47% in the promethazine group had a reduction in the VAS of >25mm

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	70 patients who met criteria for migraine were randomized using a standardized order sheet to prevent foreknowledge or the ability to alter subject assignment. A computer-generated random numbers table was used to complete the randomization of the participants.
Allocation concealment (selection bias)	Low risk	Utilized a standardized order sheet to prevent foreknowledge or the ability to alter subject assignment.
Blinding of participants and personnel (performance bias)	Low risk	All patients had an intravenous catheter placed to receive the medication. The medication was mixed by research pharmacist so participants and staff administering IV were blinded to which medication participant would be receiving.

Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment was not blinded but is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate and was confirmed through 'an intention to treat analysis' for 4 subjects that dropped out before study completion.
Selective reporting (reporting bias)	Low risk	specified outcomes were reported in a pre-specified way: headache pain was evaluated using the visual analog scale of 100mm.
Other bias	Unclear risk	Study had a potential source of bias related to the specific study design used by enrolling participants with an undifferentiated primary headache as opposed to enrolling only those that met the strict definition of migraine.

Collins_2001

Methods	Prospective, RCT, double-blind study
Participants	**Setting:** Midwestern (Indianapolis, IN), central city teaching hospital Emergency Department **Randomized:** Adult patients, age 18-65, presenting to ED with c/o headache and/or nausea, and/or vomiting that were to be treated with IV prochlorperazine Treatment group: n=50, Control group n=50 **Completed:** Treatment group n=49 Control group n=50 **Gender:** 34 male (34.3%) **Race:** 50 white (50.5%) **Inclusion criteria:** pts to receive IV prochlorperazine for the treatment of headache, nausea, and/or vomiting **Exclusion criteria:** previous self-medication in the past 12 hours with antiemetic, or in the past 24 hours with antihistamine; and excluded if taking beta blockers, selective serotonin reuptake inhibitor, tricyclic antidepressants, lithium, neuroleptic medications, or benzodiazepines. Other exclusion criteria: history of akathisia, restless leg syndrome, inability to speak or understand English, inability to be contacted by telephone. **Power Analysis:** done, sample size calculations called for 46 participants to be enrolled in intervention group
Interventions	**Treatment group:** 2 ml NS IV push over 2 minutes followed by 10 mG prochlorperazine mixed in 50 ml NS, infused over 15 minutes. n=49 **Control group:** 2 ml (10 mG) prochlorperazine IV push over 2 minutes followed by 50 ml NS, infused over 15 minutes. n=50 *Note:* there was no report of time between the 2 ml push medication and the medication infused over 15 minutes.

Outcomes	ED self-report of Akathisia, objective and subjective scales used, within 60 minutes of infusion, subjective telephone self-reported akathisia 24 and 72 hours after infusion.
Notes	Two different comparison methods were used- per protocol and ITT. Pain and nausea relief were also documented, though some patients presented with headache, some with nausea, and some with both.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT, computer generated randomized table used
Allocation concealment (selection bias)	Low risk	study medication kits were prepared by outside contract research pharmacy, all parts within kits were identical except labels "A" and "B"
Blinding of participants and personnel (performance bias)	Low risk	ED nurses and participants were blinded as to what was in each vial.
Blinding of outcome assessment (detection bias)	Low risk	ED nurses and participants were blinded as to who had received medications over what time frame
Incomplete outcome data (attrition bias)	Low risk	Assessment was done for 99% of participants after 60 minutes, 93 % after 24 hours, 80% after 72 hours.
Selective reporting (reporting bias)	Low risk	All study data is reported. Patients with a c/o akathisia in the ED were treated with IV diphenhydramine, it is unclear if these patients had akathisia improvement, and 24/72 hour follow-up calls do not differentiate which patients were treated with diphenhydramine.
Other bias	Unclear risk	

Coppola 1995

Methods	RCT, prospective, double-blind, placebo-controlled
Participants	Setting: military community hospital ED

	Randomized: 75, treatment group n=26 (metoclopramide) n=24 (prochlorperazine) n=24 (placebo) Completed: 70, treatment group n=24 (metoclopramide) n= 22 (prochlorperazine) n= 24 (placebo) Gender: unknown Inclusion criteria: Adults, cephalagia similar to previous episodes, with or without nausea, vomiting, photophobia, or phonophobia. Exclusion criteria: pregnancy, fever or meningismus, altered mental state, recent (within 24 hours) use of analgesics, drugs, or alcohol, O2<90%, Recent trauma or seizure, first episode of headache, suspicion of intracranial process, allergy, diastolic BP > 90. Power analysis: 20 patients per group offered minimum pretrial power of 0.9 to detect a difference in frequency of clinical improvement of 33% or greater
Interventions	Treatment group (metoclopramide): 2 ml (10 mG) IV push over 2 minutes Treatment group (prochlorperazine): 2 ml (10mG) IV push over 2 minutes Control group: 2 ml NS IV push over 2 minutes
Outcomes	Patient satisfaction at 30 minutes post treatment and either Reduction in pain by 50% on a 10-point scale at 30 minutes post treatment or an absolute pain score of 2.5 cm or less. Also Reduction in nausea at 30 minutes post treatment Change in sedation at 30 minutes post treatment
Notes	5 participants did not complete study, 2 metoclopramide and 2 prochlorperazine due to adverse reactions -- dystonic reactions, 1 did not meet study protocol all outcome data is continuous measurement, but only the median is reported. No mean available.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT, computer generated, double blind, placebo controlled
Allocation concealment (selection bias)	Low risk	Randomized, computer generated

Blinding of participants and personnel (performance bias)	Low risk	Patients and healthcare workers blinded
Blinding of outcome assessment (detection bias)	Unclear	Unsure if patients or healthcare workers were blinded
Incomplete outcome data (attrition bias)	Low risk	4 patients did not complete study due to adverse reactions, 1 did not meet protocol. No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is available, all outcomes reported
Other bias	Unclear risk	

Friedman 2008

Methods	RCT
Participants	**Setting:** 2 academic medical centers in different NYC boroughs, Manhattan and the Bronx. **Number randomized**: N = 77; 39 in the prochlorperazine group and 38 in the metoclopramide group **Number completing**: ED protocol N = 77, completing the 24 hour follow up N= 73 36 in the prochlorperazine group and 37 in the metoclopramide group **Gender:** 9 % male **Age:** adults ; prochlorperazine 34 +/- 10 and metoclopramide 38 +/- 12 years **Inclusion Criteria:** migraine with or without aura or probable migraine lasting longer than 72 hours **Exclusion Criteria:** secondary headache, lumbar puncture to be performed, allergy or intolerance to study medication, pregnancy, previous enrollment **Power analysis:** 38 subjects were needed per group to detect a difference of 2.0 in the primary outcome pain intensity.
Interventions	**Intervention:** prochlorperazine 10 mG IV with diphenhydramine 25 mG IV **Control:** metoclopramide 20 mG IV with diphenhydramine 25 mG IV
Outcomes	Primary outcome was pain intensity on an 11-point scale (0-10) with 0 being no pain, and 10 representing the worst pain. It is a validated pain score at one hour post treatment AND persistence of pain at 24 hours. Secondary measures include: a four point categorical pain scale describing pain as "severe", "moderate", "mild" or "none".

	a four point functional disability scale A question asked 24 hours after treatment " would you want to received the medication at a future ED visit for acute migraine/" Adverse effects at 1, 2, and 24 hours Akathisia rating scales (2). An increase of 1 point on a ten point objective scale AND an increase of 2 points on a 12 point subjective scale. This scale is a validated scale.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized in blocks of 6
Allocation concealment (selection bias)	Low risk	Assignment was only known by research pharmacist
Blinding of participants and personnel (performance bias)	Low risk	Volumes of medications were made similar, as was the process taken by the nurse who performed the infusion
Blinding of outcome assessment (detection bias)	Low risk	The research assistants who did the initial and follow-up assessments were unaware of study assignment
Incomplete outcome data (attrition bias)	Unclear risk	All were treated to 2 hours, the primary outcome. For the prolonged headache relief both treatment groups had dropouts, and they used per protocol analysis.
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear	

Ginder 2000

Methods	Prospective cohort study. RCT with before and after assessment.
Participants	**Setting**: York hospital in York, Pennsylvania.

	Randomized: 36 patients were randomized into two groups (20 for prochlorperazine and 16 for magnesium). The pharmacy randomized the study drugs by computer and premixed identical, numbered, 50-mL bags of either 2 g of magnesium sulfate or 10 mG of prochlorperazine. **Completed**: all 36 patients completed the study **Gender**: 11 male patients, 25 female patients **Inclusion criteria**: Adults, presentation to ED with complaint of headache **Exclusion criteria**: patients younger than 18 and older than 50 years, pregnancy, a known adverse reaction to phenothiazine or magnesium, use of these medications within 48h, and renal, cardiac, or diabetic disease. **Power analysis**: power analysis of the visual analog scale percentages by group was 0.65.
Interventions	**Treatment group**: 50-mL bag of 10mG of prochlorperazine, N= 20 **Control group:** 50-mL bag of 2g of magnesium sulfate N= 16
Outcomes	Primary outcome: Pain relief as determined on a 100 mm visual analog scale at 30 minutes after treatment Successful pain relief- a decrease of greater than 45 mm on the visual analog scale No pain relief- no change on the visual analog scale Secondary outcome: Use of rescue medications.
Notes	

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The patient, nurses, and physicians were blinded to which medication the patient was receiving. The pharmacy premixed the bags of IV fluids based on a computer randomization
Allocation concealment (selection bias)	Low risk	Central allocation by use of pharmacy-controlled randomization
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment completed, as data collectors were unaware of drugs used so could not influence patient responses. Patients also unaware of what drug was used so it could not influence their pain rating.
Incomplete outcome data (attrition bias)	Low risk	No loss of patients through attrition
Selective reporting (reporting bias)	Low risk	The study protocol is available and all study's pre-specified outcomes that are of interest in the review have been reported. Pain scales for pre and post IV fluids included. Side effects from both drugs reported.
Other bias	Low risk	Did not identify other sources of bias in this study

Jones 1996

Methods	RCT
Participants	**Setting:** university affiliated hospital **Number randomized**: N= 86 **Number who completed:** N=86 **Gender:** 27% male **Age:** at least 16 years old Mean age was 32.1 +/- 2.1 years **Inclusion criteria:** recurrent headaches, preceded by neurological symptom, recurrent throbbing headaches that were initially unilateral associated with nausea or vomiting, photophobia, sonophobia or mood changes **Exclusion criteria:** age greater than 60 years, a known intolerance to phenothiazine or metoclopramide, use of other drugs likely to cause extrapyramidal reactions, pregnancy or breast feeding, history of drug seeking behavior, or lack of responsible person available to care for and transport the subject when leaving the emergency department. Headache that appeared to be other than migraine by history or on physical examination **Power Analysis:** completed, 25 subjects were needed to detect a difference in clinical improvement fo 30% or more between therapies
Interventions	**Treatment group 1:** n= 28 2 ml intramuscular injection of prochlorperazine (10 mG) **Treatment Group 2:** n= 29 2 ml intramuscular injection of metoclopramide (10 mG) **Control:** n= 29 2 ml normal saline
Outcomes	10 cm visual analog scale from 'no pain' to 'worst pain imaginable" Treatment failure: subject without complete relief of pain within 60 minutes of treatment Need for rescue medication Pain relief at 48 hours

Notes	

Risk of bias table

Bias	Scholars judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Tanen 2003

Methods	RCT Prospective, Randomized, Double-Blind Trial
Participants	**Setting:** Tertiary care military ED **Randomized:** 40 patients **Treatment group** N=20 (12 female,8 male) **Control group** N=20 (14 female, 6 male) **Completed:**

	• Treatment group N=19 (11 female, 8 male) • Control group N=20 (14 female, 6 male) **Inclusion Criteria :** ED patients that met criteria for migraine headache with or without aura, as defined by the Headache Classification Committee of the International Headache Society. **Exclusion Criteria:** pregnancy, temperature of 100.5°F (38.1°C) or greater, diastolic blood pressure of 105 mm Hg or greater, altered mental status, meningeal signs, suspicion of intracranial process, allergy to sodium valproate or prochlorperazine, or use of narcotics, ergotamine, antiemetic, antipsychotics, or sedatives in the 24 hours before entry into the study. **Power analysis**: determined 18 patients were needed in each group.
Interventions	**Treatment group:** 500 mG of sodium valproate diluted to 10 mL in normal saline solution and infused over 2 minutes **Control group**: 10 mG of prochlorperazine diluted to 10 mL in normal saline solution and infused over 2 minutes
Outcomes	Scores for pain, nausea, sedation; rescue therapy
Notes	The only numbers provided were in regards to need for rescue therapy, all the other values in the study were presented in graphs or binomial confidence intervals. However, the group that received the prochlorperazine had clinically and significantly less pain. Median pain score change in prochlorperazine group was 64.5mm (range 18.1,75.6 mm) compared to 9 mm (range -3, 39.6 mm) for sodium valproate. Median changes of VAS for nausea were also significantly different prochlorperazine 35.5 mm(range13.2,47.9 mm) and sodium valproate group median VAS for nausea 2 mm (range -1.2, 11 mm). There was not a difference in median change of score for sedation. Usable data is avail for use of rescue medications.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computerized random numbers table.
Allocation concealment (selection bias)	Low risk	Medication was coded and was drawn up and administered by a nurse who was not part of the study.
Blinding of participants and	Low risk	Both the investigator and patient remained blinded to the medication delivered until the code was broken at the close of enrollment.

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	Low risk	VAS scores evaluated using ANOVA
Incomplete outcome data (attrition bias)	Low risk	Met power analysis
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Weaver 2003

Methods	RCT in Adult EDs. Enrolled subjects based on research coordinator availability
Participants	**Age:** Adults > 18 years of age; Mean age 31 y (range 18-68y) **Number randomized:** 96 subjects recruited, N= 48 per treatment group Number who completed: **Gender:** 13.5 male **Inclusion criteria:** crescendo-onset headache and normal neurological examination (uncomplicated headache) **Exclusion criteria**: first headache, febrile (>/= 38 degrees C, exhibited nuchal rigidity, thunderclap onset of the headache, self-treatment with a pain medication or a antiemetic 4 hours prior to ED presentation, history of carbon monoxide exposure, peripheral vascular disease, cancer, HIV infection, pregnancy, allergy to study medications, inability to speak or understand English, lack of telephone Power analysis
Interventions	**Treatment Group:** droperidol 2.5 mG IV followed by a 2 ml normal saline flush **Control Group**: prochlorperazine 10 mG IV followed by a 2 ml saline flush
Outcomes	**Primary outcome:** • number achieving at least 50% reduction of pain at 30 minutes on a 100mm visual analog scale (VAS) **Secondary outcomes:** • mean change in pain intensity • proportion requiring rescue medications at 30-60 minutes • incidence of akathisia and other adverse events

Notes	Akathisia was defined as the occurrence of either or both of the following: spontaneous report or change in both the objective and subjective akathisia rating score compared to baseline

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Subjects had an IV placed; drug was drawn up and injected over 2 minutes. Study drugs looked identical
Blinding of outcome assessment (detection bias)	Low risk	Drug was delivered by a contract pharmacy. Study drug kit with droperidol contained 2 vials, one with 2 mG droperidol and one vial of normal saline. Study drug kit with prochlorperazine contained two vials with 5 mG prochlorperazine. Each vial contained 1 ml. Instructions were to draw both vials into a single syringe and inject over 2 minutes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	Rescue medications were allowed after 30 minutes: meperidine 1 mG/kg/IV for headache, ondansetron 4 mG IV for nausea or vomiting, and diphenhydramine hydrochloride 20-50 mG IV for extrapyramidal side effects EXCLUDE: Study done in adults, but the study medication droperidol has a FDA "black box" warning regarding QT prolongation and torsade de pointes

Figures

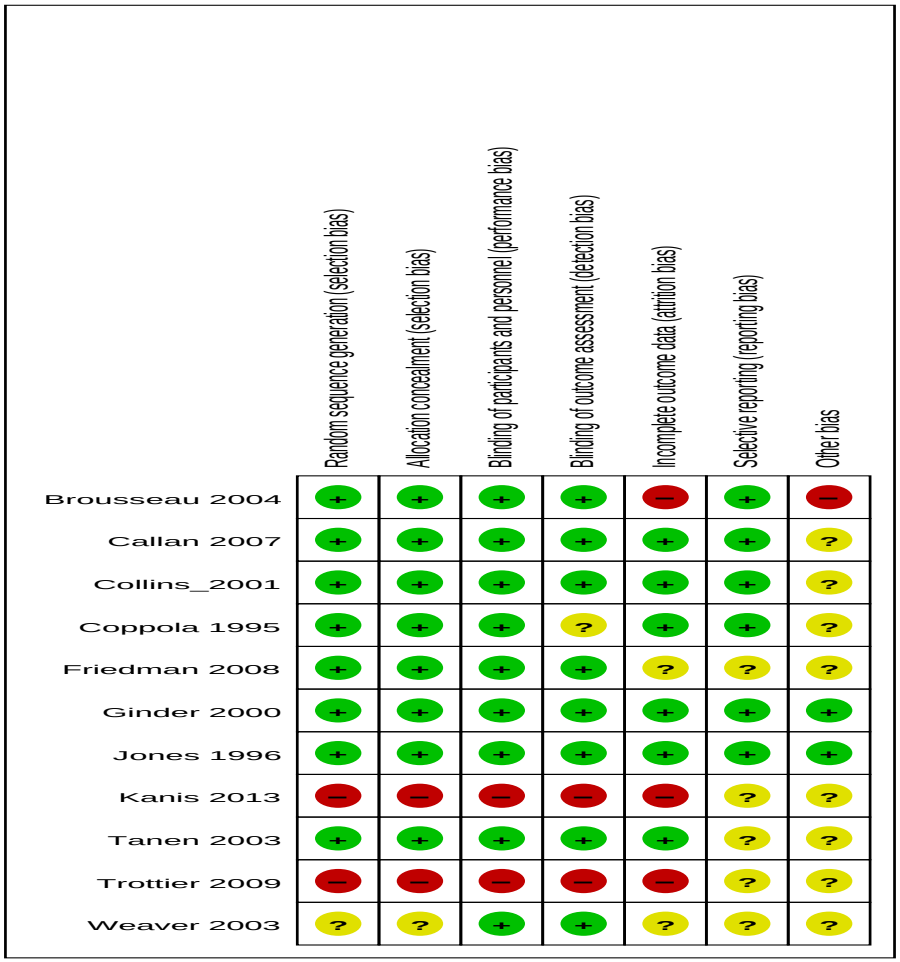
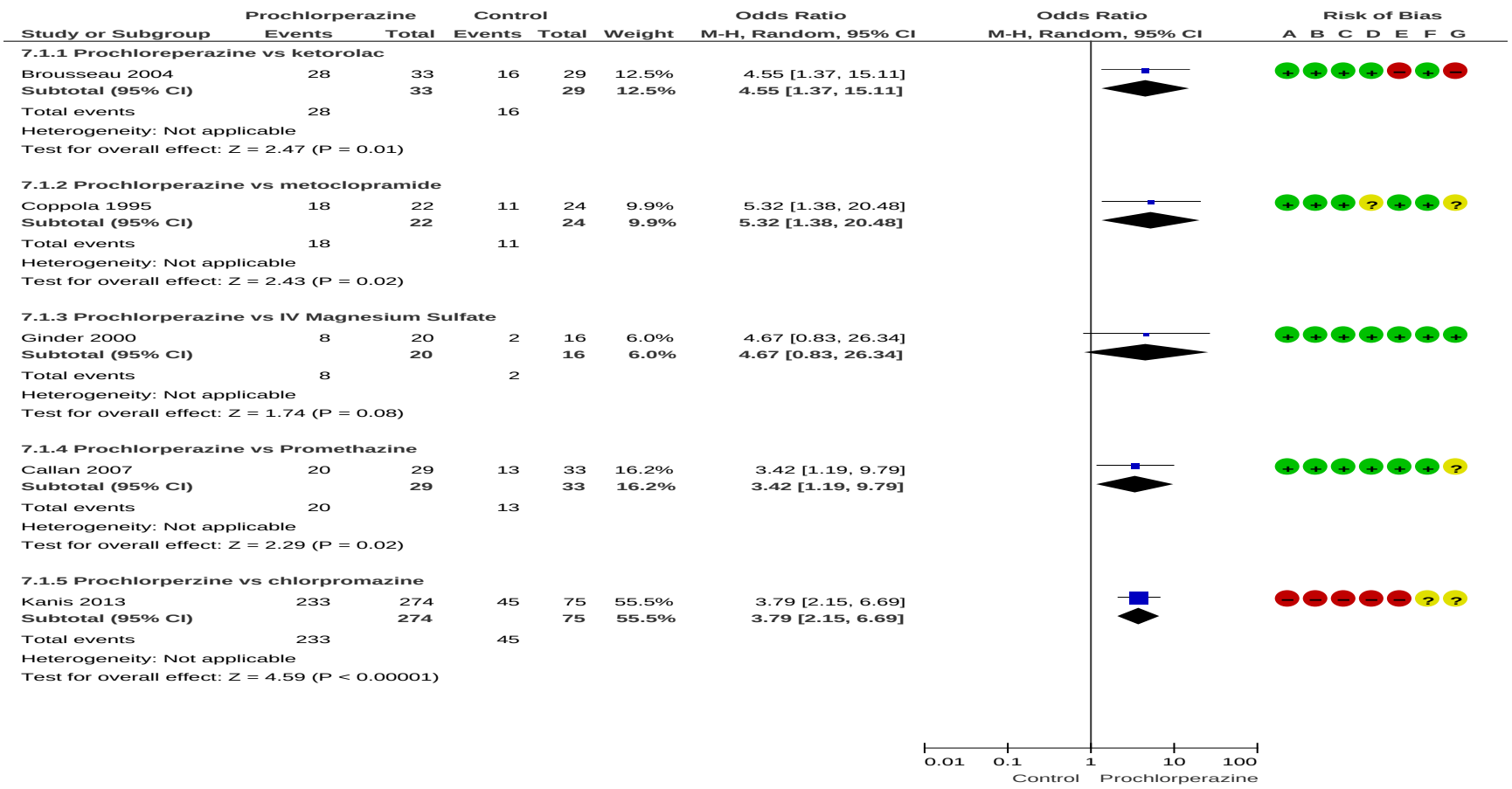


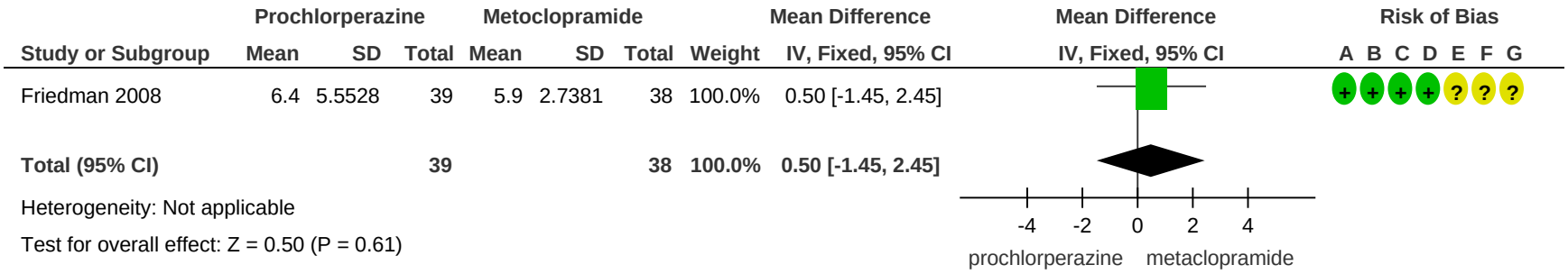
Figure 1. Risk of bias summary: Evidence Based Practice Scholars judgments about each risk of bias for each of the included studies.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 2. Comparison**:** Prochlorperazine vs. Other medications, Outcome: Treatment success 1 to 2 hours after treatment.



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure 3. Comparison: Prochlorperazine vs. metoclopramide, Outcome: Change in pain intensity

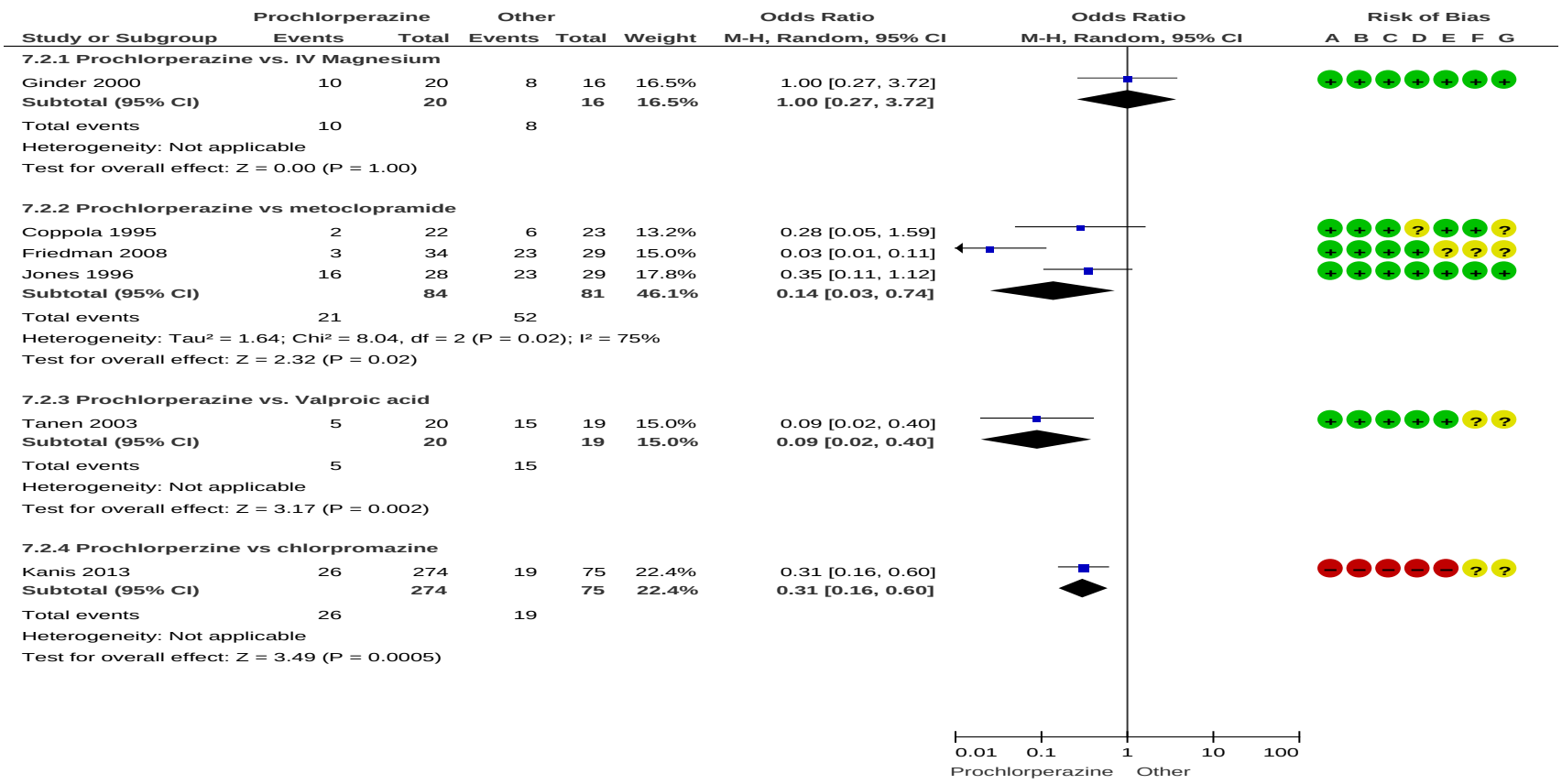


Figure 4. Comparison: Prochlorperazine vs. Other medications, Outcome: Required use of rescue medications

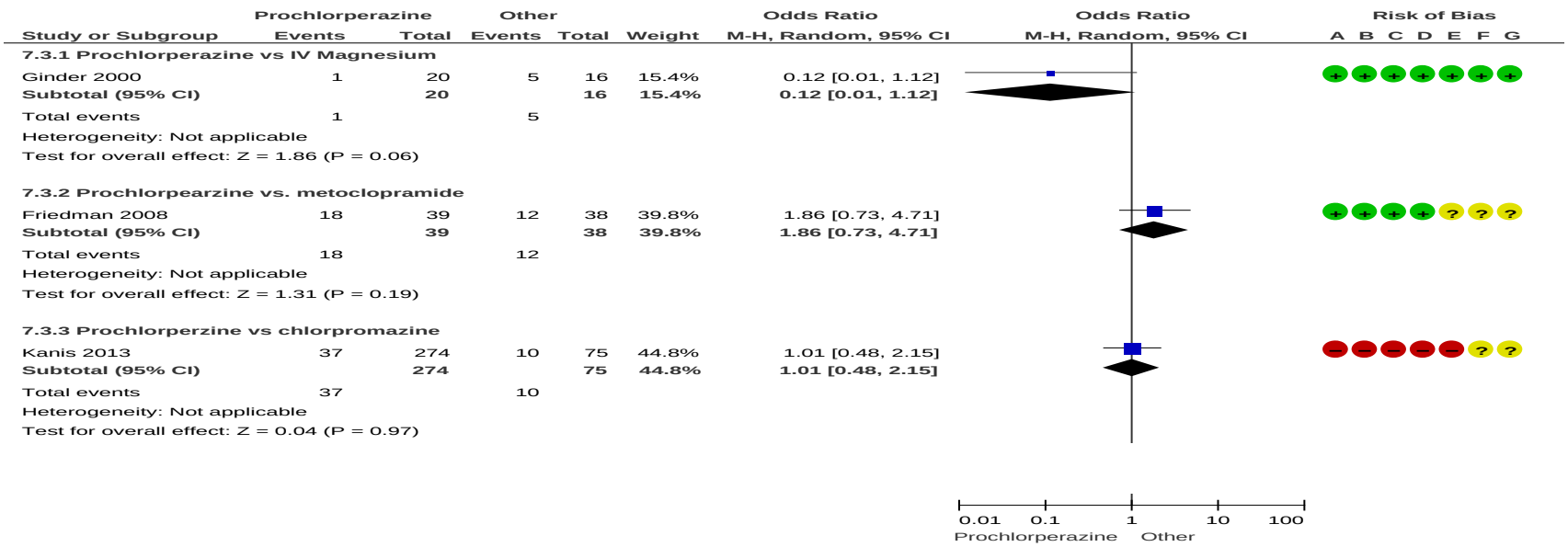


Figure 5. Comparison: Prochlorperazine vs. Other medications, Outcome: Lower Occurrence of Adverse Events

Appendix C.

Valproic Acid for Refractory Migraine in the ED

Specific Care Question :
In the pediatric patient diagnosed with refractory migraine, is valproic acid an effective treatment?

Question Originator:
Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Migraine in the ED Team Recommendations:
The Migraine in the ED Team makes a conditional recommendation to use valproic acid as a second line treatment option for children who present to the ED with a refractory migraine headache. Valproic acid is the treatment of choice if NSAIDs have been administered (ibuprofen < 6 hours from prior administration or naproxen sodium < 12 hours from prior administration). Assure pregnancy test is negative before administering valproic acid. Alternative approaches may be equally reasonable. Four randomized control trials are included in this review. The included studies are methodologically strong, but the evidence is downgraded for imprecision, due to the small number of subjects with the desired outcomes (see Figure 1).

Literature Synthesis:
Valproic acid was compared to other medications on the outcome- pain free in less than two hours. There was no significant difference between subjects treated with valproic acid and ketorolac (Friedman et al., 2014) or dihydroergotamine (Edwards, Norton, & Behnke, 2001) (see Figure 2).

Valproic acid was compared to other medications on the outcome- need for rescue medications. Subjects treated with valproic acid required significantly more rescue medications than subjects treated with metoclopramide or ketorolac (Friedman et al., 2014), or prochlorperazine (Tanen, Miller, French, & Riffenburgh, 2003)(See Figure 3).

Valproic acid was compared to other medication in the outcome- adverse events. Adverse events were not significantly different than metoclopramide, ketorolac, or dihydroergotamine (Edwards et al., 2001, Friedman et al., 2014). There were significantly less adverse events when valproic acid was compared to sumatriptan (Rahimdel, Mellat, Zeinali, Jafari & Ayatollahi, 2014) (see Figure 4).

The dose of valproic acid is 20 mG/kg with a maximum of 1 gram to be administered over one hour.

Literature read and analyzed by:

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Michelle Mills RNC-NIC
Jennifer Foley, RT(R)(N) CNMT

Office of Evidence B**ased Practice:**
Jeff Michael
Jackie Bartlett
Nancy Allen
Jarrod Dusin "Valproic Acid"[Mesh] AND ("Migraine Disorders/prevention and control"[Mesh] OR "Migraine Disorders/therapy"[Mesh]) AND (("2009/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh] AND English[lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH]))

Search Strategy and Results:

PubMed:
"Valproic Acid"[Mesh] AND ("Migraine Disorders/prevention and control"[Mesh] OR "Migraine Disorders/therapy"[Mesh]) AND (("2009/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh] AND English[lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH]))

EMBASE

No. **Query**	**Results**
#15 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de AND [embase]/lim NOT [medline]/lim	**7**
#14 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'valproic acid'**/de AND [embase]/lim NOT [medline]/lim	**12**
#13 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'valproic acid'**/de	**72**
#12 **#7** AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de	**37**
#11	**23**

#7 AND (**'controlled study'**/de OR **'major clinical study'**/de) AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de	**1**
#10 **'tryptamine'**/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**1**
#9 **'tryptamine'**/exp AND **derivative** AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**233**
#8 **#7** AND (**'controlled study'**/de OR **'major clinical study'**/de) AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk)	**1,743**
#7 **'migraine'**/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim AND [2009-2014]/py	**17,409**
#6 **'migraine'**/exp OR **migraine** AND [2009-2014]/py	

Studies included in this review:

Included studies:

Edwards, Norton, & Behnke, 2001
Friedman et al., 2014
Rahimdel et al., 2014;
Tanen, Miller, French, & Riffenburgh, 2003

Excluded Studies and Reason for Exclusion

Excluded studies	Reason for exclusion
Cherney et al., 2011	Abstract only
Cherney et al., 2012	Abstract only. Topic is treatment in an outpatient pediatric infusion center, not an ED

Duggan, Holick, Lee, & Lebron, 2013	Abstract only, Topic is treatment in an outpatient infusion center, not an ED
Hughes, Arora, & Brown, 2013	Abstract only, retrospective look at sumatriptan use. Does not answer the question
Reiter et al., 2005	Retrospective chart review of a small number of subjects, with missing data, and other medications given
Zafar, Cook, Stewart, & Baumann, 2014	Poster only

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5)

Created: Jun 9 2015 Updated June 24, 2015, March 8 2016

Characteristics of included study:

Edwards 2001

Methods	Open-label randomized study
Participants	Participants N= 40; 14 to 74 yrs old. Medically stable with migraine headache (with or without aura) None with known allergy to IV VPA (Valproate) or DHE (Dihydroergotamine)
Interventions	Patients received neuro exam and vital signs taken. Baseline headache rating form completed. Medication treatment of either 500 mG IV VPA over 15-30 min OR 10 mG IM MCLP (metoclopramide) followed 10 min later by 1 mG DHE. Headache severity and associated symptoms rated at baseline, 15, 30, and 45 minutes, and at 1,2,4, and 24 hours. Headache severity was rated from 0 = no headache, 1 = mild, 2 = moderate, and to 3 = severe
Outcomes	At 1, 2, and 4 hours: • Severity of headache • nausea • photophobia • phonophbia
Notes	Very small study group

Risk of bias table

Bias	Scholars' judgment	Support for judgment

Random sequence generation (selection bias)	High risk	Randomization of patients not described in study
Allocation concealment (selection bias)	High risk	Open-label randomization was method described by authors
Blinding of participants and personnel (performance bias)	High risk	No blinding: open-label randomization
Blinding of outcome assessment (detection bias)	Unclear risk	No blinding described
Incomplete outcome data (attrition bias)	High risk	Outcome data reported according to study design
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Friedman 2014

Methods	RCT
Participants	**Setting** ED- proficient bilingual (English and Spanish) staff **Number randomized** : N= 330, 110 per treatment group Ketorolac 30 mG, valproate 1 gram and metoclopramide 10 mG **Number completed:** N= 320, 106 ketorolac, 107 valproate and 107 metoclopramide **Gender:** 14% male **Age:** 34 years (range: 25-44 years) **Inclusion criteria:** met the criteria of the International Headache Society's International Classification of Headache Disorders 2nd Ed. Also accepted those who did not meet the criteria for • insufficient number of lifetime headaches (<5) • prolonged duration of headache (>72 hrs) **Exclusion criteria:** those who would received a lumbar puncture in the ED, fever present (>/= to 100.4 degrees F), a new neurologic abnormality, seizure disorder, concurrent use of an investigational medication, pregnancy, lactation,

	previous enrollment, allergy or intolerance to study medications-- including hepatic dysfunction, peptic ulcer disease or concurrent use of immunosuppressive or monoamine oxidase inhibitors medications **Power analysis:** sample size 100 for each arm of the study
Interventions	Three interventions 1. 1 g of IV valproate vs. 10 mG IV metoclopramide 2. 1 g IV valproate vs. 30 mG IV ketorolac 3. 10 mG of metoclopramide vs. 30 mG IV ketorolac
Outcomes	Primary outcome: Headache relief at one hour Secondary outcomes: 1. Use of rescue medication in the ED- this was considered failure for all other secondary outcomes 2. Patient's overall assessment of efficacy and tolerability - Y/N to "Do you want the to receive the same medication the next time you visit the ED with a headache?" 3. Sustained headache relief- four point scale severe, moderate, mild, none within two hours and maintained for 24 hours Functional outcomes 1. Yes/no to "Do you think you could now perform all your usual daily activities?" Assessed at one hour Safety outcomes 1. One hour after medication: assessment of drowsiness on a 3 point scale: (a) no drowsiness. (b) a little bit drowsy, but able to function normally, and (c) too drowsy to function normally 2. Twenty four hours after medication (follow up phone call) 1. Did you feel restless: (a) no restlessness, (b) a little bit restless, or (c) very restless 3. At one, two and 24 hours subjects were asked if they had any other symptom
Notes	**Primary outcome:** pair wise comparison, Mean difference in pain score (0-10, lower is better) (95% CI) between baseline and one hour Valproate vs. metoclopramide : [- 1.9 (-2.8. -1.1)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving metoclopramide. Valproate vs. ketorolac: [- 1.1 (-2.0, -0.2)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving ketorolac Metoclopramide vs. ketorolac [0.8 (-1.1, 1.7)] The positive mean difference means that subjects who received metoclopramide had a larger improvement in pain score than subjects receiving ketorolac

Risk of bias table

Bias	Scholars' judgment	Support for judgment

Random sequence generation (selection bias)	Low risk	randomized using an online random number generator, in blocks of six, by the research pharmacy
Allocation concealment (selection bias)	Low risk	The pharmacist placed filled medication vials into the designated container that was numbered in sequence by the randomization schedule. Only the research pharmacist, who was not in the ED knew the allocation. All doses were made to 10 mL to match the volume of ketorolac which came as a 10 mL solution from the manufacturer. Vials were the same.
Blinding of participants and personnel (performance bias)	Low risk	ED nurse who was blinded to the allocation, placed the medication into a 50 mL bag of normal saline for infusion IV drip over 15 minutes
Blinding of outcome assessment (detection bias)	Low risk	Research associates who were blinded to allocation asked subjects questions at 1 and 2 hours after medication was administered. Subjects were contacted at 24 hours after medication administration as well. All data collection tools were standardized
Incomplete outcome data (attrition bias)	Low risk	They used intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	They did not give data that can be used in a meta analysis for their primary outcomes, but did for their secondary outcomes
Other bias	Low risk	

Rahimdel 2014

Methods	RCT
Participants	Setting: Subjects with common migraine (without aura) Hospital in Iran Number randomized: 90 subjects Number completed: 90 subjects Gender: 26% male Age: mean age 30.1 +/- 3.5 years Inclusion Criteria: normal physical exams Exclusion Criteria: hepatic disease, special forms of migraine such as hemiplegic, basilar, ophthalmic, and retinal; uncontrolled hypertension, coronary artery disease, unstable angina, peripheral vascular diseases, history of myocardial infarction; pregnancy and lactation. Classic migraine (with aura)
Interventions	Treatment: 400 mG sodium valproate in 200 cc normal saline + 2 ml normal saline SQ Control: 6 mG sumatriptan SQ + 200 cc of normal saline IV over 20 minutes

Outcomes	Headache severity, pretreatment and 1, 2 hours after treatment on a 1-10 numerical scale,
Notes	

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computerized randomization
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	All completed
Selective reporting (reporting bias)	High risk	Cannot use the headache severity data. They report pain scores, but the initial pain score was significantly higher in the sumatriptan group. Therefore, the decrease in pain score was not significantly different, although the actual numerical scores were significantly different. Numbers for reduction in pain scores are not reported.
Other bias	Low risk	

Tanen 2003

Methods	RCT Prospective, Randomized, Double-Blind Trial
Participants	**Setting:** Tertiary care military ED **Randomized:** 40 patients

	Treatment group N=20 (12 female,8 male) Control group N=20 (14 female, 6 male) **Completed:** Treatment group N=19 (11 female, 8 male) Control group N=20 (14 female, 6 male) **Inclusion**: ED patients that met criteria for migraine headache with or without aura, as defined by the Headache Classification Committee of the International Headache Society. **Exclusion:** pregnancy, temperature of 100.5°F (38.1°C) or greater, diastolic blood pressure of 105 mm Hg or greater, altered mental status, meningeal signs, suspicion of intracranial process, allergy to sodium valproate or prochlorperazine, or use of narcotics, ergotamine, anti-emetics, antipsychotics, or sedatives in the 24 hours before entry into the study. **Power analysis:** determined 18 patients were needed in each group.
Interventions	**Treatment group:** 500 mG of sodium valproate diluted to 10 mL in normal saline solution and infused over 2 minutes **Control group:** 10 mG of prochlorperazine diluted to 10 mL in normal saline solution and infused over 2 minutes
Outcomes	scores for pain, nausea, sedation
Notes	Only need for rescue therapy was recorded in a format that is useable by this program. Other results are presented narratively below Median improvement in VAS pain- 64.5mm for prochlorperazine vs. 9mm for sodium valproate Median improvement in VAS nausea score - 35.5 mm for prochlorperazine vs. 2 mm for sodium valproate Not difference in sedation VAS Significantly less rescue treatment was required by those receiving prochlorperazine (79% did not) vs. valproic (25% did not)

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computerized random numbers table was used
Allocation concealment (selection bias)	Low risk	Medication was coded and was drawn up to be administered by a nurse who was not part of the study.

Blinding of participants and personnel (performance bias)	Low risk	Both the investigator and patient remained blinded to the medication delivered until the code was broken at the close of enrollment.
Blinding of outcome assessment (detection bias)	Low risk	VAS scores evaluated using ANOVA
Incomplete outcome data (attrition bias)	Low risk	Met power analysis
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

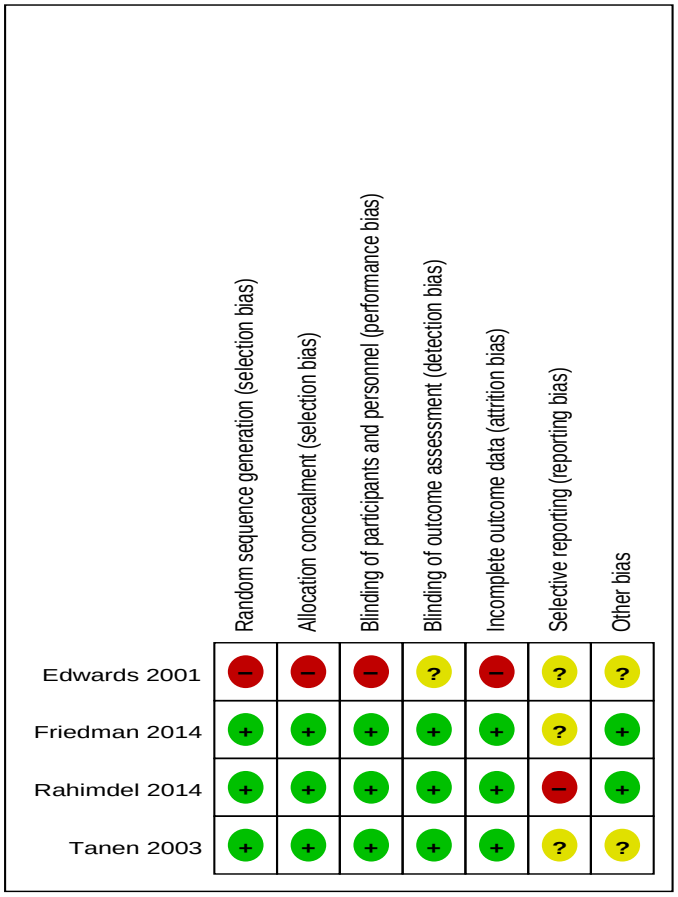


Figure 1. Risk of bias summary: Review of Scholar's judgment about each risk of bias item for each included study

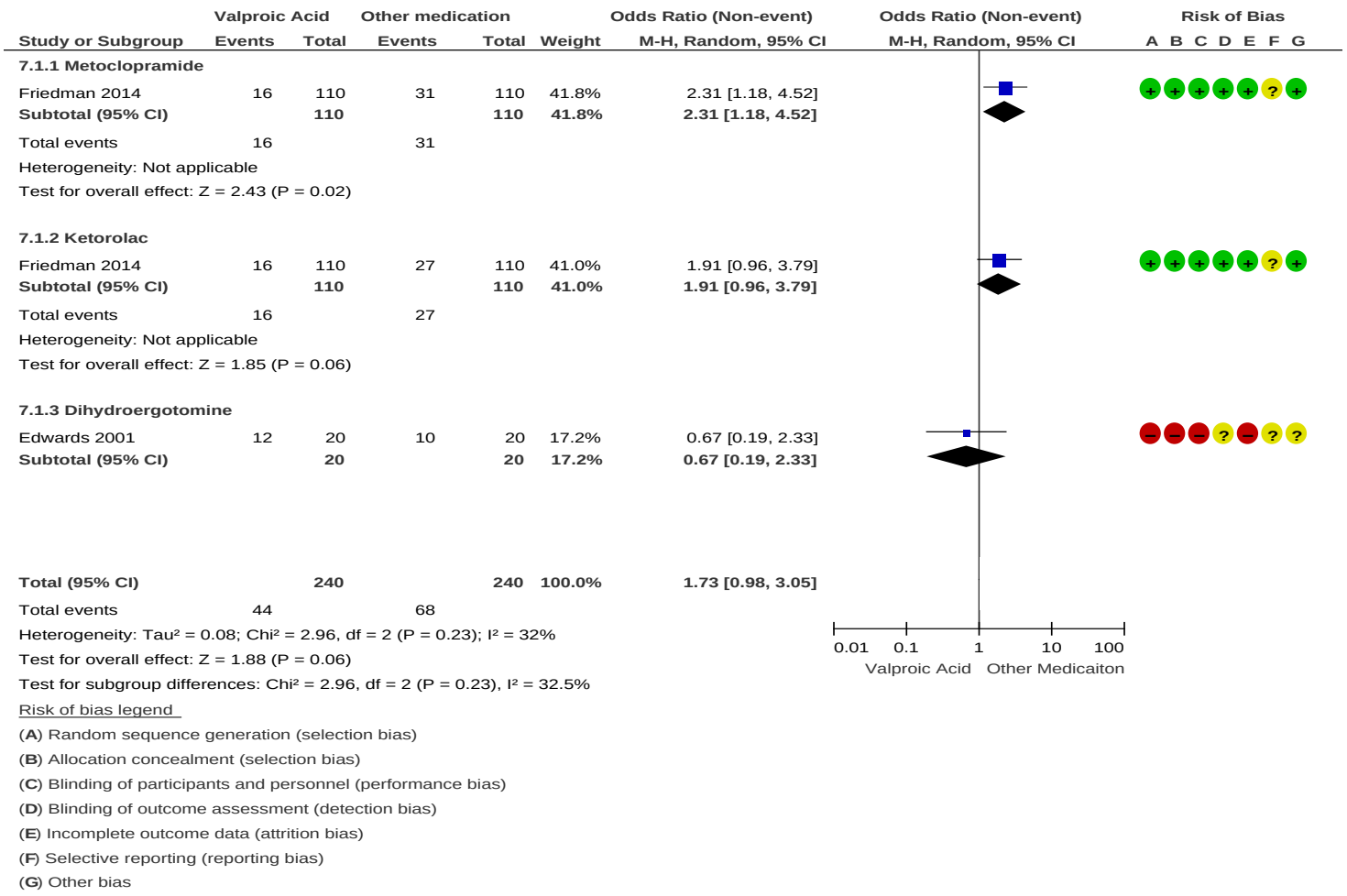


Figure 2. Comparison: Valproic Acid vs. Other medications Outcome: Pain Fee in Less Than 2 Hours

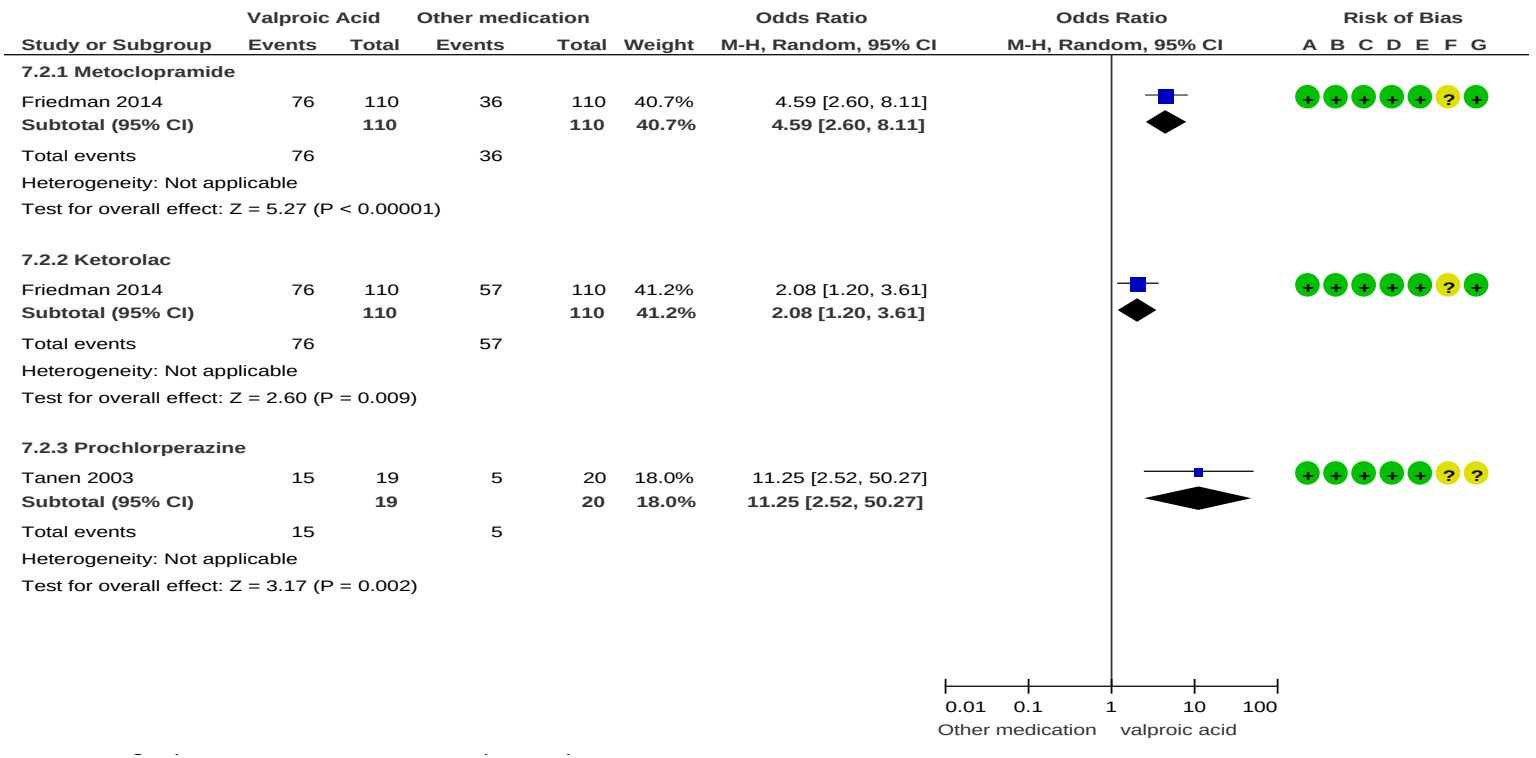


Figure 3. Comparison: Valproic Acid vs. Other Medications, Outcome: Use of Rescue Medications

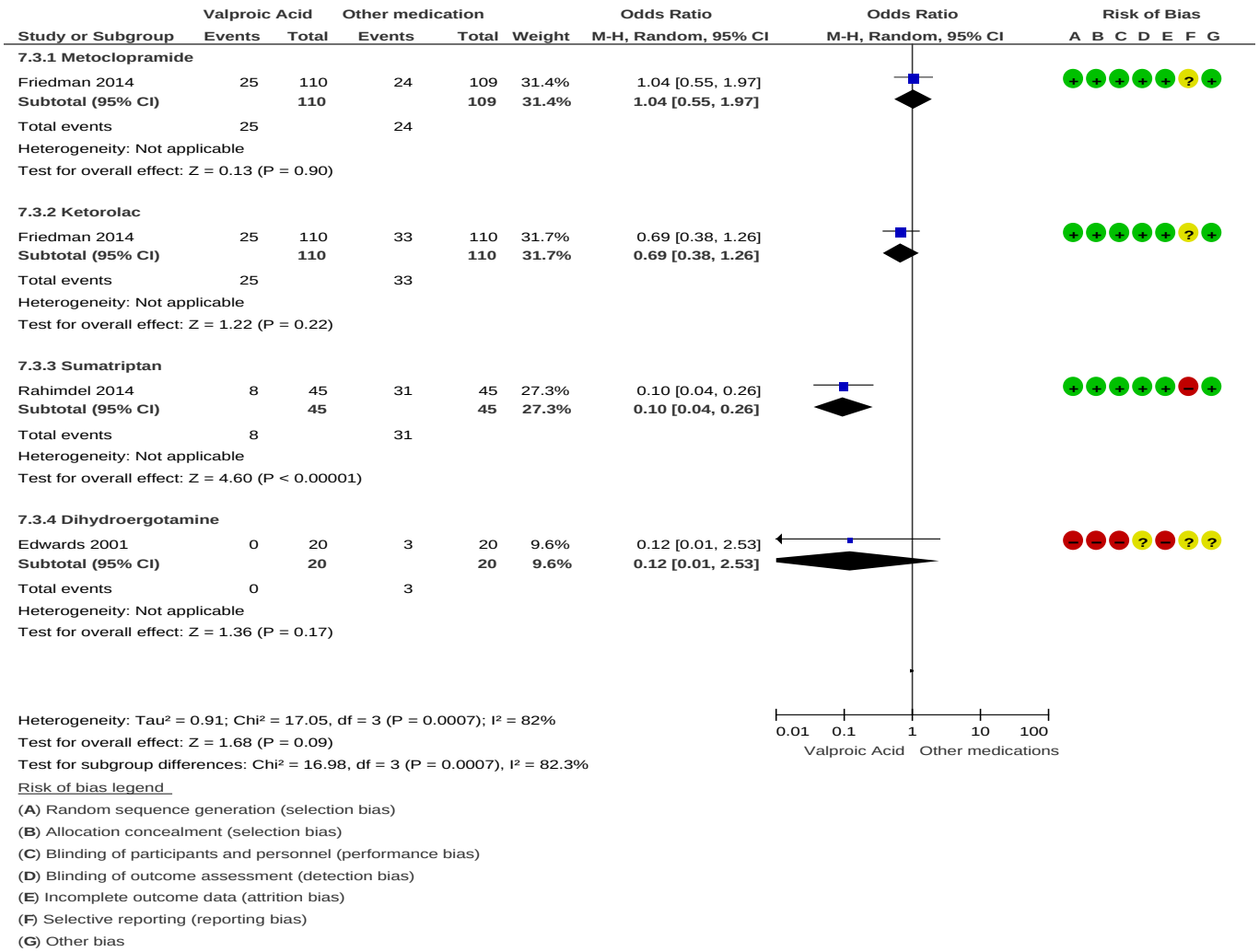


Figure 4. Valproic Acid vs. Other Medications, Outcome: Adverse Events References

Appendix D

Dihydroergotamine For Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with a refractory migraine, what is the efficacy of DHE IV to decrease migraine pain in the Emergency Department?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Migraine in the ED Team Recommendations: Based on very low quality evidence the Migraine in the ED CPG Teams makes a conditional recommendation against the use of DHE as the first line treatment of refractory migraine in the ED. However, it may be considered if:

- Hospital admission is anticipated
- Triptans have not been administered in the previous 24 hours.
- Subsequent doses of DHE can be administered

The key points are:

- Response to treatment with DHE may not be apparent until after the fifth dose and it is dosed every 8 hours (Kabbouche, et al., 2009)
- DHE cannot be given if the patient has received triptans with the previous 24 hours (Lexi-Comp, 2016).

Dose: Dihydroergotamine-
IV: 1mG, repeat 8 hours, improvement usually seen after the fifth dose
IM/SC: 0.5- 1mG, repeat hourly if needed (max 3mG/day)
Nasal: 0.5mG each nostril Q15 min (max 3mG/day)

Literature read and analyzed by:

Patricia Lanzer, RN, NNP-BC
Jamie Menown, RN, CPN
Joyce McCollum, RN, CNOR

Office of Evidence based Practice:

Nancy H. Allen, MS, MLS, RD,LD, EBP Program Manager

Search Strategy and Results:
December 2014

PubMed
"Dihydroergotamine"[Mesh] AND ("Migraine Disorders/prevention and control"[Mesh] OR "Migraine Disorders/therapy"[Mesh]) Filters: From 2009/01/01 to 2014/12/31, Humans, English, Child: birth-18 years

EMBASE
#5
#4 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py) **92 #4**#2 AND #3 **3,869**
#3 'migraine'/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim **128**
#2 'dihydroergotamine'/exp AND [english]/lim AND ([infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim) AND [embase]/lim **5,518**
#1 'dihydroergotamine'/exp OR 'dihydroergotamine'

Studies included in this review:
Seven studies were identified; six were excluded, and one included. The included study Kabbouche, et al. (2009) is indirectly applicable to the ED setting. It is included here because DHE cannot be given if triptans have been administered to the patient within the previous 24 hours.

Excluded Studies and Reason for Exclusion

Study	Reason for Exclusion
Aurora 2009	Inhaled DHE
Aurora 2011	Inhaled DHE
Charles 2010	Outpatient IV DHE administration- Does not answer the question
Fisher 2007	Inhaled DHE
Raina 2013	Case study of abdominal migraine
Tepper 2011	Inhaled DHE Conference presentation

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5.

Updated March 9 2016

Characteristics of included study:

Table:

Kabbouche, et al., 2009

Methods	Retrospective cohort-
Participants	All pediatric patients admitted for inpatient treatment of status migraine and intractable headache. Over a six week period. Abortive therapy in the outpatient setting (NSAIDs and or a triptan). All triptan treatment must have been administered at least 24 hours prior to DHE administration N=32 consecutive charts All received hydration (20ml/kg D5NS), all received either prochlorperazine or metoclopramide as antiemetic for the first 3 DHE doses. After 3 DHE doses, ondansetron was used as an antiemetic. mean age 14.52 +/- 1.91 years
Interventions	Dose • Children > 9 years old or > 25 kgs Dose 1 mG IV over 3 minutes every 8 hours • Children < 9 year old or < 25 kgs Dose 0.5 mG IV over 3 minutes every 8 hours A test dose of one half the initial dose appropriate for age and weight If test dose was tolerated the remainder of the dose was given half an hour later The DHE dose ws continued every 8 hours until headache freedom plus one additional dose or until the maximum of 20 doses were given (Aurora, et al., 2011)
Outcomes	Pain response- number of doses to reach 50% improvement on VAS (0-10),lower is better Pain response- number of doses to reach 100% improvement on VAS (0-10),lower is better
Notes	Mean severity of headache was 8.45 +/- 2.41 on a ten point scale. LOS was 2.6 +/- 1.8 days in the inpatient unit Did not report number of doses to attain 50% reduction in pain score. 40% of subjects were headache free by the fifth dose of DHE (13/32) 74% of subjects were headache free at hospital discharge (24/32) Mean pain score was 1.1 +/- 2.2 on a ten point scale at discharge Adverse effects: Nausea and vomiting 91.4%; chest tightness 6%; hives 2.8%; face flushing 2.8%; increased blood pressure 2.8%; no side effects 8.6% Response to treatment generally occurred after the 5 dose

Appendix E

Magnesium Sulfate IV for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with a refractory migraine, what is the efficacy of intravenous magnesium sulfate to decrease migraine pain in the Emergency Department?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Migraine in the ED Team Recommendations:

Based on very low quality evidence, the Migraine in the ED CPG team makes a conditional recommendation against treating with IV magnesium sulfate as a first line treatment for refractory migraine in the ED. The desirable effect of reducing symptom scores were not apparent and the proportion of subjects who incurred an adverse event was greater. The evidence to support this recommendation is graded as very low quality (see Table 1). The recommendation is based on the systematic review with meta-analysis by Choi & Parmar (2014) that includes five RCTs. The evidence is graded as very low quality due to indirectness (adult populations), inconsistency (the dose of IV magnesium varied across studies), and imprecise findings (the number of subjects studied in individual studies is low).

Choi & Parmar (2014) performed a systematic review. The meta-analysis showed for the outcome "Difference in Pain within 60 Minutes" there was no difference between the groups treated with magnesium sulfate (IV) and placebo or metoclopramide, *RR* = 1.05 95% CI [0.70, 1.57]. When a sensitivity analysis was done to see if there was a difference if the control group received metoclopramide or normal saline, the estimate of the effect still showed no difference between the groups. (See Figure 1)

For the outcome "Need for Rescue Medication" there was no difference between the groups treated with magnesium sulfate (IV) and placebo or metoclopramide, RR= 0.98 95% CI [0.80, 1.22]. Again, when sensitivity analysis was done to see if normal saline or metoclopramide were used as control, there was no difference in the estimate of the effect. (See Figure 2)

For the outcome "Adverse Events" there were significantly more adverse events, predominantly flushing, followed by dizziness and burning at the IV site for those treated with magnesium sulfate *RR*= 2.53 95% CI [1.53, 4.18]. When a sensitivity analysis was done to see if normal saline or metoclopramide was used as control, there were still significantly more adverse events in the groups treated with magnesium sulfate (IV) (See Figure 3).

Dose: Magnesium sulfate (IV) -50mG/kg (max 2gm) IV over one hour

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Nancy H. Allen, MS, MLS, RD,LD

Search Strategy and Results:
Searches performed on March 10 2014
PubMed
"Migraine Disorders/drug therapy"[Mesh] AND (("Cohort Studies"[Mesh] OR (Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb])) AND ("2009/01/01"[PDAT] : "2014/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

EMBASE
'migraine'/exp/mj/dm_dt AND ([internal medicine]/lim OR [neurology and psychiatry]/lim OR [pediatrics]/lim OR [pharmacology and pharmacy]/lim) AND ([infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2009-2014]/py

Studies included in this review:
Choi & Parmar (2014)

Study excluded in this review and reason for exclusion

Study	Reason for exclusion
Gertsch et al., 2014	Although the it is a pediatric case series of children treated with magnesium sulfate (IV) for migraine, subjects were treated with other medications such as ketorolac, diphenhydramine and prochlorperazine, or ondansetron prior to magnesium IV

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) (Higgins & Green, 2011), was used to recreate the meta-analysis reported in Choi (2014). GradePro ws used to assess the methodological quality of the meta-analysis.

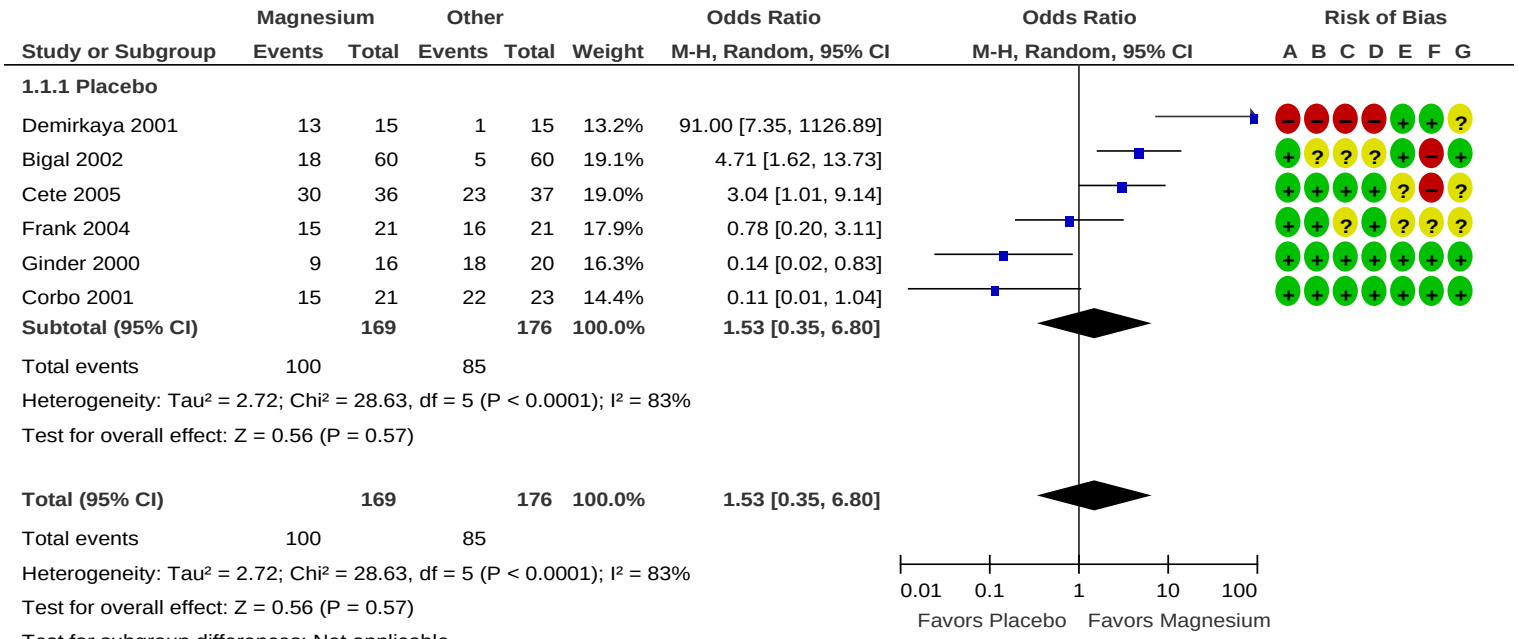
Updated March 4 2016, March 8 2016 May 16 2016

Characteristics of included study :

Tables:

Table 1. Grade Summary of Included Studies Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Magnesium sulfate IV**	**Other treatments**	**Relative (95% CI)**	**Absolute**	
Headache response assessed less than or equal to 60 minutes											
5	randomized trials	no serious risk of bias	serious[1,2]	no serious indirectness	very serious[3]	none	87/123 (70.7%)	84/131 (64.1%)	OR 0.95 (0.22 to 4.16)	12 fewer per 1000 (from 359 fewer to 240 more)	VERY LOW
Adverse effects											
4	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[3]	none	35/94 (37.2%)	14/101 (13.9%)	OR 4.93 (2.22 to 10.94)	304 more per 1000 (from 125 more to 499 more)	VERY LOW
Need for rescue medications											
3	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[3]	none	50/78 (64.1%)	46/79 (58.2%)	OR 1.32 (0.66 to 2.66)	66 more per 1000 (from 103 fewer to 205 more)	VERY LOW

[1] Various medications were used as comparison.
[2] The I2 statistic is 80%, less than 50% is desired
[3] Low number of events, with low numbers of subjects in each group



Study or Subgroup	Magnesium Events	Total	Other Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Placebo						
Demirkaya 2001	13	15	1	15	13.2%	91.00 [7.35, 1126.89]
Bigal 2002	18	60	5	60	19.1%	4.71 [1.62, 13.73]
Cete 2005	30	36	23	37	19.0%	3.04 [1.01, 9.14]
Frank 2004	15	21	16	21	17.9%	0.78 [0.20, 3.11]
Ginder 2000	9	16	18	20	16.3%	0.14 [0.02, 0.83]
Corbo 2001	15	21	22	23	14.4%	0.11 [0.01, 1.04]
Subtotal (95% CI)		**169**		**176**	**100.0%**	**1.53 [0.35, 6.80]**
Total events	100		85			
Heterogeneity: Tau² = 2.72; Chi² = 28.63, df = 5 (P < 0.0001); I² = 83%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Total (95% CI)		**169**		**176**	**100.0%**	**1.53 [0.35, 6.80]**
Total events	100		85			
Heterogeneity: Tau² = 2.72; Chi² = 28.63, df = 5 (P < 0.0001); I² = 83%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Not applicable						

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

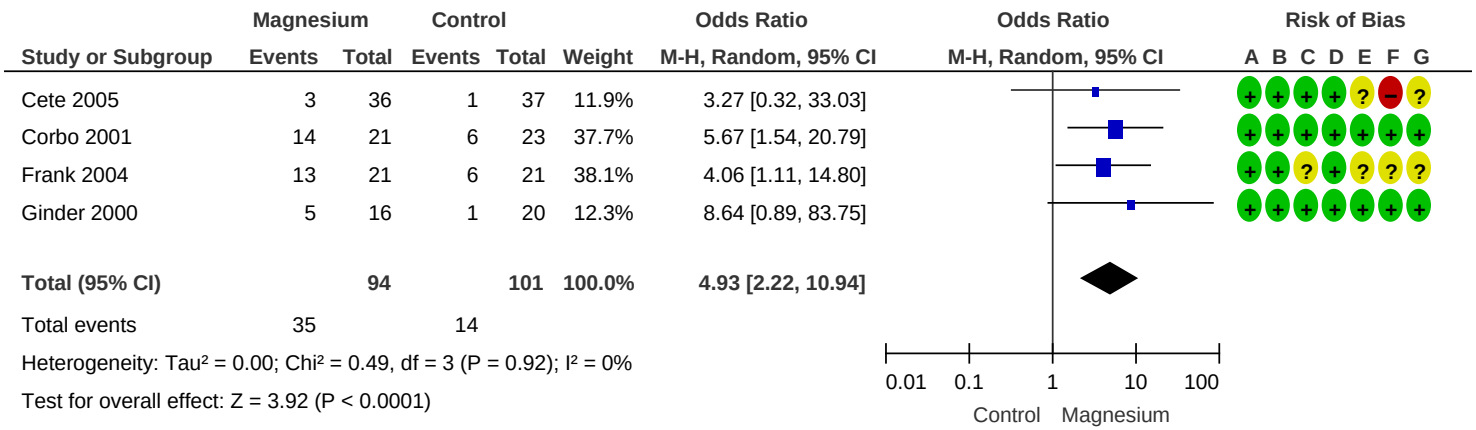
(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure 1. Comparison: Magnesium sulfate (IV) versus Other treatments: Outcome Headache response at 60 min



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

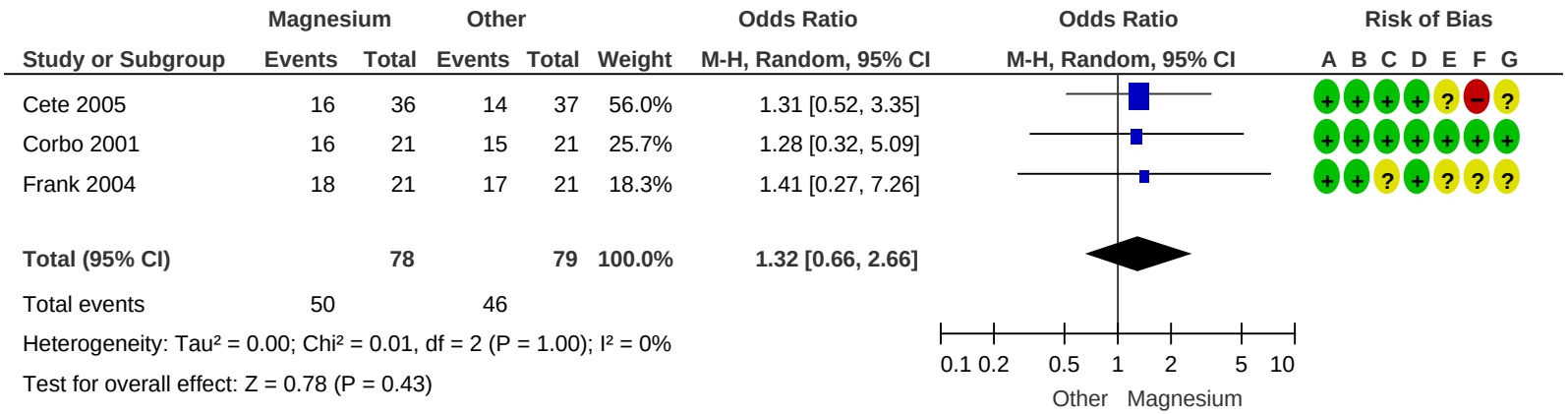
(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure 2. Comparison: Magnesium sulfate (IV) versus Other treatments: Outcome, Adverse effects



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure 3. Comparison: Magnesium sulfate (IV) vs. Other treatments: Outcome: Need for rescue medications

Appendix F

Glucocorticosteroids for Refractory Migraine in the ED

Specific Care Question:

In the pediatric patient diagnosed with a refractory migraine, is glucocorticosteriods an effective treatment for the prevention of migraine relapse (return to ED or provider for relapse of the same migraine within 24-72 hours)?

Question Originator:
Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on very low quality evidence, the Migraine in the ED CPG Team makes a conditional recommendation against the use of glucocorticosteriods for either the treatment of acute migraine headache, or the prevention of migraine relapse. Huang et al. (2013) conducted a sound systematic review with meta-analysis on eight RCTs that evaluated this question (See Table 1). For the outcome prevention of relapse of migraine headache, treatment with dexamethasone had the absolute effect of preventing relapse in 11 of 100 subjects (range 5-15 fewer). It did not have a significant treatment effect on the outcome total headache resolution (4 more subjects of 100 subjects had total headache resolution after being treated with dexamethasone, but the range is form 2 fewer to 12 more total headache resolutions per 100 subjects) The only adverse event that was significantly different between treatment groups was dizziness. It occurred more frequently in the group treated with dexamethasone. Dexamethasone had the absolute effect of causing dizziness in 3 of 100 subjects (range 0-12 more). Although the results of the meta-analysis are promising, the characteristics of patients who would benefit from glucocorticosteriods are not clear. Long-term effects of chronic glucocorticosteriods use were not evaluated, nor were the appropriate doses of glucocorticosteriods determined.

The evidence is graded as very low quality evidence due to different doses of dexamethasone (inconsistency) all of the studies were performed in adults (indirectness), and finally in the combined studies there are small number of events, (imprecision). The results of a case series reported by (Legault, Eisman, and Shevell (2011) did not find a difference in "bounce" backs in children treated with steroids, versus those who were not. Larger, prospective studies are needed to clarify the migraine recurrence and treatments that are efficacious to prevent migraine headache and recurrence.

Literature read and analyzed by:
Jamie Menown, BSN, RN
Office of Evidence Based Practice
Nancy H. Allen, MS, MLS, RD,LD

Search Strategy and Results:

No.	**Query**	**Results**
#18	#7 AND [embase]/lim NOT [medline]/lim AND 'antihistaminic agent'/de	**2**
#17		**15**

#7 AND [embase]/lim NOT [medline]/lim AND 'steroid'/de

966

#16
#7 AND [embase]/lim NOT [medline]/lim

7

#15
#7 AND ('drug therapy':lnk OR 'prevention':lnk OR 'therapy':lnk) AND 'triptan derivative'/de AND [embase]/lim NOT [medline]/lim

12

#14
#7 AND ('drug therapy':lnk OR 'prevention':lnk OR 'therapy':lnk) AND 'valproic acid'/de AND [embase]/lim NOT [medline]/lim

72

#13
#7 AND ('drug therapy':lnk OR 'prevention':lnk OR 'therapy':lnk) AND 'valproic acid'/de

37

#12
#7 AND ('drug therapy':lnk OR 'prevention':lnk OR 'therapy':lnk) AND 'triptan derivative'/de

23

#11
#7 AND ('controlled study'/de OR 'major clinical study'/de) AND ('drug therapy':lnk OR 'prevention':lnk OR 'therapy':lnk) AND 'triptan derivative'/de

Studies included in this review:
Huang et al., 2013
Legault et al., 2011

Excluded Studies and Reason for Exclusion:

Study	Reason for exclusion
Singh, Alter, & Zaia, 2008	Huang MA includes more recent studies
Soleimanpour et al., 2012	Does not answer the question

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) (Higgins & Green, 2011), was used to recreate the meta-analysis reported in Huang 2013. GradePro was used to assess the methodological quality of the meta-analysis.

Updated March 7 2016

Tables:

Table 1. GRADE Summary of Huang, 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glucocorticosteroids**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Migraine recurrence (follow-up 24-72 hours)												
8	randomized trials	serious	no serious inconsistency	serious[1]	serious	none	128/469 (27.3%)	166/436 (38.1%)	OR 0.6 (0.45 to 0.79)	111 fewer per 1000 (from 54 fewer to 164 fewer)	⋅ ⋅ ⋅ ⋅ VERY LOW	CRITICAL
Adverse events- Dizziness (follow-up 24-48 hours)												
4	randomized trials	no serious risk	serious[2]	serious[1]	serious[3]	none	15/246 (6.1%)	4/226 (1.8%)	OR 0.35 (0.12 to 0.96)	11 fewer per 1000 (from 1	⋅ ⋅ ⋅ ⋅ VERY LOW	CRITICAL

		of bias								fewer to 16 fewer)		
Totally resolved migraine headache (follow-up median 48-72 hours)												
6	randomized trials	no serious risk of bias	serious[2]	serious[1]	serious	none	160/368 (43.5%)	131/340 (38.5%)	OR 0.82 (0.6 to 1.12)	46 fewer per 1000 (from 112 fewer to 27 more)	⋅ ⋅ ⋅ ⋅ VERY LOW	CRITICAL

[1] Although heterogeneity was assessed at 0%, there were different doses of dexamethasone (10, 15, and 24 milligrams); route for the medication varied among studies (IV, IM, or oral) and two of the eight studies described the "standard" therapy while six did not.
[2] All studies were done in adults
[3] Small sample sizes with small number of events

Table 2. Risk of Adverse Events when treating with dexamethasone that did not reach significance

Adverse events that were not different	Number of reporting studies	Risk ratio, fixed effects [95% Confidence Interval]
Restlessness	2	1.46 [0.74, 2.90]
Drowsiness	3	0.75 [0.46, 1.23]
Nausea or vomiting	5	0.76 [0.46, 1.48]
Tingling, numbness, or swelling	5	1.56 [0.57, 4.26]
Mood change	2	0.80 [1.18, 3.52]
Other adverse events	6	0.71 [0.41, 1.21]

Note: Table is from Huang et al. (2013)

Characteristics of included studies (from Huang 2013):

Figures:

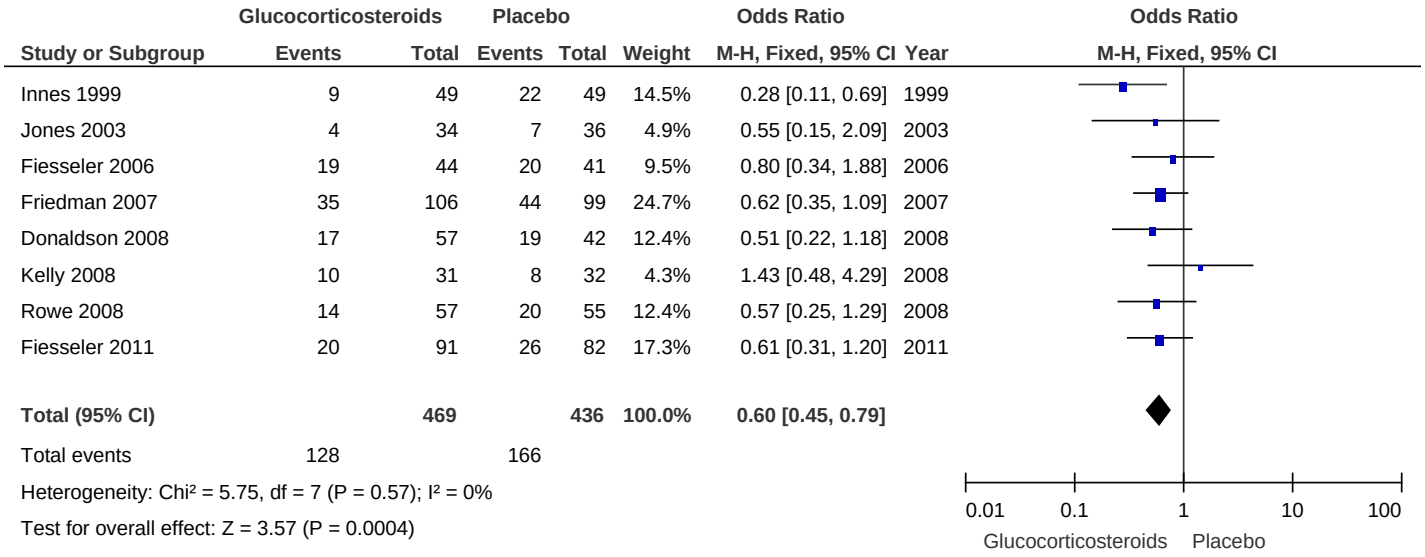


Figure 1. Comparison: Glucocorticosteroids versus. Placebo, Outcome: Migraine recurrence

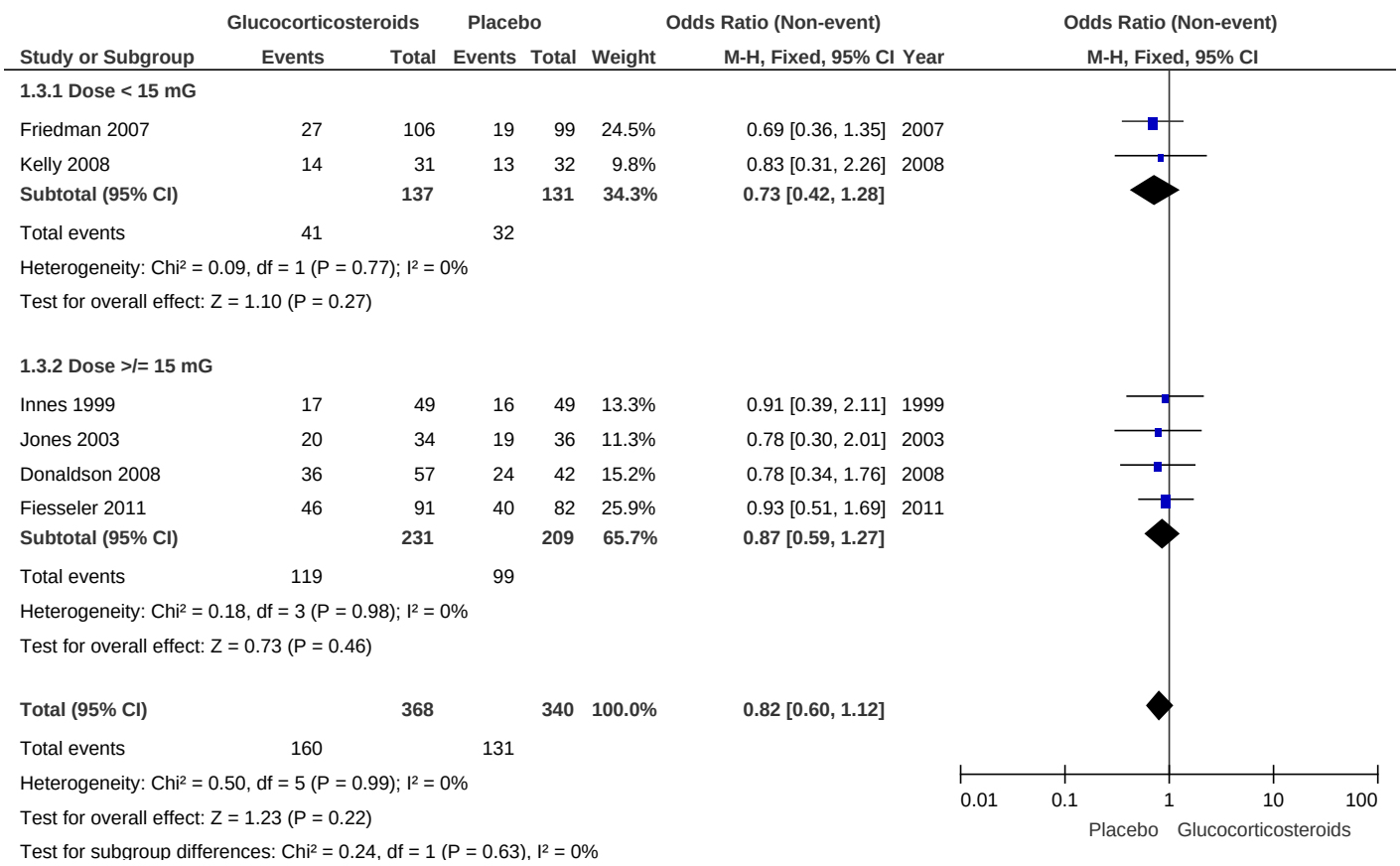


Figure 2. Comparison: Glucocorticosteroids versus Placebo, Outcome: Totally resolved migraine

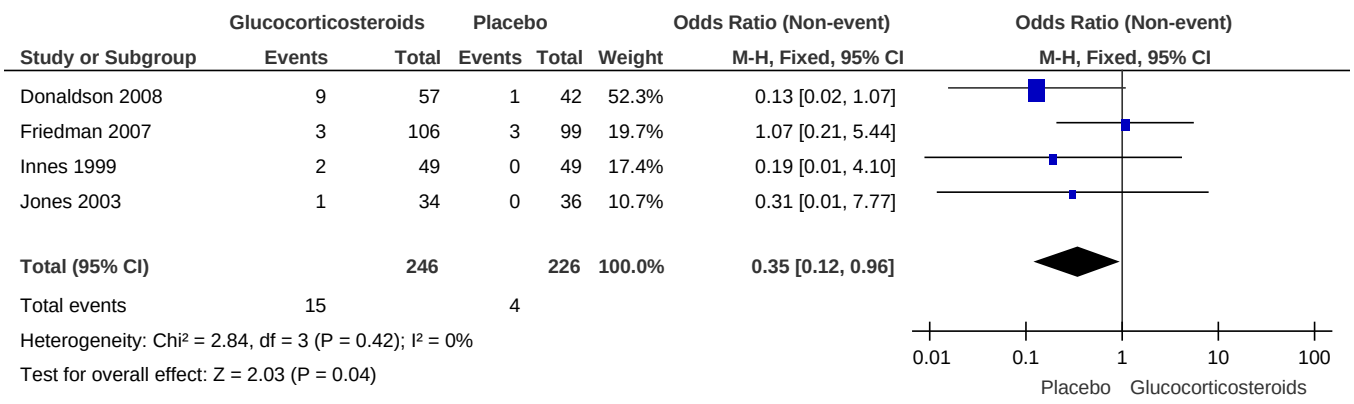


Figure 3. Comparison: Glucocorticosteroids versus placebo, Outcome: Adverse event (dizziness)

Appendix G.

Ketorolac for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with refractory migraine is ketorolac an effective treatment?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on very low quality evidence, the Migraine in the ED CPG Teams makes a ***Conditional* Recommendation** to use ketorolac or valproic acid as the second line treatment, with the potential to use valproic acid if needed based on prior NSAID exposure. Friedman et al. (2014) reported there was no difference when comparing ketorolac vs. valproic acid for pain relief at 2 hours. However, the use of rescue medications was lower in the group who received ketorolac. Although ketorolac appears to have greater efficacy, it should not be used if NSAIDs were recently taken*. If valproic acid is used, pregnancy testing in females must be negative.

*Caution: Ketorolac should not be used if NSAIDs were taken within the following timeframes:

- ibuprofen < 6 hours prior administration
- naproxen sodium < 12 hours prior administration

Although the included studies are methodologically strong, they are only three studies that include a small number of subjects (see Figure 1). Meta- analysis cannot be performed.

- Friedman et al (2014) compared 30 mG IV ketorolac to 1 gram IV valproic acid and found there was:
  - No difference in pain relief at two hours after medication administration. *OR* = 1.91, 95% CI [0.96, 3.79], p= 0.06.
  - Significantly less use of rescue medications when ketorolac was administered OR= 0.48, 95% CI [0.28, 0.83], p= 0.009.
- Brousseau, Duffy, Anderson, & Linakis (2004) compared 0.5 mG/kg; (maximum 30 mG) IV ketorolac to 0.15 mG/kg IV prochlorperazine (maximum 10 mG). The study was stopped early due to the overwhelming benefit of pain relief within two hours in the group treated with prochlorperazine. (*OR*= 4.55, 95% CI [1.37. 15.11], p= 0.01. The odds of having pain relief if treated with prochlorperazine was 4.5 times greater than if treated with ketorolac.
- Meredith, Wait, & Brewer (2003) compared IV ketorolac to nasal sumatriptan and reported pain scores within two hours of treatment. The group treated with IV ketorolac had significantly lower pain scores than subjects treated with nasal sumatriptan *MD* = -40.76, [-60.35, -21.16].

The dose of ketorolac is 0.5 mG/kg IV (max 30mG) and 1 mG/kg IM (max 60 mG)

EBP Scholar's responsible for analyzing the literature:

Jamie Cailteux. RN, BSN, CPN
Jackie Bartlett, PhD, RN
EBP team member responsible for reviewing, synthesizing, and developing this literature:
Allen, Nancy

Search Strategy and Results:
Studies included in this review:
March 10 2014
EMBASE
'**migraine**'/exp/mj/dm_dt AND ([internal medicine]/lim OR [neurology and psychiatry]/lim OR [pediatrics]/lim OR [pharmacology and pharmacy]/lim) AND ([infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2009-2014]/py

Studies included in this review:
Friedman et al., 2014
Brousseau et al., 2004
Meredith et al., 2003

Studies <u>not</u> included in this review with rationale for exclusion:
Duarte 1992- Does not answer the question

Method Used for Appraisal and Synthesis:
Review Manager 5.3.5 (Higgins & Green, 2011).

Updated August 5 2015, August 7, 2015, August 18 2015 March 8 2016, May 16 2016

Characteristics of included study:

Tables:

Brousseau et al., 2004

Methods	Prospective 2-center double-blind RCT
Participants	**Setting:** 2 pediatric EDs within 2 separate children's hospitals **Randomized:** 62 subjects were randomized **Completed:** 60 subjects completed **Age:** mean of 13.8 (SD 3.0) for prochlorperazine, 13.7 (SD 2.6) for ketorolac **Gender:** 18/33 female for prochlorperazine, 18/29 female for ketorolac **Inclusion:** Prensky & Sommer criteria (recurrent headaches with pain-free intervals and at least 3 of the following: 1-an aura, 2-unilateral location, 3-throbbing pulsatile pain, 4-nausea, vomiting, or abdominal pain, 5-relief after sleep, 6-a family history of migraines **Exclusion:** Subjects with any contraindication to use of two study drugs and those unable to complete a Nine Faces Pain Scale **Power analysis:** Sample size was determined by assuming a 30% difference between groups in the proportion of patients classified as experiencing treatment successes represented the minimal limit of clinical significance. A 65% success rate was assumed for the more efficacious treatment. Using an α value of 0.05 and a β value of 0.80, the sample size goal was set at 49 patients per group. At the recommendation of an independent study monitor, it was determined a priori that an interim analysis of the data would be performed at approximately 50% of desired enrollment. Because the interim analysis disclosed a clear difference between the 2 treatments, the study monitor recommended termination of the study at the 50% enrollment point.
Interventions	All subjects received a 10 mL/kg bolus of normal saline solution over a 30-minute period. **Treatment group:** prochlorperazine (0.15 mG/kg; maximum 10 mG) intravenous over 10 minutes **Control group:** ketorolac (0.5 mG/kg; maximum 30 mG) intravenous over 10 minutes
Outcomes	Treatment success = a reduction of 50% or greater in the child's Nine Faces Pain Scale score at 30 or 60 minutes or a complete resolution of symptoms.
Notes	They stopped the study before achieving 49 subjects per group because the prochlorperazine, the "control" treatment was significantly better than the ketorolac the "experimental" treatment.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Block randomization performed by hospital pharmacy
Allocation concealment (selection bias)	Low risk	Block randomization performed by hospital pharmacy
Low risk	Low risk	Treating nurse, physician and patient were all blinded. Code for blinding was maintained in the pharmacy and not available to any investigator until completion of the study.
Blinding of outcome assessment (detection bias)	Low risk	Treating nurse, physician and patient were all blinded. Code for blinding was maintained in the pharmacy and not available to any investigator until completion of the study.
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	Low risk	

Friedman, et al., 2014

Methods	RCT
Participants	**Setting** ED- proficient bilingual (English and Spanish) staff **Number randomized** : N= 330, 110 per treatment group Ketorolac 30 mG, valproate 1 gram and metoclopramide 10 mG **Number completed:** N= 320, 106 ketorolac, 107 valproate and 107 metoclopramide **Gender:** 14% male **Age:** 34 years (range: 25-44 years) **Inclusion criteria:** Subjects met the criteria of the International Headache Society's International Classification of Headache Disorders 2nd Ed. Also accepted those who did not meet the criteria for • insufficient number of lifetime headaches (<5) • prolonged duration of headache (>72 hrs)

	Exclusion criteria: those who would received a lumbar puncture in the ED, fever present (>/= to 100.4 degrees F), a new neurologic abnormality, seizure disorder, concurrent use of an investigational medication, pregnancy, lactation, previous enrollment, allergy or intolerance to study medications--including hepatic dysfunction, peptic ulcer disease or concurrent use of immunosuppressive medications or monoamine oxidase inhibitors medications **Power analysis:** sample size 100 for each arm of the study
Interventions	Three interventions 1. 1 g of IV valproate vs. 10 mG IV metoclopramide 2. 1 g IV valproate vs. 30 mG IV ketorolac 3. 10 mG of metoclopramide vs. 30 mG IV ketorolac
Outcomes	Primary outcome: Headache relief at one hour Secondary outcomes: 1. Use of rescue medication in the ED- this was considered failure for all other secondary outcomes 2. Patient's overall assessment of efficacy and tolerability - Y/N to "Do you want to receive the same medication the next time you visit the ED with a headache?" 3. Sustained headache relief- four point scale severe, moderate, mild, none within two hours and maintained for 24 hours Functional outcomes 1. Yes/no to "Do you think you could now perform all your usual daily activities?" Assessed at one hour Safety outcomes 1. One hour after medication: assessment of drowsiness on a 3 point scale: (a) no drowsiness. (b) a little bit drowsy, but able to function normally, and (c) too drowsy to function normally 2. Twenty four hours after medication (follow up phone call) 1. Did you feel restless: (a) no restlessness, (b) a little bit restless, or (c) very restless 3. At one, two and 24 hours subjects were asked if they had any other symptom
Notes	Primary outcome: pair wise comparison, Mean difference in pain score (0-10, lower is better) (95% CI) between baseline and one hour Valproate vs. metoclopramide: [- 1.9 (-2.8. -1.1)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving metoclopramide. Valproate vs. ketorolac: [- 1.1 (-2.0, -0.2)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving ketorolac Metoclopramide vs. ketorolac [0.8 (-1.1, 1.7)] The positive mean difference means that subjects who received metoclopramide had a larger improvement in pain score than subjects receiving ketorolac

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	randomized using an online random number generator, in blocks of six, by the research pharmacy
Allocation concealment (selection bias)	Low risk	The pharmacist placed filled medication vials into the designated container that was numbered in sequence by the randomization schedule. Only the research pharmacist, who was not in the ED knew the allocation. All doses were made to 10 mL to match the volume of ketorolac which came as a 10 mL solution from the manufacturer. Vials were the same.
Blinding of participants and personnel (performance bias)	Low risk	ED nurse who was blinded to the allocation, placed the medication into a 50 mL bag of normal saline for infusion IV drip over 15 minutes
Blinding of outcome assessment (detection bias)	Low risk	Research associates who were blinded to allocation asked subjects questions at 1 and 2 hours after medication was administered. Subjects were contacted at 24 hours after medication administration as well. All data collection tools were standardized
Incomplete outcome data (attrition bias)	Low risk	Used intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	They did not give data that can be used in a meta analysis for their primary outcomes, but did for their secondary outcomes
Other bias	Low risk	

Meredith, et al., 2003

Methods	Prospective double-blind RCT
Participants	**Participants:** Adults **Setting:** urban emergency department **Number randomized:**29 subjects **Number completed:** 29 subjects **Age:** 33 years (range 18-56 years) **Gender:** 14% male

	Inclusion criteria: Modified International Headache Society (IHS) criteria for migraine without aura was used. **Exclusion criteria:** known allergy to sumatriptan or ketorolac, active peptic ulcer disease, use of an ergotamine containing medication, monoamine oxidase inhibitor or antidepressant, hemiplegic or basilar migraine headache, renal impairment or dialysis dependent, menstruation, pregnancy or nursing. Subjects were excluded if they had taken a non-steroidal anti-inflammatory medication or sumatriptan. Also, if the subject was thought to have a life threatening illness such as stroke (either intracranial hemorrhage or vascular occlusion) meningitis, or encephalopathy. Power analysis: not reported
Interventions	Group 1: Ketorolac IV, 30 mG -n= 13 Group 2: Sumatriptan Nasal, 20 mG - n= 16 All patients rated their pain using a visual analog scale from 0-100. Pain assessment was repeated 1-hour post study medication.
Outcomes	Change in pain score on a visual analog scale (100 mm) left endpoint "no pain" and right endpoint "pain as bad as it could possibly be"
Notes	Used a RMANOVA to compare pre-and post-treatment scores (RMANOVA= repeated measures analysis of variance). They used the term "power analysis" in an unusual manner..

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Low risk	Low risk	Randomization was done by a computer-generated random-number program
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Treating physician, nurse and patient were all blinded. Unblinding did not occur until post treatment pain score was recorded.
Blinding of outcome assessment (detection bias)	Low risk	

Incomplete outcome data (attrition bias)	Low risk	No attrition reported.
Selective reporting (reporting bias)	High risk	They report findings in this way: one hour after treatment the mean pain score was decreased significantly by 61.7 mm (SD = +/- 35.01; power = 80-90% at P </= 0.05
Other bias	Low risk	

Figures:

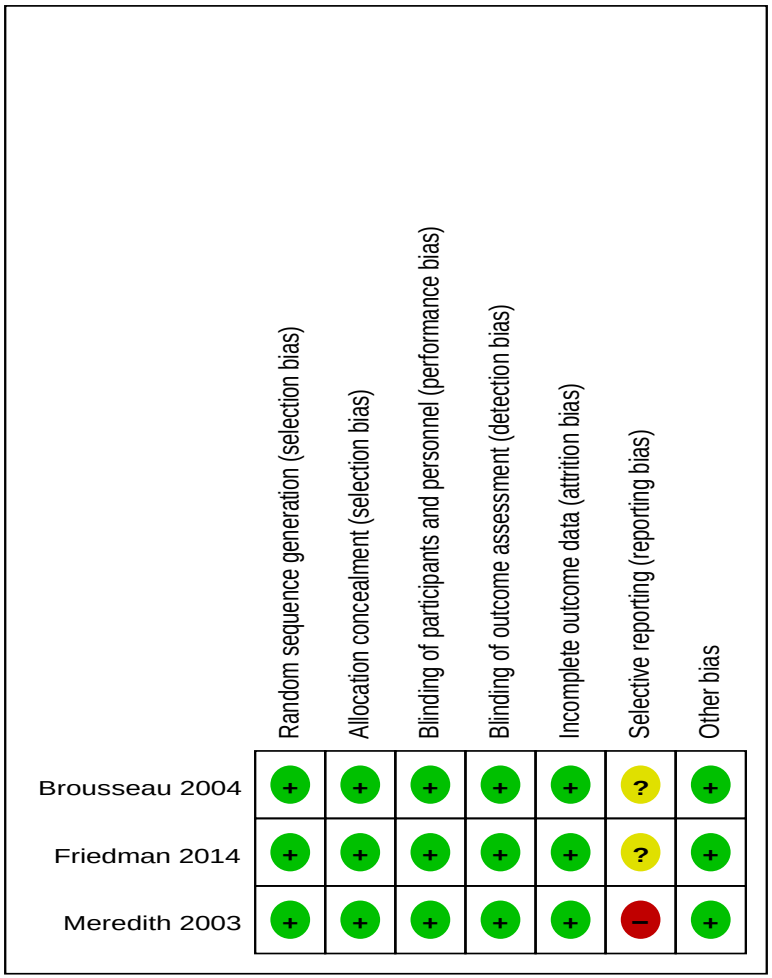


Figure 1. Risk of bias summary: Scholars judgments about each risk of bias item for each included study

Appendix H

Metoclopramide for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with refractory migraine, is metoclopramide an effective treatment?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on very low quality evidence, the Migraine Therapy in the ED CPG team makes a conditional recommendation to use metoclopramide as the back-up medication for the treatment of refractory migraine during shortages of prochlorperazine. Of metoclopramide, valproic acid, or ketorolac, metoclopramide is more likely to relieve headache pain within two hours of administration. Rescue medications to relieve continued pain are less likely to be administered when metoclopramide is administered versus the other two potential back-up medications, and the number of adverse drug events is similar among the three medications. The comparison of metoclopramide versus valproic acid and ketorolac is from a single study performed by Friedman et al. (2014). Although the study is methodologically strong, as more evidence becomes of available, the estimates of effect may change. Further research, if performed will have an important influence on our confidence in the estimate of the effect.

Dose: Metoclopramide -0.1 mG/kg (max 10 mG) IV, over 15 minutes

Review of literature:

Metoclopramide is significantly less likely to produce pain relief within two hours of administration than prochlorperazine (OR= 0.34, 95% CI [0.16,0.71], and is more likely to require the administration of rescue medications than prochlorperazine (OR= 3.05, 95% CI [1.32, 7.02] (Coppola, Yealy, & Leibold, 1995; Friedman et al., 2008; Jones, Pack, & Chun, 1996) (see Figures 2-4). Friedman et al. (2014) reported that metoclopramide provided greater reduction in headache pain on an 11-point visual analog scale within 2 hours of dosing than either valproic acid or ketorolac *OR* = 1.90, 95% CI [1.21, 2.59] and 0.80, 95% CI [0.03, 1.57], respectively. Subjects who received metoclopramide received less rescue medication than those who received valproic acid (*OR*=0.22, 95% CI [0.12, 0.38] or ketorolac *OR*= 0.45, 95% CI [0.26, 0.78].

Friedman et al. (2008) performed a dose finding study, comparing a 10 mG IV dose to a 20 mG and 40 mG IV dose, and a 20 mG IV dose to a 40 mG IV dose. There was no difference in the number of subjects with pain relief within two hours, or need for rescue medication (see Figure 5).

The individual studies are strong studies; biases were not identified (see Table XX)For the comparison of metoclopramide vs. prochlorperazine, the three included studies are inconsistent. Two studies use IV dosing, and the other uses IM dosing. Studies did not control for the concomitant use of diphenhydramine. These factors increase the inconsistency among the studies, decreasing confidence in the results. The studies are also downgraded for imprecision. There are small numbers of subjects in the included studies, with small number of events. Therefore, the precision

of the outcome measurement is low. Finally, the evidence is indirect, as the subjects in all studies were primarily adults. However, we value pain relief with the least amount of rescue medication needed to be administered (see Table 1).

For the comparison of metoclopramide vs. valproic acid and ketorolac, only one study was identified, and meta-analysis could not be performed (Friedman et al., 2014). Further research is likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate. Since the desirable effects of effective pain reduction and less use of rescue medications are met with metoclopramide compared with valproic acid or ketorolac, it is our recommendation when a prochlorperazine shortage is in effect.

EBP Scholar's responsible for analyzing the literature:
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EBP team member responsible for reviewing, synthesizing, and developing this literature:
Nancy Allen, MS, MLS, RD, LD

Search Strategy and Results:
Studies included in this review:
Coppola et al., 1995
Friedman et al., 2008
Friedman et al., 2014
Friedman et al., 2011
Jones et al., 1996

Studies <u>not</u> included in this review with rationale for exclusion:

Study	Reason for exclusion
Edwards, Norton, & Behnke, 2001	Does not answer the question. It compares valproic acid versus dihydroergotamine plus metoclopramide

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager 5.3.5 (Higgins & Green, 2011).

Updated March 29 2016

Characteristics of included study :
Tables:

Table 1. Grade Summary of Prochlorperazine vs. Metoclopramide for Migraine in the ED

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prochlorperazine**	**Metoclopramide**	**Relative (95% CI)**	**Absolute**		
Pain Relief Within 2 Hours												
3	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	44/90 (48.9%)	59/87 (67.8%)	OR 0.34 (0.16 to 0.71)	261 fewer per 1000 (from 79 fewer to 426 fewer)	⨁⨁◯◯ LOW	CRITICAL
Rescue Meds												
3	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	35/89 (39.3%)	20/84 (23.8%)	OR 3.05 (1.32 to 7.02)	250 more per 1000 (from 54 more to 449 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse Reactions												

2	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	17/67 (25.4%)	23/67 (34.3%)	OR 0.65 (0.3 to 1.39)	90 fewer per 1000 (from 208 fewer to 78 more)	⋅ ⋅ ⋅ ⋅ LOW	CRITICAL

[1] Doses of drugs varied among the studies, two compared 10 mG metoclopramide to 10 mG of prochlorperazine, while one study compare 10 mG metoclopramide to 20 mG of prochlorperazine. Route of administration varied as well, two studies reported on medications given IV, while the other administered the medications IM.

[2] Low number of events decreases the precision of the findings.

Coppola 1995

Methods	RCT, prospective, double-blind, placebo-controlled
Participants	**Setting:** military community hospital ED **Randomized:** 75, treatment group n=26 (metoclopramide) n=24 (prochlorperazine) n=24 (placebo) **Completed:** 70, treatment group n=24 (metoclopramide) n= 22 (prochlorperazine) n= 24 (placebo) **Gender:** unknown **Inclusion criteria:** CEPHALGIA SIMILAR TO PREVIOUS EPISODES, WITH OR WITHOUT NAUSEA, VOMITING, PHOTOPHOBIA OR PHONOPHOBIA **Exclusion criteria:** pregnancy, fever or meningismus, altered mental state, recent (within 24 hours)use of analgesics, drugs, or alcohol, O2<90%, recent trauma or seizure, first episode of headache, suspicion of intracranial process, allergy, diastolic BP > 90. **Power analysis:** 20 patients per group offered minimum pretrial power of 0.9 to detect a difference in frequency of clinical improvement of 33% or greater
Interventions	**Treatment group** (metoclopramide): 2 ml (10 mG) iv over 2 minutes **Treatment group** (prochlorperazine): 2 ml (10mG) iv over 2 minutes **Control group:** 2 ml NS iv over 2 minutes
Outcomes	Patient satisfaction + reduction in pain by 50% at 30 minutes, reduction in nausea, change in sedation, all measured at 30 minutes after administration

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT, computer generated, double blind, placebo controlled
Allocation concealment (selection bias)	Low risk	Randomized, computer generated
Blinding of participants and personnel (performance bias)	Low risk	Patients and healthcare workers blinded
Blinding of outcome assessment (detection bias)	Low risk	Patients self assessed outcome assessment.

Incomplete outcome data (attrition bias)	Low risk	4 patients did not complete study due to adverse reactions, 1 did not meet protocol. No missing outcome data
Selective reporting (reporting bias)	Low risk	study protocol is available, all outcomes reported
Other bias	Low risk	

Friedman 2008

Methods	Randomized, double-blind, clinical trial
Participants	**Setting:** 2 academic EDs in discrete neighborhoods of New York City. **Randomized into study:** n=192 screened, 97 eligible, 77 randomized • Group 1 (control): Prochlorperazine = 39 • Group 2 (experimental): Metoclopramide = 38 **Completed study:** n=73 • Group 1 = 36 • Group 2 = 37 **Gender, females:** • Group 1 = 85% • Group 2 = 95% **Age, years, mean(SD):** • Group 1 = 34 (10) • Group 2 = 39 (12) **Inclusion criteria:** • Migraine with or without aura as classified by ICHD • probable migraine lasting longer than 72 hours **Exclusion criteria:** • concomitant secondary headache • if pt was to receive an lumbar puncture in the ED • allergy or intolerance to study medications • pregnancy • previous enrollment\ **Power analysis:** • sample size of 38 subjects in each group to give power of 0.8 to detect a difference of 2.0 in the primary outcome.

	• Numeric rating scale change of 2.0 chosen as a worthwhile cutoff because it has been previously shown to have robust clinical significance.
Interventions	• **Group 1 (control):** 10mG IV prochlorperazine + 25mG IV diphenhydramine • **Group 2 (experimental):** 20mG IV metoclopramide + 25mG IV diphenhydramine
Outcomes	**Primary outcome:** HA relief within 2 hours =pain intensity was a 11-point numeric rating scale (0=no pain, 10=worst pain) **Other outcomes:** Pain relief at 2 hours**,** need for rescue meds, adverse events

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Used random-number table generated online to generate medication packages
Allocation concealment (selection bias)	Low risk	• central allocation by research pharmacist • drug containers of identical appearance
Blinding of participants and personnel (performance bias)	Low risk	Nurses/research assistants blinded to assignment
Blinding of outcome assessment (detection bias)	Low risk	Pain/akathisia scales used were the same between the two groups
Incomplete outcome data (attrition bias)	Low risk	For the included outcomes, all who were randomized were analyzed. For the outcomes Pain Relief at 2 hours and Requested Rescue Medication they reported on a per protocol basis The data was entered into RevMan on an intent to treat basis, and there continued to be no difference between the groups see Table XXX
Selective reporting (reporting bias)	Low risk	All study objectives have been included and accounted for
Other bias	Low risk	Study reported per protocol analysis for outcomes collected at 24 hours

Friedman 2011

Methods	randomized, double-blind, 3-armed clinical trial comparing 3 doses of metoclopramide
Participants	**Setting:** ED of Montefiore Medical Center, an urban ED

	Randomized into study: N=356 •Group 1- n=113 •Group 2- n=118 •Group 3- n=118 **Completed Study:** N=324 •Group 1- n=107 •Group 2- n=111 •Group 3- n=106 **Gender, % males:** unknown **Age, years (mean):** range 37-39 mean age across groups **Inclusion Criteria:** • Adults younger than 70 • acute exacerbation of a migraine without aura (as defined by the International Classification of Headache Disorders) • acute headache that met a migraine criteria, with the exception of prolonged duration (>72 hours) or insufficient duration (< 4 hours) were included **Exclusion Criteria:** • secondary headache (an organic headache) • if the patient was to receive a lumbar puncture in the ED • if they had a maximum documented temperature greater than 100.3 degrees F. • new objective neurologic abnormality • allergy or intolerance to study medication • previous enrollment • pregnancy • After randomization but before un-blinding, it was determined that some patients received off-protocol ketorolac at the same time as the investigational medication. We excluded these patients from all analyses. **Power Analysis:** we calculated the need for 100 subjects in each arm, for a total of 300 subjects. After adding to this a 10% rate for protocol violations, we planned to enroll 330 subjects (110 patients per arm).
Interventions	•Group 1:metoclopramide 10mG + 25mG diphenhydramamine infused via IV during 20 minutes •Group 2:metoclopramide 20mG + 25mG diphenhydramamine infused via IV during 20 minutes •Group 3:metoclopramide 40mG + 25mG diphenhydramamine infused via IV during 20 minutes o To prevent adverse effect of akathisia, 25mG of diphenhydramamine was prophylactically co-administered to all subjects. (Because diphenhydramine may have independent migraine activity, administering diphenhydramine to all subjects maintained the internal validity of this study).

Outcomes	**Primary Outcomes:** • Improvement in pain on an 11-point numeric rating scale at 1 hour. **Secondary Outcomes:** • sustained pain freedom at 2 hours and maintaining for 48 hours • patient request for rescue medication • dwell time in ED • adverse effects • desire to receive the same medication at next ED visit for a migraine

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The research pharmacist generated a randomization list in blocks of 6, using computer-generated random-number tables. This was done in a location removed from the ED and inaccessible to ED personnel.
Allocation concealment (selection bias)	Low risk	These research bags were then used in order by the research team. Only the pharmacist knew the assignment. The pharmacist inserted medication into identical vials and placed these vials into sequentially numbered identical research bags.
Blinding of participants and personnel (performance bias)	Low risk	Identical vials
Blinding of outcome assessment (detection bias)	Low risk	Patients were blinded outcome assessors
Incomplete outcome data (attrition bias)	Low risk	For power needed 110 per group and had 111, 106, 107 completed
Selective reporting (reporting bias)	Low risk	Reported on all they stated

Friedman 2014

Methods	Randomized, double-blind, comparative efficacy trial
Participants	**Setting:** ED of Montefiore Medical Center starting October 2011 and continuing for 30 months. **Randomized into study:** *N=330*

	• **Group 1:** Ketorolac 30mG IV n = 110 • **Group 2**: Valproate 1 gm IV n=110 • **Group 3:** Metoclopramide 10mG IV n=110 **Completed Study:** *N=320* • **Group 1:** Ketorolac 30mG n = 106 • **Group 2**: Valproate 1 gm n=107 • **Group 3:** Metoclopramide 10mG n=107 **Gender, males:** (16%) **Age, years (Range):** 25-44 **Inclusion Criteria:** • Adult patients who presented to ED with acute migraine or acute probable migraine headache (HA) **Exclusion Criteria:** • Secondary HA • Pt to receive lumbar puncture in the ED • Temperature of $\geq$ 100.4^{o}F • New objective neurologic abnormality • Seizure disorder • Concurrent use of any of the investigational medications • Pregnancy • Lactation • Previous enrollment • Allergy, intolerance, or other contraindication to any of the investigational medications, including hepatic dysfunction, peptic ulcer disease, or concurrent use of immunosuppressives or a monoamine oxidase inhibitor **Power Analysis:** 100 needed for each arm, for a total of 300. 10% sample size per arm added for anticipated attrition.
Interventions	• **Group 1:** Ketorolac 30mG IV • **Group 2**: Valproate 1 gm IV • **Group 3:** Metoclopramide 10mG IV * All interventional medications mixed in 50-mL of normal saline and administered parenterally over 15 minutes.
Outcomes	**Primary Outcome:** • Between-group difference in improvement of HA 1 hour after baseline, as determined by an assessment of pain on the verbal 0 to 10 scale. **Secondary Outcomes:**

	• Receipt of rescue medication at any time during the ED visit. • The patient's overall assessment of efficacy and tolerability, expressed as a dichotomous response to the question "Do you want to receive the same medication the next time you visit the ER with a migraine?" • Sustained headache freedom, defined as achieving a level of "none" on the severe, moderate, mild, and none scale within 2 hours of investigational medication administration and maintaining this level continuously for 24 hours without use of rescue medication. Other efficacy outcomes included the following: • Headache relief in the ED, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none without the use of rescue medication • Headache freedom in the ED, defined as achieving a headache level of "none" within 2 hours without use of rescue medication • Sustained headache relief, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none without use of rescue medication, and maintaining this level of relief continuously for 24 hours. **Safety outcomes:** • Presence of drowsiness at 1 hour after medication administration. • Restlessness following administration of medication.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Online random-number generator used for selection of intervention by the research pharmacist.
Allocation concealment (selection bias)	Low risk	The pharmacist then filled vials with medication and placed these vials into sequentially numbered research containers in the order determined by randomization
Blinding of participants and personnel (performance bias)	Low risk	"The contents of the vials were clear and indistinguishable" "Clinical nurse, also blinded to assignment, placed the contents of each research container into a 50-mL bag of normal saline for administration..."
Blinding of outcome assessment (detection bias)	Low risk	"The (PI), who remained blinded to randomization and allocation assignment, transcribed the data into SPSS version 19."
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcome data listed.

Selective reporting (reporting bias)	Low risk	Study outcomes are pre-specified and reported.

Jones 1996

Methods	Randomized, double-blind, placebo-controlled trial

Participants	**Setting**: Community teaching hospital in Grand Rapids, MI
	Randomized into study: N = 86
	• **Group 1:** Prochlorperazine = 28
	• **Group 2:** Metoclopramide n = 29
	• **Group 3:** Saline placebo n= 29
	Completed Study: *N = 86*
	• **Group 1:** n= 28
	• **Group 2:** n = 29
	• **Group 3:** = 29
	(2 subjects unaccounted for)
	Gender, males: 27% of study participants were male, 8 subjects in each group.
	Age, years (mean):
	• Overall mean age 32.1 $\pm$ 2.1 years
	Inclusion Criteria:
	• At least 16 years old
	• Normal ability to communicate
	• One or more of the following:
	  ○ Recurrent headaches preceded by neurological symptoms
	  ○ Recurrent throbbing headaches consistently associated with significant nausea or vomiting
	  ○ photophobia
	  ○ sonophobia
	  ○ mood changes
	Exclusion Criteria:
	• Age older than 60 years
	• Known intolerance to phenothiazines or metoclopramide
	• Use of other drugs likely to cause extrapyramidal behavior
	• Lack of responsible person available to care for and transport the patient when departing ED
	Power Analysis: Sample size determination to detect a difference in clinical improvement of 30% or better between therapies was 25 subjects per group.

Interventions	• **Group 1:** Prochlorperazine 2 ml IM (10 mG) • **Group 2:** Metoclopramide 2 ml IM (10 mG) • **Group 3:** Saline placebo 2ml IM
Outcomes	**Primary outcomes:** • Median post-treatment pain scores on a visual analog scale • Rescue analgesic therapy by 60 minutes post initial treatment **Safety outcome:** • Adverse effects
Notes	No data for adverse reactions for saline placebo comparisons

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computerized randomization
Allocation concealment (selection bias)	Low risk	Tinted syringes used to deliver medications
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	Subjects rated pain
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (2 enrolled in study were not reported)
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes have been reported
Other bias	Low risk	

Figures:

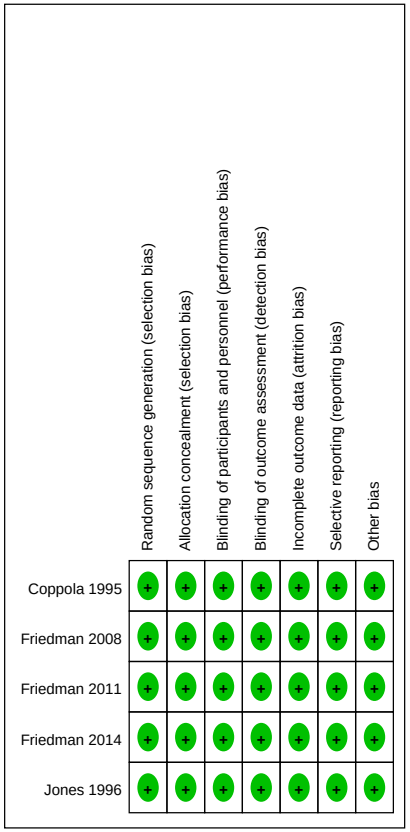


Figure 1. Risk of bias summary: Scholars' judgments about each risk of bias item for each included study

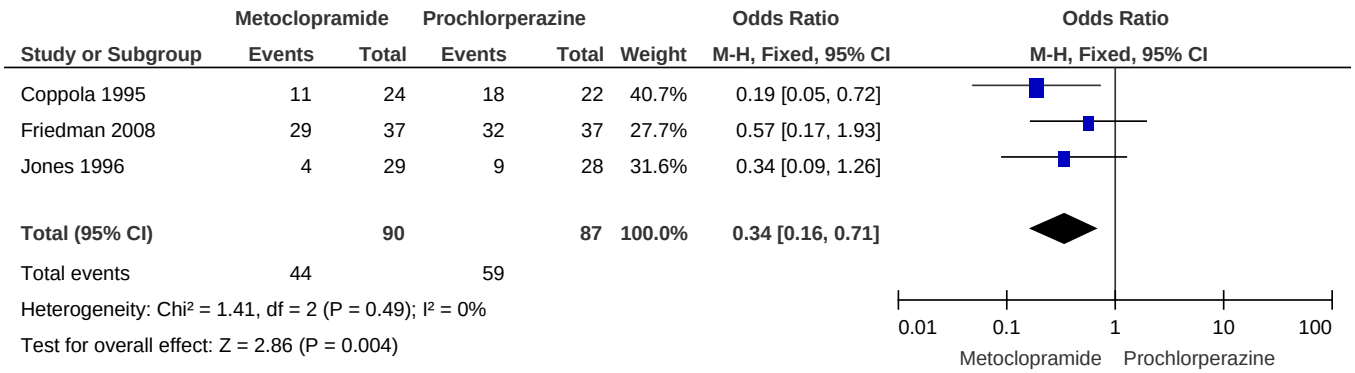


Figure 2. Comparison: Prochlorperazine vs. Metoclopramide, Outcome: Pain relief within two hours (Higher is better; metoclopramide had significantly less pain relief than prochlorperazine at two hours).

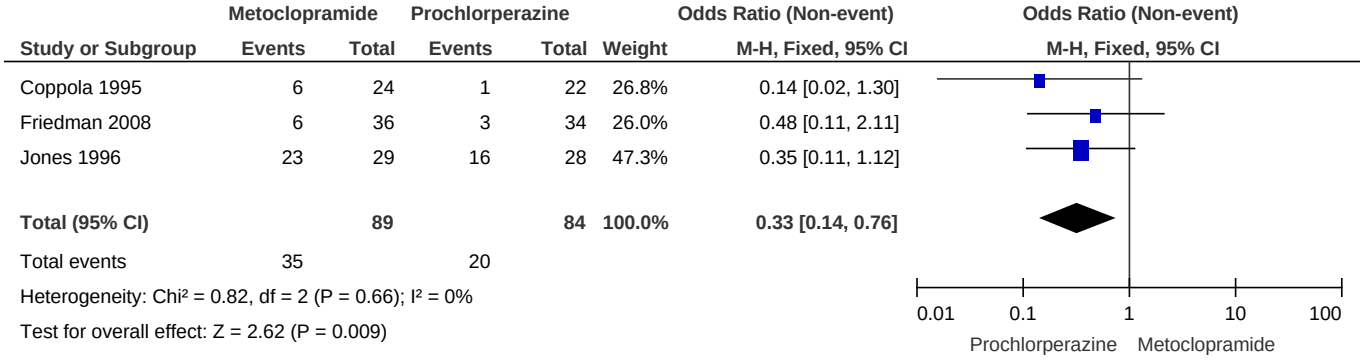


Figure 3. Comparison: Prochlorperazine versus Metoclopramide, Outcome: Use of rescue medication (Lower is better; there is significantly less use of rescue medication when treated with prochlorperazine.

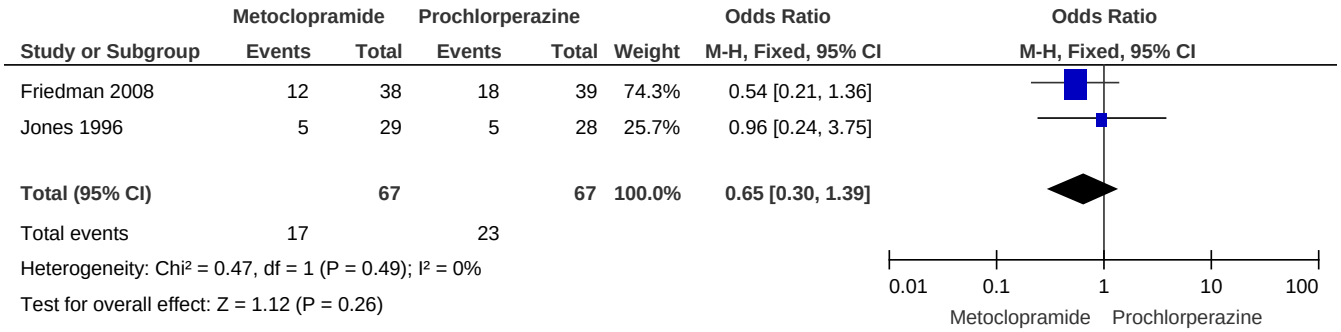
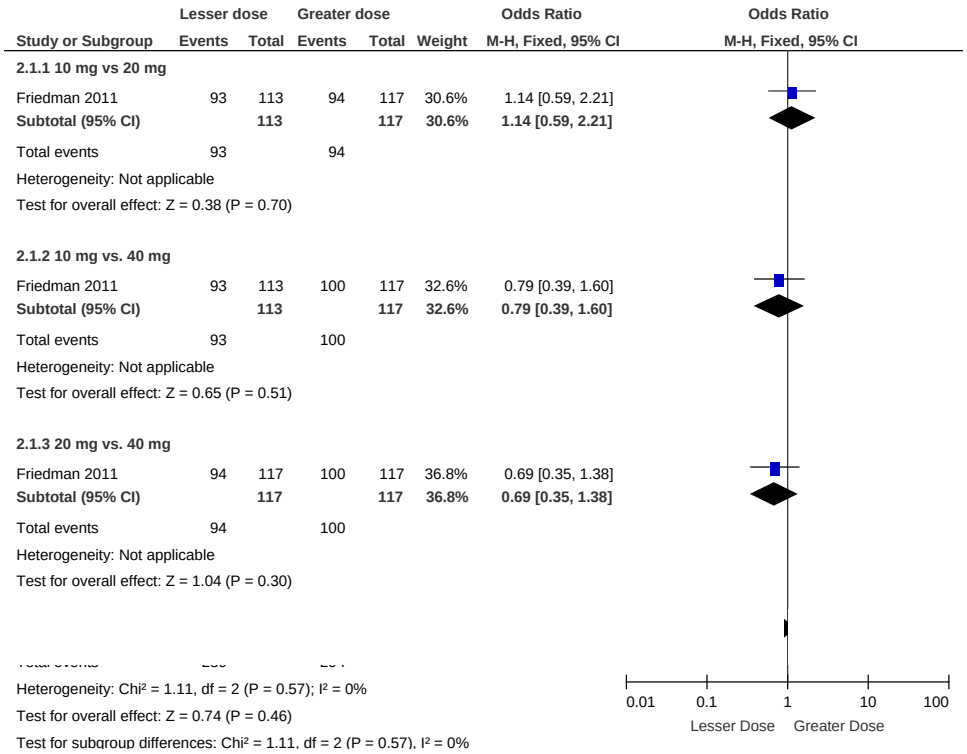


Figure 4. Comparison: Prochlorperazine vs. Metoclopramide, Outcome: Occurrence of adverse events (Lower is better; there is no significant difference in the number of reported adverse events).



Appendix I

Sumatriptan for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with refractory migraine is sumatriptan an effective treatment for refractory migraine in the ED?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Children's Mercy

Based on very low quality evidence, the Migraine in the ED CPG team makes a conditional recommendation that sumatriptan may be considered to treat a patient who presents with a refractory migraine. The AAN Practice Parameter (Lewis et al., 2004) states sumatriptan is effective for acute migraine. However, (Hamalainen, Hoppu, & Santavuori, 1997) reported no difference in pain at 2 hours between children treated with sumatriptan (PO) or placebo (N= 46) OR = 0.09, 95% CI [0.17, 0.34]. (Winner, Rothner, Wooten, Webster, & Ames, 2006) compared sumatriptan nasal spray at two doses to placebo. They report pain relief at two hours was significantly better at 2 hours with 20mG of sumatriptan (nasal spray).There is reporting and attrition bias in this report. Although they report ITT analysis, per protocol analysis was used in the report, and the denominator of included subjects varies. (McDonald et al., 2011) reported the results of a long term cohort study on use of sumatriptan (PO) on migraine. Ninety-one percent (7791/8517) migraines were treated with sumatriptan/naproxen alone and rescue medications were not needed. Forty-two percent of the migraines were pain free within two hours of administration, and rescue medications were not required. This study is indirect evidence to the question, as treatment was started at home, at first sign of a migraine, not in the ED. It is recommended that sumatriptan be taken when migraine symptoms are first noticed (Scholpp, Schellenberg, Moeckesch, & Banik, 2004). Patients who present to the ED for the management of their migraine pain have usually had a migraine for a longer time.

Dihydroergotamine should not be administered if sumatriptan has been taken within the past 24 hours. (Lexicomp Online, 2013)

EBP Scholar's responsible for analyzing the literature:
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Jarrod Dusin, MS, RD, LD, CNSC
EBP team member responsible for reviewing, synthesizing, and developing this literature:
Allen, Nancy, MS, MLS, RD, LD

Search Strategy and Results:
Studies included in this review:
Hamalainen 1997
McDonald 2011
Winner 2006
Studies <u>not</u> included in this review with rationale for exclusion:

Author	Reason for Exclusion
Ahonen 2004	Home treatment with sumatriptan spray
(Berenson et al., 2010)	Not acute treatment in an ED or UCC
(Bhattacharyya, Laha, & Gangopadhyay, 2012)	Did not randomize; this is a case series
(Boureau, Chazot, Emile, Bertin, & d'Allens, 1995)	Did not blind subjects or providers

(Burstein, Collins, & Jakubowski, 2004)	Not blinded, allocation was not concealed
(Derosier et al., 2012)	Adult subjects, study of the efficacy of butalbital containing products
(Dodick, Brandes, Elkind, Mathew, & Rodichok, 2005)	Adult subjects, and treatment to begin at home, not the ED
(Hewitt et al., 2013)	Home treatment with rizatriptan orally disintegrating tablet
(Ho et al., 2012)	Did not include sumatriptan
(Kelly, Ardagh, Curry, D'Antonio, & Zebic, 1997)	Adult subjects; poor randomization- by date of presentation; non-inferiority study of sumatriptan vs. chlorpromazine
(Lampl, Huber, Haas, Rittberger, & Diener, 2008)	Subjects were randomized after self selection by asking if they wanted to in re-evaluate their migraine attacks
(Linder et al., 2008)	Did not include sumatriptan
(Meredith, Wait, & Brewer, 2003)	Adult subjects, included in the ketorolac CAT
(Rahimdel, Mellat, Zeinali, Jafari, & Ayatollahi, 2014)	Adult subjects, included in the valproic acid CAT
(Rothner, Wasiewski, Winner, Lewis, & Stankowski, 2006)	Adult subjects, zolmitriptan study
	Adult subjects, answers the question abo
(Tfelt-Hansen, Bach, Daugaard, Tsiropoulos, & Riddersholm, 2006)	Adult subjects
(Winner et al., 2002)	Did not include sumatriptan
(Winner, Adelman, Aurora, Lener, & Ames, 2006)	Adult subjects

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) (Higgins & Green, 2011),

Tables:

Characteristics of included study:

Hamalainen 1997

Methods	Randomized placebo-controlled, double-blind, crossover

Participants	**Setting:** Helsinki, Finland in 3 Pediatric Hospitals between February 1994 and October 1995 **Randomized:**31 -crossover study- all received both medications-study does not give info for who got what first **Completed:** 23-crossover study- all received both medications-study does not give info for who got what first **Gender:** 48% male **Age:** Children age 8.3-16.4 years **Inclusion:** Children over 8 years who suffered at least two migraine attacks per month, Meeting IHS criteria, had not benefitted from previous meds **Exclusion:** Children with renal, hepatic, or cardiovascular disease, who needed other treatment for their headache, on any continuous daily oral drug therapy, prophylactic drug therapy for migraine **Power analysis:** 11 to 20 children were required for 80% power and 5% significant level
Interventions	50mG Sumatriptan tablet for body surface area of 0.75 to 1.5m² (corresponding to approx. 6 to 12 yrs of age), and 100mG Sumatriptan for a body surface area of 1.5m² or more (approximate age over 12 years) Each patient received two identical packages, both containing either one or two 50mG capsules of sumatriptan or placebo
Outcomes	**Primary outcome**: reduction of pain intensity by at least 50% after 2 hours, 100 pt VAS **Secondary:** Headache severity using visual analog scale (VAS) at time points before treatment, at 30 min, at 60 min, and continuing hourly for 5 hours, Parents report-nausea, mobility, and expressions of pain, grading of headache, and choosing which treatment worked best at end of study
Notes	Pain Intensity Difference- (PID) is an estimate of pain relief at each time point Summed Pain Intensity Difference (SPID) gives an estimate of overall pain relief during a time period

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	randomized, double-blind, placebo-controlled, crossover trial
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Investigators were blinded as well as participants.

Blinding of outcome assessment (detection bias)	Low risk	Treatment was recorded as a success or a failure before the blind was broken.
Incomplete outcome data (attrition bias)	High risk	8 of 31 did not complete the study, the study reports on the 23 completers (74% of those recruited), Reasons for non-participation may affect results, tablet too large to swallow, inappropriate recruiting- not enough headaches in the study period
Selective reporting (reporting bias)	Low risk	primary and secondary outcomes are reported
Other bias	Unclear risk	Although randomized, initial pain score was higher in the placebo group, and remained higher throughout the study.

McDonald 2011

Methods	Open-Label Cohort
Participants	**Setting:** This study was an open-label, uncontrolled, long-term (12 months), multi-center (70) study (USA) of adolescents, from July 2007 to August 2009. **Participants:** N = 656 subjects enrolled, N = 622 (95%) treated at least 1 migraine with sumatriptan/naproxen sodium. **Age (mean):** N = 14.7 (1.68) **Completed:** Of the 656 subjects in the enrolled population, 78% (511/656), 66% (435/656), 59% (390/656), and 55% (363/656) completed the study visits at 3, 6, 9, and 12 months respectively. **Gender:** Male = 255 (41%) Female = 367 (59%) Race: 85% White (Caucasian); 12% African American; 2% Native American; 1% Other **Inclusion Criteria:** Subjects were to be 12-17 years old and were to have had an average of 2-8 migraines per month meeting the International Classification of Headache Disorders (ICHD-II) which typically lasted 2 hours, if untreated, for >6 months. **Exclusion Criteria:** Uncontrolled hypertension; 3 cardiovascular or any cerebrovascular risk factors; contraindications or hypersensitivities to sumatriptan or naproxen; weighed <75 pounds (33.3 kg); history of epilepsy or structural brain lesions; use of methysergide or dihydroergotamine in the past 3 months; use of daily medications that were not stabilized (dose changes in the past 2 months) or had taken or were planning to take monoamime oxidase inhibitor, preparations containing St. John's Wort (Hypericum perforatum) within 2 weeks of screening through 2 weeks after last treatment; 15 headache days per month; retinal, basilar, or hemiplegic migraine, as well as secondary headaches; positive pregnancy test or the presence of substances on toxicology screen that could not be attributed to treatment of an underlying medical condition. In addition, female

	adolescents of childbearing potential were required to perform urine pregnancy tests at all study visits and every 6 weeks.
Interventions	All subjects were instructed to treat migraines with a single fixed-dose tablet of sumatriptan and naproxen sodium (sumatriptan 85 mG and naproxen sodium 500 mG) and beginning 2 hours post dose, they were allowed to rescue with a single dose of a naproxen containing product, over-the-counter pain reliever (not to exceed the daily recommended dose), or anti-emetics; repeat doses of sumatriptan/naproxen sodium were required to be separated by a 24-hour pain-free period.
Outcomes	Evaluate the long-term safety, tolerability, effectiveness, impact on quality of life, and medication satisfaction of sumatriptan/naproxen sodium in the acute treatment of migraine headache in adolescents.
Notes	**Baseline Symptoms and Pain Freedom Post Treatment:** • 602 subjects recorded data in the electronic diary, of which 591 provided post-baseline data. • On average, subjects treated 86% (8517) of their migraines with sumatriptan/naproxen sodium during the study. **Rescue Medication:** • Of the 8517 migraine attacks, 91% (7791) were not associated with rescue medication use. • Of the 8517 migraine attacks, 90% (7657) were not associated with rescue medication use or prohibited medication use. **2-hour pain Free:** • 42% (3596) of attacks were migraine pain-free within 2hours of administration of sumatriptan/naproxen sodium, without rescue or prohibited medication use. **Adverse Events:** • Of subjects who took at least 1 dose of sumatriptan/naproxen sodium, at least 1 adverse event was reported: of any severity (63%; 393/622); of moderate-to-severe intensity (42%; 264/622); potentially related to study drug (27%; 170/622); or that met criteria for serious (<1%; 4/622). • Within 3 days of taking sumatriptan/naproxen sodium, at least 1 adverse event was reported: of any severity (11%; 1116/9989); of moderate-to-severe intensity (5%; 492/9989); potentially related to study drug (9%; 906/9989); • The most commonly reported adverse events across both age groups (4%) were nausea (9%), upper respiratory tract infection (9%), nasopharyngitis (8%), sinusitis (6%), and dizziness (4%). Nausea (44/622; 7%) remained the most common adverse event deemed treatment-related by investigators, followed by dizziness (20/622; 3%), muscle tightness (18/622; 3%), and chest discomfort (16/622; 3%). • There were minor differences (<5%) between the age groups in the incidence of the most commonly reported adverse events.

Winner 2006

Methods	Randomized, placebo-controlled, double-blind, parallel-group, multi-center, single-attack, out-patient study
Participants	**Setting**: Multi-site: Palm Beach Headache Center, The Cleveland Clinic, Raleigh Neurology Associates, GlaxoSmithKline, Research Triangle Park, **Randomized:** Intent to treat=888 subjects • Per protocol=738 • Placebo=245 • Sumatriptan NS 5mG=255 • Sumatriptan NS 20mG=238 **Completed:** • Placebo- (ITT=244, PP=233) • Sumatriptan NS 5mG-(ITT=250,PP=239) • Sumatriptan 20mG-(IT=237, PP=222) **Gender:** Majority was female **Inclusion criteria**: 12 to 17yrs of age, history of migraine of at least 6 months, IHS criteria **Exclusion criteria:** Ischemic or vasospastic coronary artery disease, confirmed or suspected cardiovascular disease, Prinzmetal's angina, systemic lupus erythematosus, Kawasaki disease, homozygous sickle cell anemia, recurrent syncope, cardiac arrhythmias requiring medication, atherosclerotic disease (including ischemic bowel disease) uncontrolled hypertension for age, Raynaud's syndrome, or epilepsy or chronic daily headaches. **Power analysis:** 232 subjects per treatment group were needed to detect a statistically significant difference (with a power analysis of 0.90 at a significance level of 0.50)
Interventions	**Intervention 1:** Sumatriptan Nasal Spray 5mG -up to 2 doses prn N=239 **Intervention 2:** Sumatriptan Nasal Spray 20mG-up to 2 doses prn N=222 **Placebo Nasal Spray:** up to 2 doses prn N=233
Outcomes	1hour headache relief, sustained relief from 1 to 24 hours,
Notes	There is a discrepancy here between the Scholar's use of the terms Per Protocol and Intent to treat and my understanding. They dropped subjects from the study if they did not get a complete data set from them, and thereby reducing both the per protocol and the intent to treat numbers. I am reporting the full numbers in the table here which are not fully disclosed on Fig. 1 in the article.

Risk of bias table

Bias	Scholar's judgment	Support for judgment

Random sequence generation (selection bias)	Low risk	computer generated randomization sequence in blocks of 6
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	identical NS devices for all groups
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	

Figures:

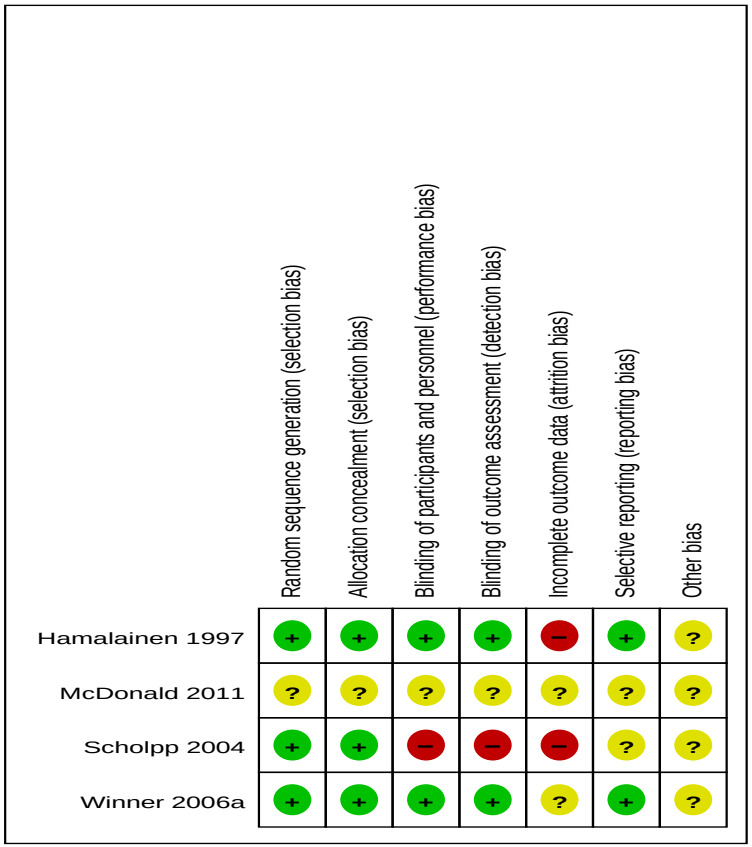

Figure 1. Risk of bias in included studies

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Figure 5. Comparison of Doses of Metoclopramide, Outcome: Pain relief within two hours (higher is better)