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.

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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**
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#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 **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	**0**
#22 **#7** AND **#21**	**1**
	4

#21
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4

#20
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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
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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
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1

#9
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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

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	Low risk	Volumes of medications were made similar, as was the process taken by the nurse who performed the infusion

personnel (performance bias)		
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 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	

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

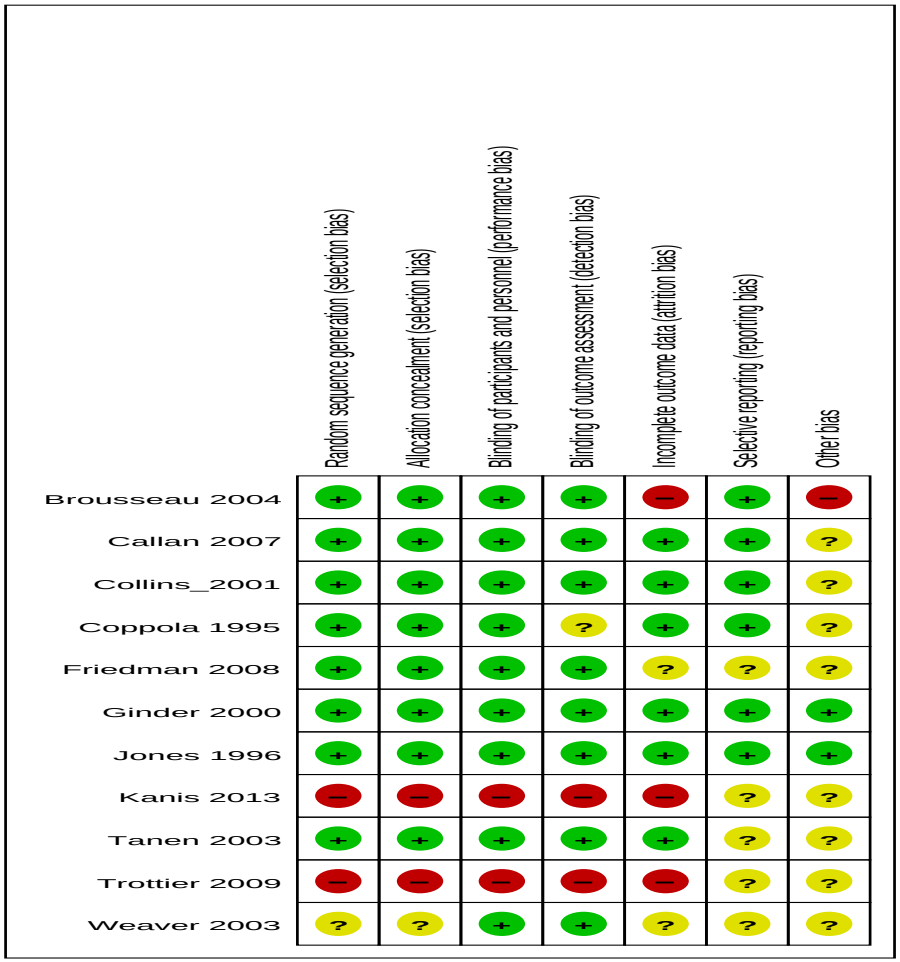


Figure 1. Risk of bias summary: Evidence Based Practice Scholars judgments about each risk of bias for each of the included studies.

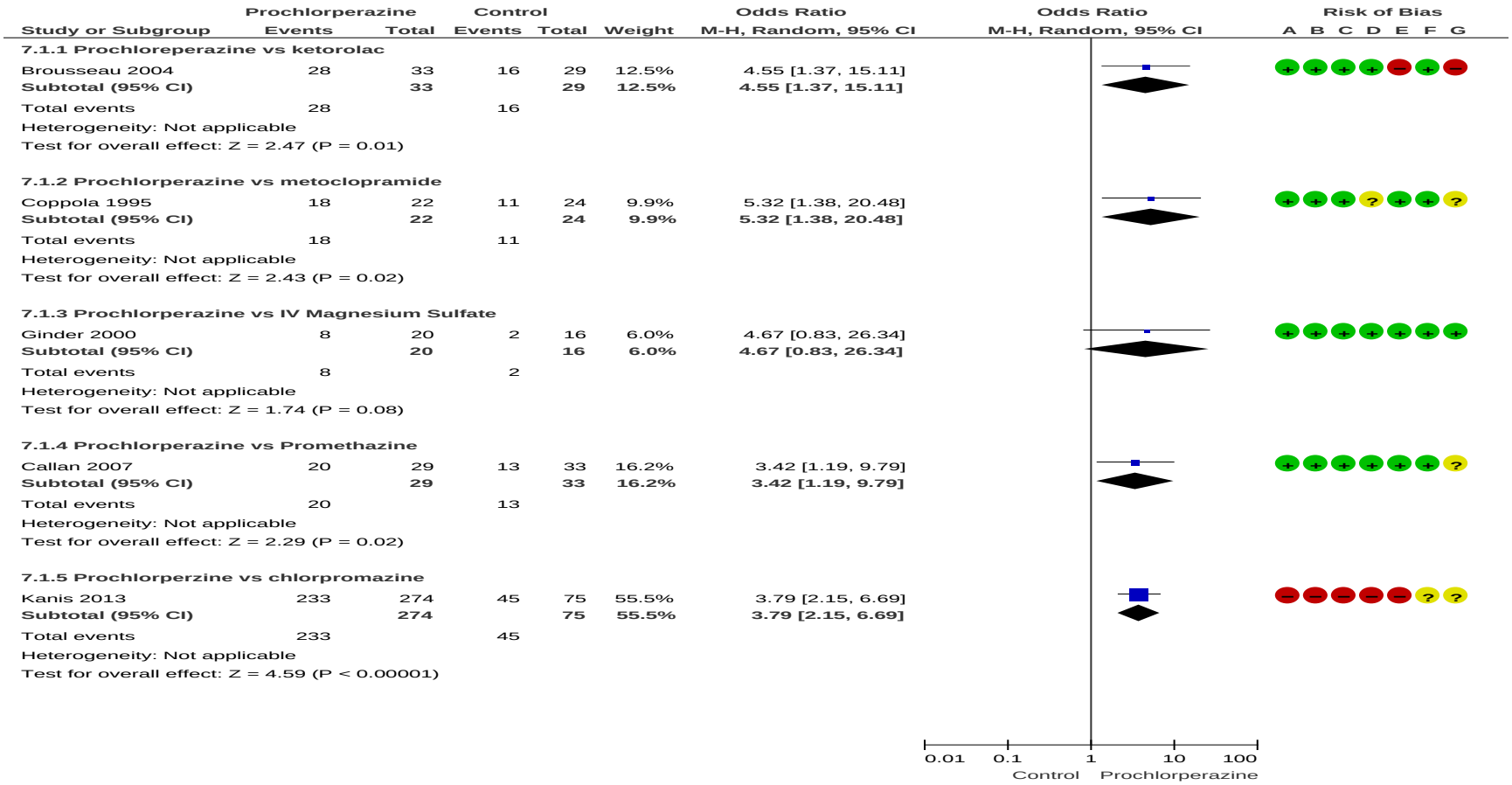
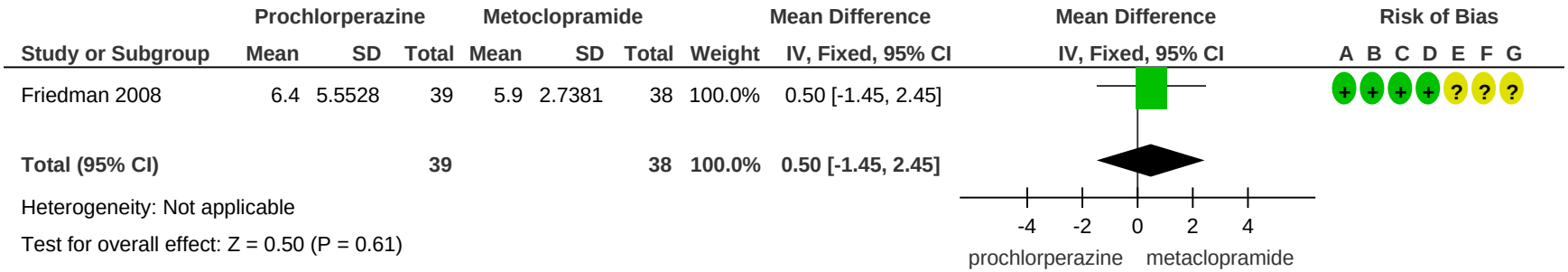


Figure 2. Comparison**:** Prochlorperazine vs. Other medications, Outcome: Treatment success 1 to 2 hours after treatment.



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

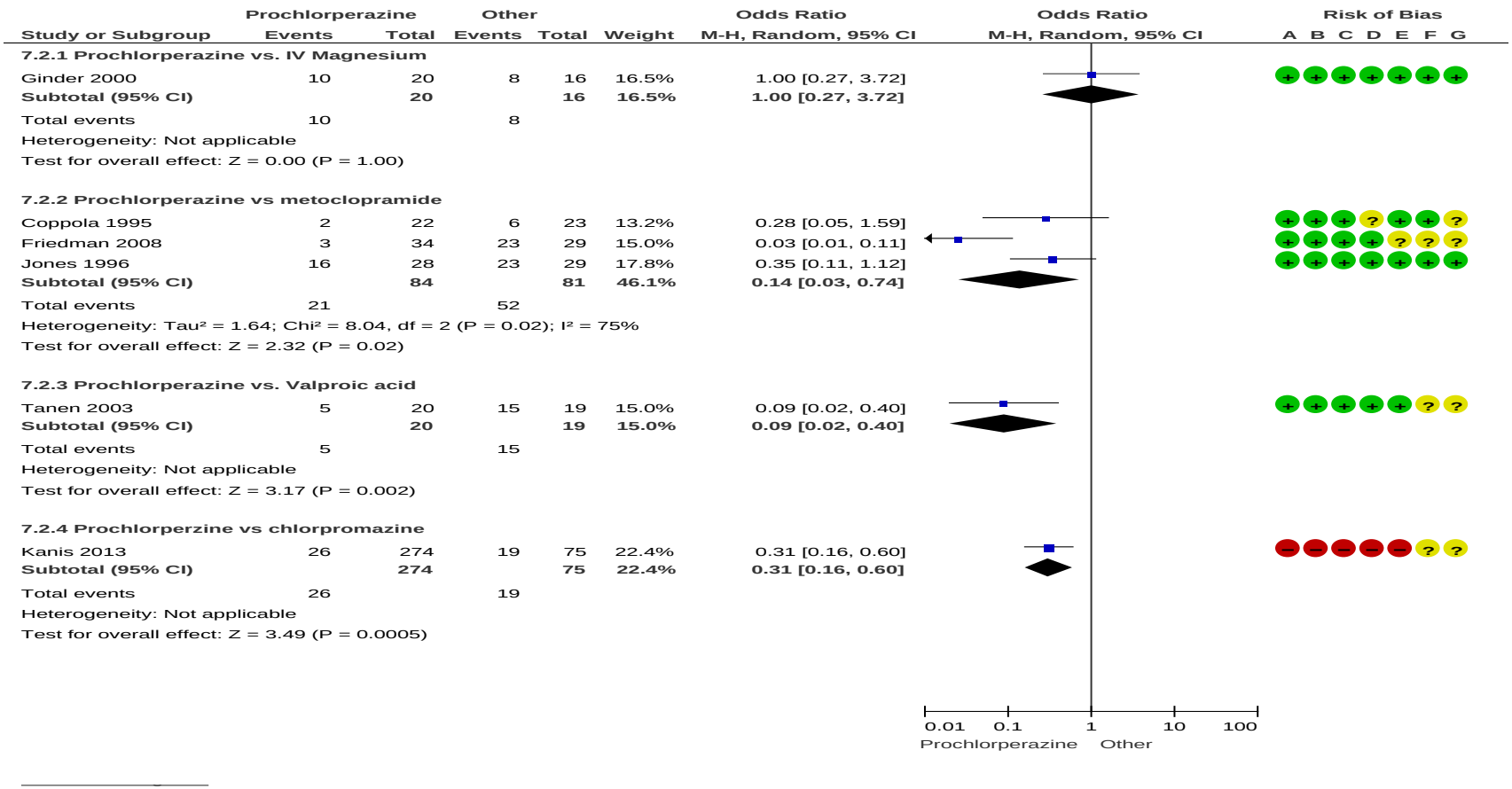


Figure 4. Comparison: Prochlorperazine vs. Other medications, Outcome: Required use of rescue medications

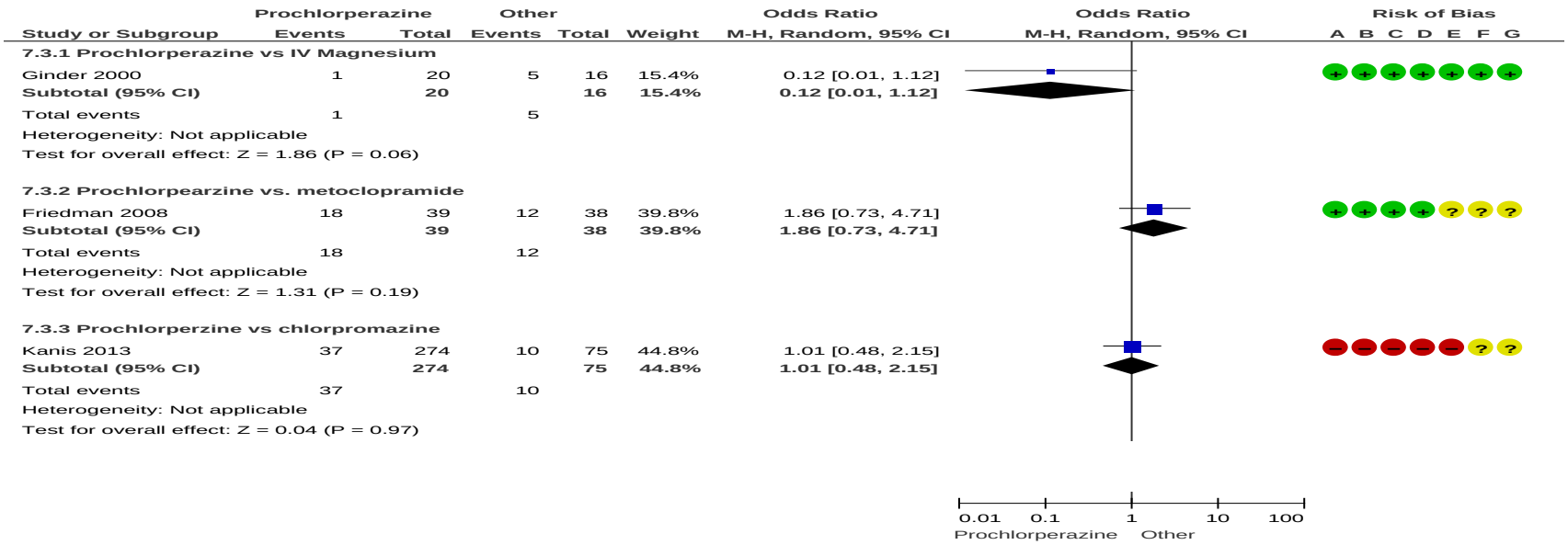


Figure 5. Comparison: Prochlorperazine vs. Other medications, Outcome: Lower Occurrence of Adverse Events