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.

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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**	**Indirect-ness**	**Impreci-sion**	**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:** 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 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 the subject 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 ○ 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 immuno-suppressives 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:

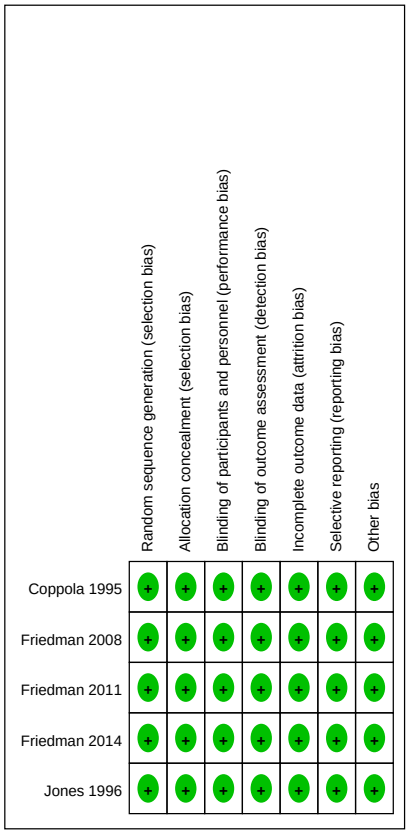


Figure 1. Risk of bias summary: Scholars' judgments about each risk of bias item for each included study

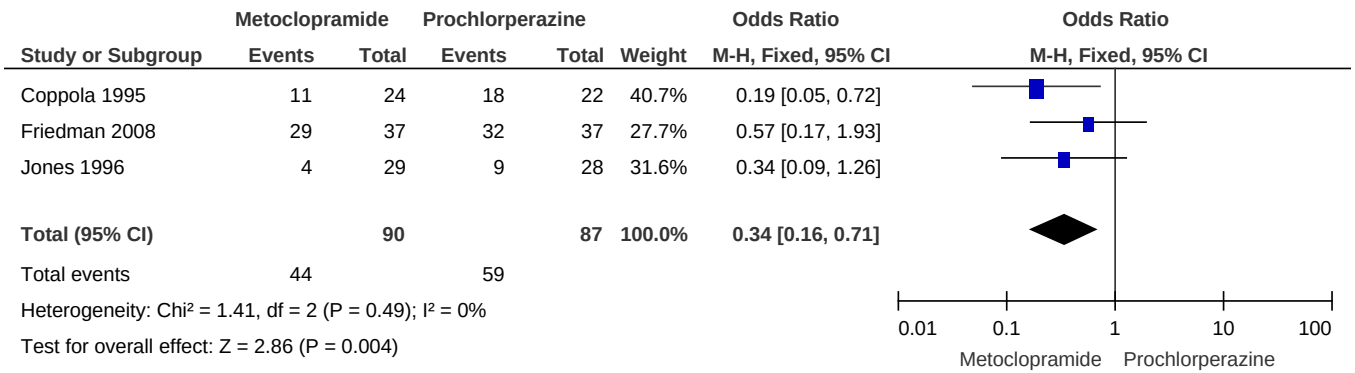


Figure 2. Comparison: Prochlorperazine vs. Metoclopramide, Outcome: Pain relief within two hours (Higher is better; metoclopramide had significantly less pain relief than prochlorperazine at two hours).

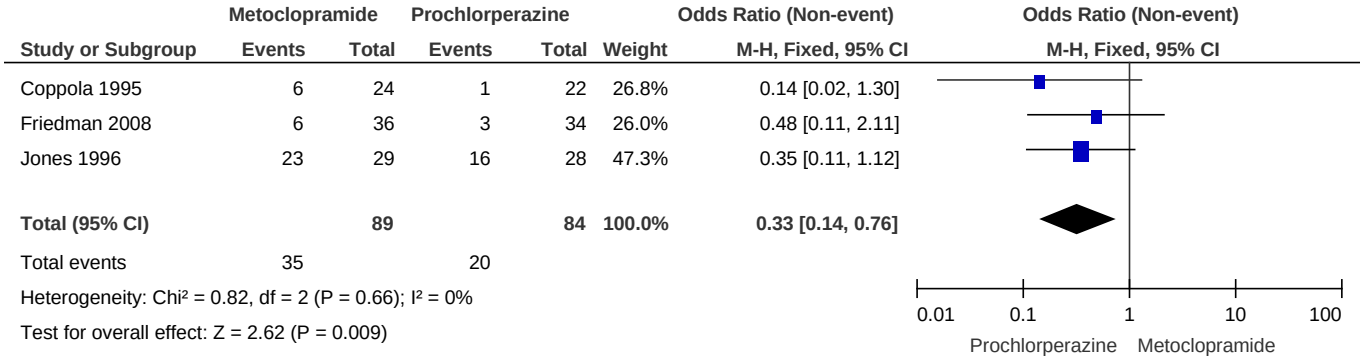


Figure 3. Comparison: Prochlorperazine versus Metoclopramide, Outcome: Use of rescue medication (Lower is better; there is significantly less use of rescue medication when treated with prochlorperazine.

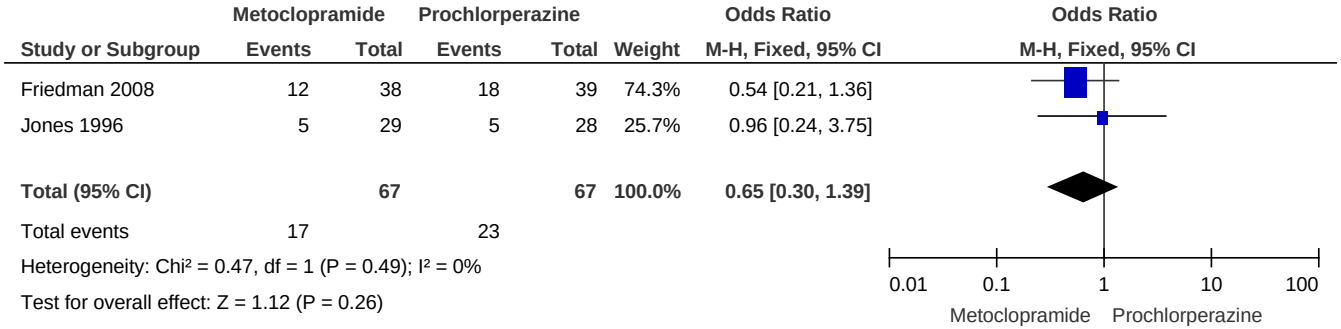
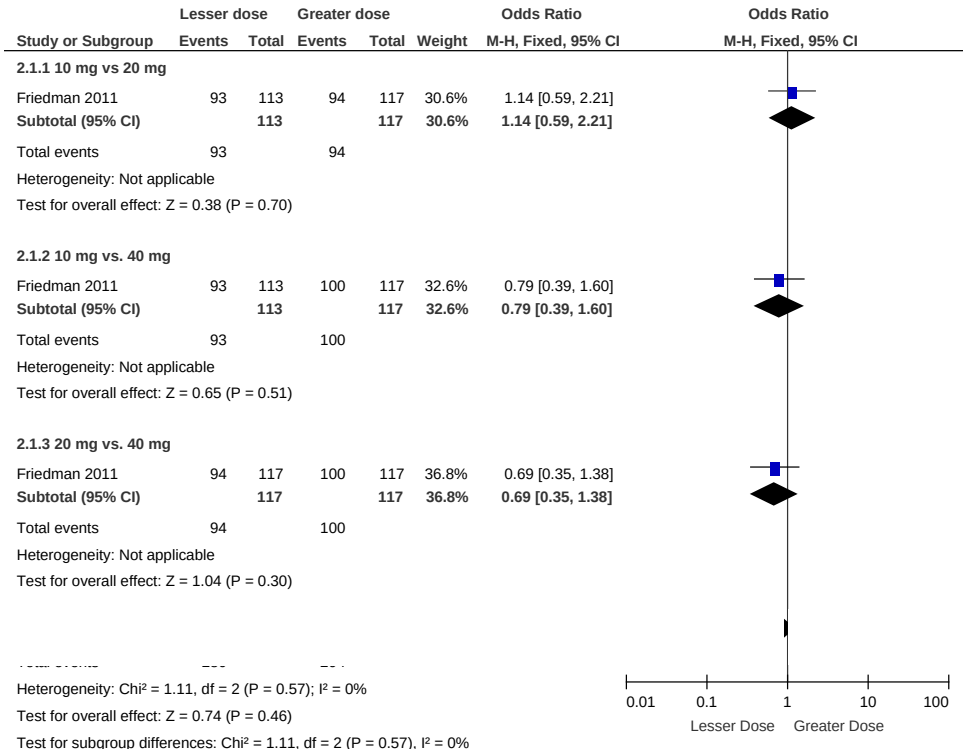


Figure 4. Comparison: Prochlorperazine vs. Metoclopramide, Outcome: Occurrence of adverse events (Lower is better; there is no significant difference in the number of reported adverse events).


Lesser dose
Greater dose
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.1.1 10 mg vs 20 mg
Friedman 2011 93 113 94 117 30.6% 1.14 [0.59, 2.21]
Subtotal (95% CI) 113 117 30.6% 1.14 [0.59, 2.21]
Total events 93 94
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
2.1.2 10 mg vs. 40 mg
Friedman 2011 93 113 100 117 32.6% 0.79 [0.39, 1.60]
Subtotal (95% CI) 113 117 32.6% 0.79 [0.39, 1.60]
Total events 93 100
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
2.1.3 20 mg vs. 40 mg
Friedman 2011 94 117 100 117 36.8% 0.69 [0.35, 1.38]
Subtotal (95% CI) 117 117 36.8% 0.69 [0.35, 1.38]
Total events 94 100
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Heterogeneity: Chi² = 1.11, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Chi² = 1.11, df = 2 (P = 0.57), I² = 0%
0.01
0.1
1
10
100
Lesser Dose
Greater Dose