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.

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).

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).

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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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 **#7** AND (**'controlled study'**/de OR **'major clinical study'**/de) AND (**'drug therapy'**:lnk OR **'prevention'**:lnk OR **'therapy'**:lnk) AND **'triptan derivative'**/de	**23**
#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**
	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
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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 • phonophobia
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 receive 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 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	

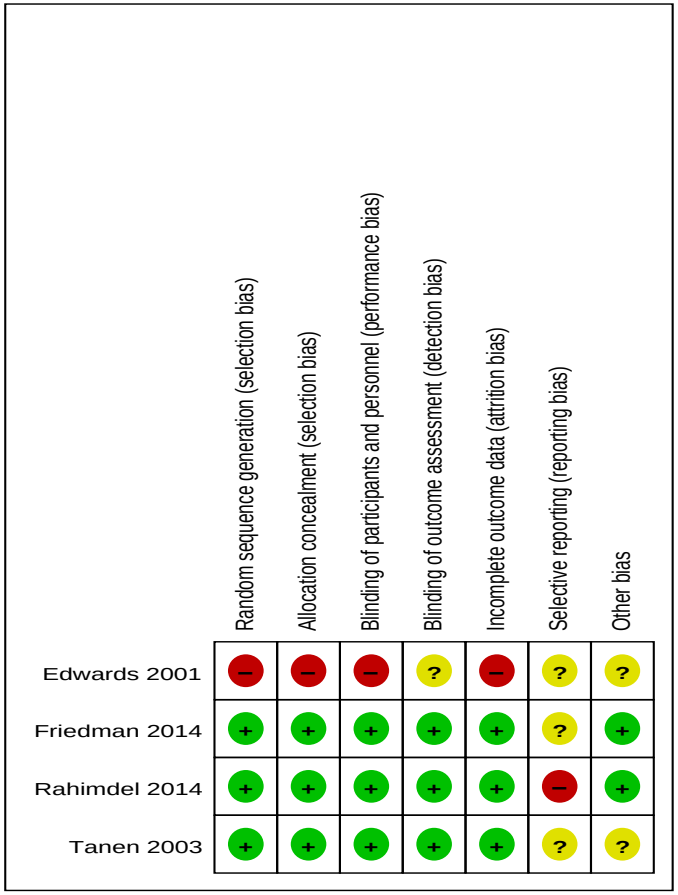

Figure 1. Risk of bias summary: Review of Scholar's judgment about each risk of bias item for each included study

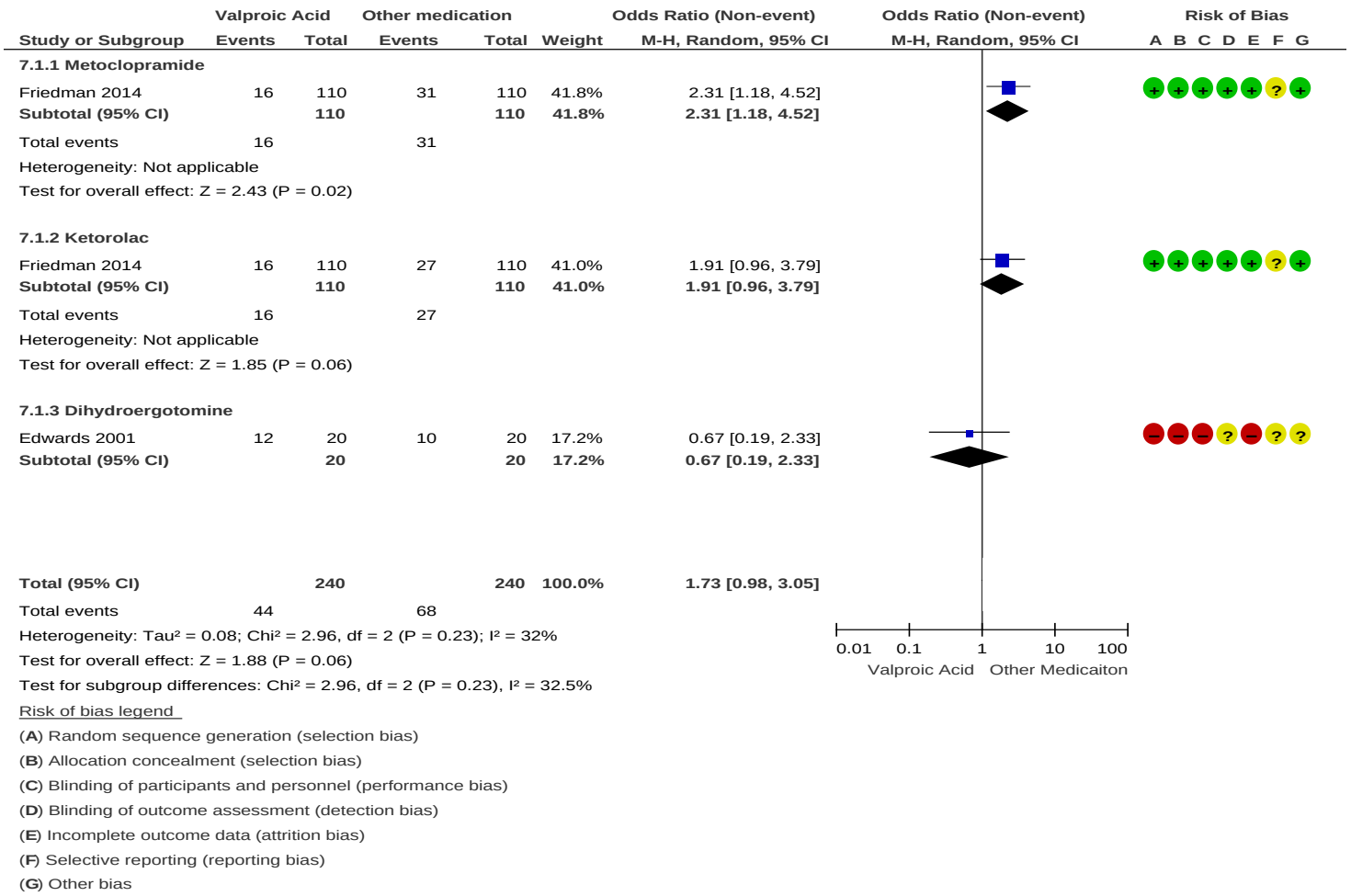

Figure 2. Comparison: Valproic Acid vs. Other medications Outcome: Pain Fee in Less Than 2 Hours

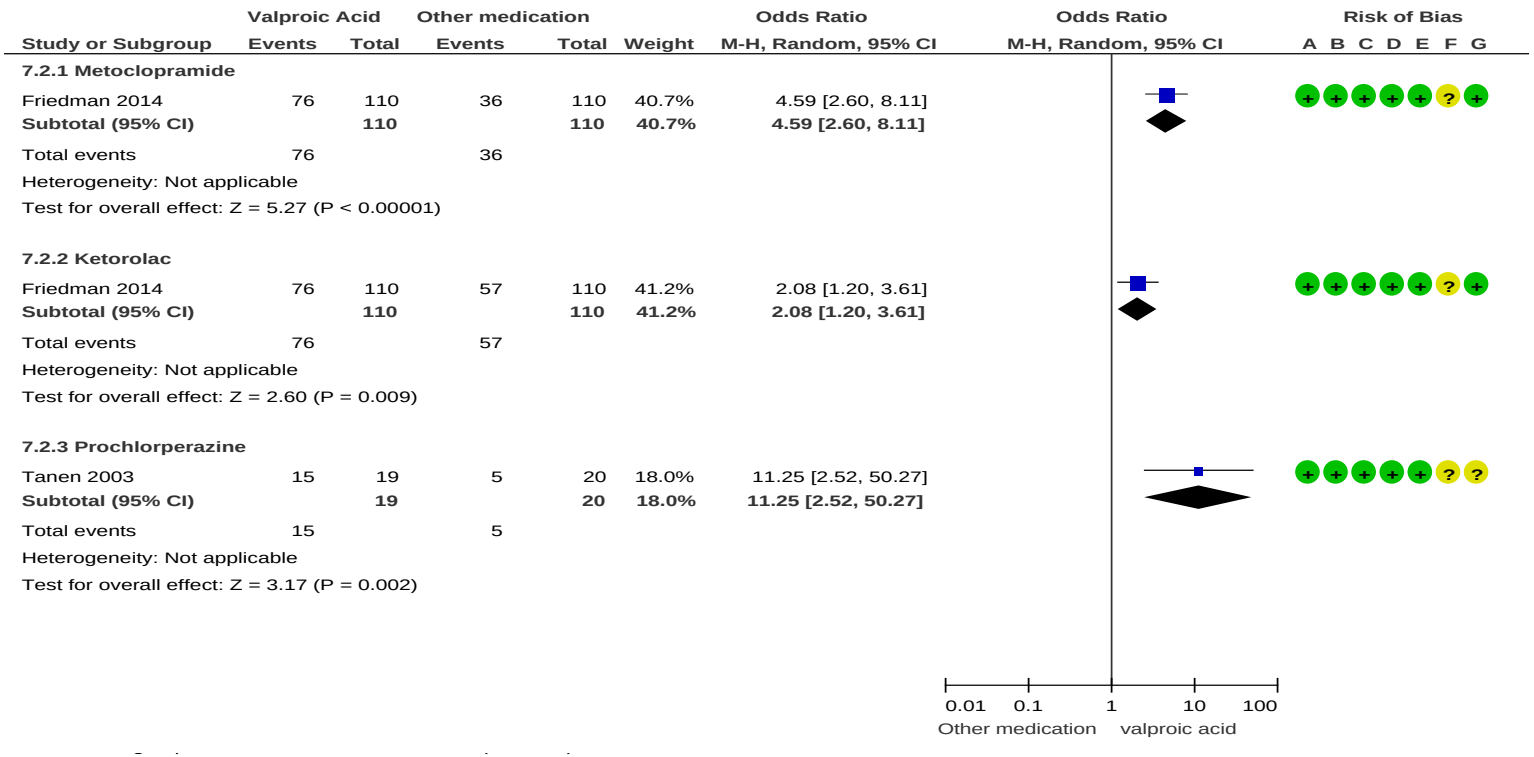

Figure 3. Comparison: Valproic Acid vs. Other Medications, Outcome: Use of Rescue Medications

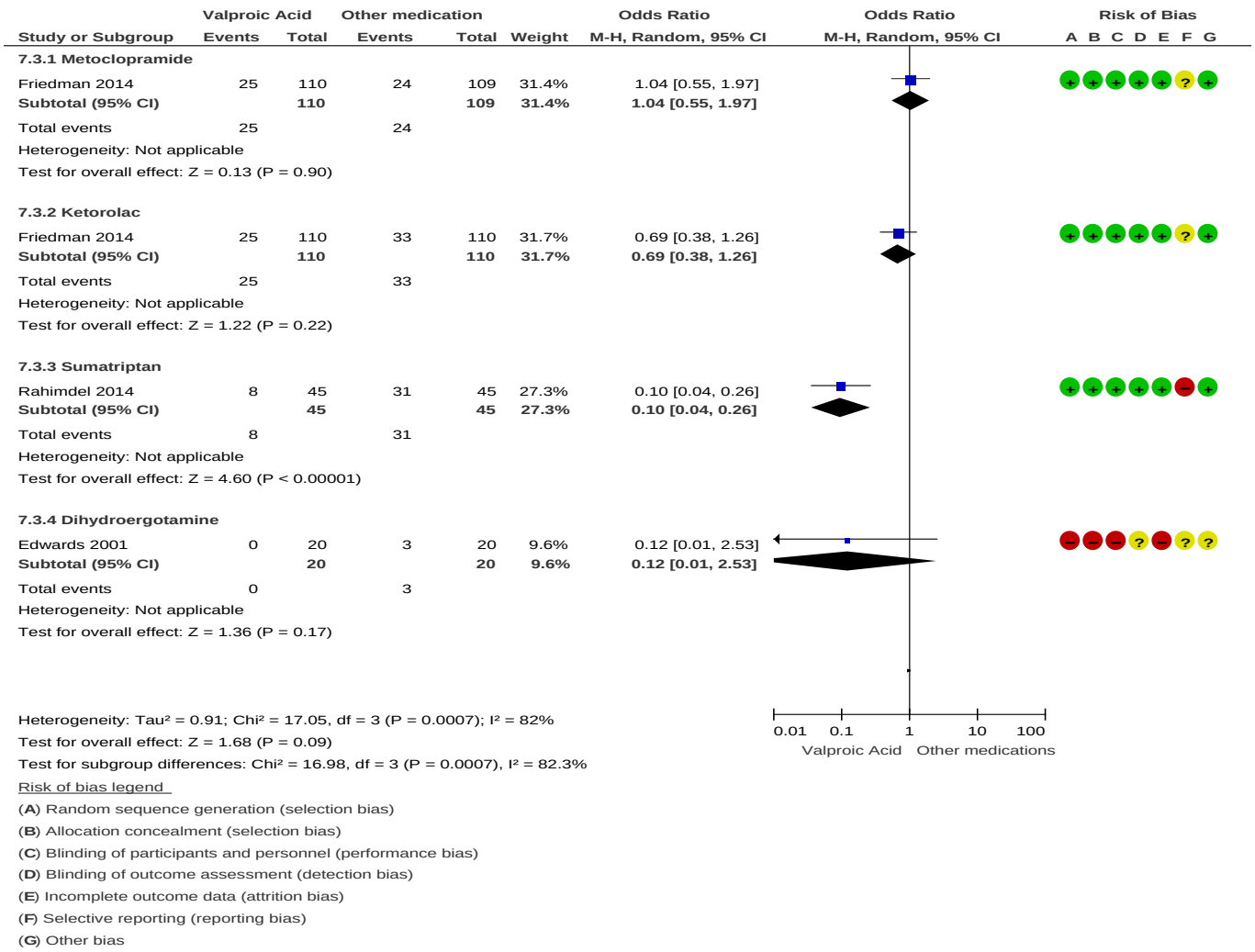

Figure 4. Valproic Acid vs. Other Medications, Outcome: Adverse Events References