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Research Submission

The Relative Efficacy of Phenothiazines for the Treatment of Acute Migraine: A Meta-Analysis

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Objective and Background.—Ranges of agents are used in the emergency departments to treat migraine headache. Some experts suggest that phenothiazines are among the most effective; clinical trials have been small with varied results. We performed a systematic review and meta-analysis to determine the relative effectiveness of phenothiazines compared with placebo and other active agents for the treatment of acute migraine.

Methods.—We searched MEDLINE, EMBASE, CINAHL, Cochrane database, and international clinical trial registers for randomized controlled trials comparing parenteral phenothiazines with placebo or another active parenteral agent for treatment of acute migraine in adults. The primary outcome was relief of headache, and secondary outcome was clinical success. Analysis was for phenothiazines vs placebo, pooled other active agents, and metoclopramide for each outcome. Odds ratios (ORs) were calculated and pooled by using a random effects model (RevMan v5).

Results.—Thirteen trials were appropriate and had available data. Phenothiazines were compared with placebo in 5 trials and to another active agent in 10 (metoclopramide 4). Phenothiazine was more effective than placebo for headache relief (OR 15.02, 95% confidence interval [CI] 7.57-29.82) and clinical success (OR 8.92, 95% CI 4.08-19.51). Phenothiazines were more effective than other agents combined (OR 2.04, 95% CI 1.25-3.31) and the metoclopramide subgroup (OR 2.25, 95% CI 1.29-3.92) for clinical success, but no differences were found for headache relief. The clinical success rate of phenothiazines was 78% (95% CI 74-82).

Conclusion.—Phenothiazines are more effective than placebo for the treatment of migraine headache and have higher rates of clinical success than other agents against which they have been compared.

Key words: migraine, pharmacotherapy, phenothiazine

Abbreviations: CI confidence interval, ED emergency department, N number, OR odds ratio, NICS National Institute of Clinical Studies Australia

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Migraine is a common condition. Most migraine headaches are managed by the patient and/or community family doctor; however, a small proportion fails to improve and seeks treatment at emergency departments (ED). In Australia there is considerable variation in ED treatment of migraine. A recent study found that the most commonly used agents in the ED were metoclopramide (alone or in combination) 43%, phenothiazines 36%, and paracetamol (alone or in combination) 38%, with aspirin used in 21% of cases and parenteral opiates in 12% (NCIS, unpublished data). Parenteral opioids are the most commonly used agents in US and Canadian ED.[1,2]

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Conflict of Interest: None

The National Institute for Clinical Studies (NICS) has published evidence-based guidelines for the treatment of migraine in Australia.[3] They recommend parenteral phenothiazines (chlorpromazine, prochlorperazine) or sumatriptan for patients with moderate to severe symptoms. It also strongly discourages use of opiates, in particular pethidine (meperidine). Despite this recommendation, uptake of phenothiazines as first line treatment has been only moderate (NICS, unpublished data). A possible explanation is that physicians are not convinced of their efficacy. Clinical trials of phenothiazines to date have been small, and some have had conflicting results. We performed a systematic review and meta-analysis to determine the relative efficacy of phenothiazines compared with placebo and other active agents for the treatment of acute migraine.

METHODS

Study Design.—We undertook a systematic review and meta-analysis to determine the efficacy of parenteral phenothiazines compared with placebo and to other parenterally administered active agents for the treatment of acute migraine.

We searched MEDLINE, EMBASE, CINAHL, the Cochrane database, and international clinical trial registers for randomized controlled trials comparing parenteral phenothiazines with placebo or another active parenteral agent for the treatment of acute migraine in adults from earliest indexing until December 31, 2008. We used the terms "migraine" or "headache" and "phenothiazine" or "chlorpromazine" or "prochlorperazine" and limited to outputs to therapeutics and clinical trials. In addition, we searched for similar systematic reviews and meta-analyses and used the PubMed "related articles" feature for all identified trials. Where studies were recorded as "completed" on clinical trials registers but not yet published, we attempted to contact the chief investigators to obtain data.

Studies were selected for inclusion if they were randomized controlled trials of a parenterally administered phenothiazine (chlorpromazine, prochlorperazine, and methotrimeprazine) vs either placebo or an active parenterally administered comparator for the treatment of acute migraine. Studies were considered to have studied acute migraine if they used the defining criteria established by the International Classification of Headache Disorders[4] or if a reasonable attempt had been made to include migraine headaches rather than all benign headaches. Use of the term "physician diagnosed migraine" or uses of defined criteria attempting to accurately identify migraine were considered reasonable attempts to discriminate migraine headache from benign headache. Studies were only included if they presented data on headache intensity/ clinical outcome within 2 hours of treatment and were published as a peer-reviewed short report or original research paper. Data presented only in abstract form were excluded.

Data Collection and Processing.—One author (A.-M.K.) screened all abstracts identified by the search for potential eligibility. If eligibility was possible, the article was requested and submitted to 2 other authors for review (T.W., B.G.). Primary data abstraction was performed by 2 of the study authors (T.W., B.G.). Disagreements were resolved by consensus when possible or by review of a third author (A.-M.K.).

Outcome Measures.—The primary outcome was relief of headache. Secondary outcome was clinical success as defined by the authors of each study. If clinical success was not reported, we included use of rescue medication as a proxy. A substudy of phenothiazines vs metoclopramide was also performed given the popularity of this agent as a treatment in recent studies (NICS, unpublished data).

The Jadad score was calculated for each study.[5] Two reviewers (T.W., B.G.) independently recorded the Jadad score. Disagreements were resolved by consensus.

Primary Data Analysis.—In the primary analysis, we calculated the odds ratio (OR) and 95% confidence intervals (CIs) for headache relief in the phenothiazine group vs the comparator or placebo for each included study. We chose to take the more conservative approach of pooling studies with a random-effects analysis. We performed all analyses using RevMan version 5 (The Cochrane Collaboration, Copenhagen, Denmark).

Table 1.—Characteristics of Included Trials with Placebo as Comparator

Author, year	Headache type	Phenothiazine, dose, route	Coadministered agents	*N*	Jadad score
Bigal et al 2002[6]	IHS criteria	Chlorpromazine, 0.1 mg/kg, i.v.	Nil	128	4
Coppola et al 1995[7]	IHS criteria	Prochlorperazine, 10 mg, i.v.	Nil	46	5
Jones et al 1989[8]	Physician-diagnosed	Prochlorperazine, 10 mg, i.v.	Nil	82	5
Jones et al 1996[9]	IHS criteria	Prochlorperazine, 10 mg, i.m.	Nil	58	5
McEwen et al 1987[10]	IHS criteria and physician-diagnosed	Chlorpromazine, 0.04 mg/kg, i.m.	Nil	36	3

IHS, International Headache Society; i.m., intramuscular; i.v., intravenous.

RESULTS

From 236 citations, 19 clinical trials were identified, of which 13 were appropriate and had available data.[6-18] Characteristics of the included trials are shown in Tables 1 and 2. Characteristics of excluded studies are shown in Table 3. Phenothiazines were compared with placebo in 5 trials and to another active agent in 10 (metoclopramide 4, meperidine 2, ketorolac 2, valproate/sumitriptan 1 each).

Regarding comparison with placebo, 4 studies reported outcomes for complete headache relief and 5 for clinical success. Phenothiazines were clearly superior to placebo with OR for complete relief of 15.02 (95% CI 7.57-29.82, Table 4) and for clinical success of 8.92 (95% CI 4.08-19.51, Table 5).

Regarding comparison with an active agent, 5 studies reported outcomes for complete headache relief and 10 for clinical success. Phenothiazines were more effective than other agents for clinical success (OR 2.04, 95% CI 1.25-3.31, Table 6), but no difference was evident for complete relief (OR 1.39, 95% CI 0.85-2.29, Table 7).

Pooling all studies, the proportion of patients reporting complete relief of headache with phenothiazines was 48% (95% CI 43-54), and the proportion reporting clinical success was 78% (95% CI 74-82).

When compared with metoclopramide, 3 studies reported the outcome of complete headache relief and 4 reported clinical success. Phenothiazines had greater rates of clinical success (OR 2.25, 95% CI 1.29-3.92, Table 8), but proportions with complete relief were similar (OR 1.60, 95% CI 0.89-2.87, Table 9).

DISCUSSION

Wide variation in the agents used in the ED to treat acute migraine has been reported (NICS, unpublished data;[1,2]). Although several guidelines for the treatment of headache have been published, few give specific recommendations for treatment of migraine, particularly in the ED setting. Reasons given include lack of robust evidence. In 2006, the National Institute of Clinical Studies (Australia) published guidelines for the treatment of migraine[3] with phenothiazines cited as one of the recommended treatments for moderate or severe symptoms in the ED setting. Despite these recommendations, the use of phenothiazines for this migraine has been suboptimal, only being used 36% of the time in a recent study (NICS, unpublished data). A possible reason for this is that physicians are unconvinced about the effectiveness of phenothiazines. This meta-analysis found that phenothiazines are clearly superior to placebo for both the outcomes of complete headache relief and clinical success. We also found that, when compared with other active agents, phenothiazines had greater rates of clinical success. This was also true for comparison with the metoclopramide subgroup, although no difference in the likelihood of complete headache relief was found for either the pooled active agent group or the metoclopramide subgroup. One explanation for this is small sample size with only 298 patients studied for the pooled active agent comparison (146 active vs 152 phenothiazines) and 225 for the metoclopramide comparison (111 vs 114). Given the proportion with complete relief from phenothiazines

Table 2.—Characteristics of Included Trials with Active Agent as Comparator

Author, year	Headache type	Phenothiazine, dose, route	Coadministered agents	Active comparator, dose	Coadministered agents	*N*	Jadad score
Cameron et al 1995[11]	IHS criteria/physician-diagnosed	Chlorpromazine, 0.1 mg/kg, i.v., up to 3 doses	Nil	Metoclopramide, 0.1 mg/kg, i.v., up to 3 doses	Nil	91	5
Coppola et al 1995[7]	IHS criteria	Prochlorperazine, 10 mg, i.v.	Nil	Metoclopramide, 10 mg, i.v.	Nil	46	5
Friedman et al 2008[12]	IHS criteria	Prochlorperazine, 10 mg, i.v.	Diphenhydramine, 20 mg	Metoclopramide, 20 mg, i.v.	Diphenhydramine	77	5
Jones et al 1996[9]	IHS criteria	Prochlorperazine, 10 mg, i.m.	Nil	Metoclopramide, 10 mg, i.m.	Nil	57	5
Kelly et al 1997[13]	Physician-diagnosed	Chlorpromazine, 12.5 mg, i.v., up to 3 doses	Metoclopramide, 10 mg	Sumatriptan, 6 mg, i.m.	Metoclopramide,	43	1
Lane et al 1989[14]	Physician-diagnosed	Chlorpromazine, 0.1 mg/kg, i.v., up to 3 doses	Nil	Meperidine, 0.4 mk/kg up to 3 doses, i.v.	Dimenhydrinate	46	4
Seim et al 1998[15]	Physician-diagnosed	Prochlorperazine, 10 mg, i.v.	Nil	Ketorolac, 30 mg, i.v.	Nil	64	4
Shrestha et al 1996[16]	IHS criteria	Chlorpromazine, 25 mg, i.v.	Nil	Ketorolac, 60 mg, i.m.	Nil	30	5
Stiell et al 1991[17]	Defined criteria	Methotrimeprazine, 37.5 mg, i.m.	Nil	Meperidine, 75 mg, i.m.	Dimenhydrinate	74	5
Tanen et al 2003[18]	IHS criteria	Prochlorperazine, 10 mg, i.v.	Nil	Na valproate, 500 mg, i.v.	Nil	39	5

IHS, International Headache Society; i.m., intramuscular; i.v., intravenous.

found in this study of 48%, it would take approximately 800 patients to show a 10% difference in effectiveness between agents for this outcome.

Our findings support the recommendation of phenothiazines as effective agents for treatment of migraine in the ED. That said, only one of the studies of phenothiazine vs active agent reported a statistically significant difference. That study compared prochlorperazine with sodium valproate and reported an OR for clinical success of 11.25 (95% CI 2.52-50.27) favoring prochlorperazine.[18] Although 7 of the remaining 9 studies that reported clinical success have ORs favoring phenothiazines, 95% CIs include results favoring both the phenothiazine and the other active agent, potentially because of small sample sizes. When the valproate study is excluded from the analysis, the results still favor phenothiazine over the other active agents (OR 1.73, 95% CI 1.13-2.65), suggesting that the finding of phenothiazines' superiority is robust.

Two phenothiazines were commonly used in the included studies: prochlorperazine and chlorpromazine 6 studies each (Tables 1 and 2). These agents have not been compared head-to-head. Pooled clinical success rates from the data used in this study are 81% for chlorpromazine (95% CI 75-86%) and 77% for prochlorperazine (95% CI 71-83%). These proportions are not statistically different ($P = .42$, chi-square).

We chose to study agents principally considered to be phenothiazines and did not include drugs with other principal actions and some phenothiazine-like additional effect such as promethazine, which we considered to be principally an antihistamine. This decision is open to question. There are no published studies of promethazine as a sole agent for the treatment of migraine headaches, so inclusion of promethazine would not change our findings. There is, however, a recent randomized trial compared prochlorperazine with promethazine for treatment of the broader benign headache group treated in ED.[19] That study found that prochlorperazine resulted in a higher proportion of patients with a >25 mm reduction in visual analog scale pain score at 30 minutes (69% vs 39%, $P = .006$) and a greater rate of reduction in pain score ($P = .013$). Promethazine resulted in

Table 3.—Characteristics of Excluded Studies

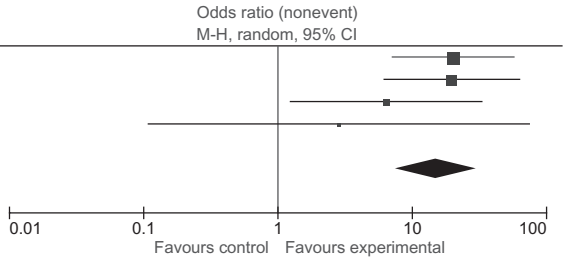
Author, year	Phenothiazine, dose, route	Comparator	*N*	Results	Reason for exclusion
Ginder et al 2000[20]	Prochlorperazine, 10 mg, i.v.	Magnesium, 2 g, i.v.	36	At 30 minutes, complete relief in 8/20 in prochlorperazine group compared with 2/16 in magnesium group	All acute headaches; not migraine
Bigal et al 2002[21]	Chlorpromazine, 0.1 mg/kg, i.v.	Placebo	60	At 60 minutes, 21/30 in chlorpromazine group were pain-free compared with 6/30 in placebo group	Tension-type headache; not migraine
Weaver et al 2004[22]	Prochlorperazine, 10 mg, i.v.	Droperidol, 2.5 mg, i.v.	96	At 30 minutes, 18/47 in prochlorperazine group had complete relief compared with 26/48 in droperidol group. 34/47 in prochlorperazine group had >50% reduction in VAS compared with 40/48 in droperidol group	All acute headaches; not migraine
Miner et al 2001[23]	Prochlorperazine, 10 mg, i.v. or i.m.	Droperidol, 5 mg, i.m. or 2.5 mg, i.v.	168	At 60 minutes, 59/86 in prochlorperazine group had >50% reduction in VAS compared with 74/82 in droperidol group	Benign headache; not migraine
Bell et al 1990[24]	Chlorpromazine, 12.5 mg, i.v., up to 3 doses	DHE, 1 mg, i.v., up to 2 doses; or lidocaine, 50 mg, i.v., up to 3 doses	76	8/24 in chlorpromazine group had complete relief compared with 6/26 for DHE and 2/26 for lidocaine	Time frame of pain outcome not specified
Callan et al 2008[19]	Prochlorperazine, 10 mg, i.v.	Promethazine, 25 mg, i.v.	70	At 60 minutes, 21/23 in prochlorperazine group had >25 mm reduction in VAS compared with 16/23 in promethazine group	Benign headache; not migraine

DHE, dihydroergotamine; IH, International Headache Society; i.m., intramuscular; i.v., intravenous; VAS, visual analog scale.

Table 4.—Forest Plot of Phenothiazines vs Placebo for Complete Relief

Study or subgroup	Placebo Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI
Bigal et al 2002[6]	5	60	44	68	43.3%	20.17 [7.11-57.16]
Jones et al 1989[8]	5	40	31	42	34.8%	19.73 [6.17-63.08]
Jones et al 1996[9]	2	29	9	28	17.5%	6.39 [1.24-32.99]
McEwen et al 1987[10]	0	17	1	19	4.4%	2.84 [0.11-74.42]
Total (95% CI)		146		157	100.0%	15.02 [7.57-29.82]
Total events	12		85			

Heterogeneity: Tau² = 0.00; Chi² = 2.56, d.f. = 3 (*P* = .46); *I*² = 0%
Test for overall effect: Z = 7.74 (*P* < .00001)



more drowsiness. Rates of rescue medication and patient satisfaction were similar.

This study has some limitations that should be considered when interpreting the results. Publication bias may have influenced the data available for analysis. We attempted to minimize this risk by also searching clinical trials registers and attempting to contact authors of as yet unpublished results. Definitions of migraine used were not consistent between studies, with a significant number using physician-diagnosed migraine as their criterion. This may have resulted in nonmigraine headaches being included in some cohorts. Some studies used adjunctive agents in both phenothiazine and other agent

Table 5.—Forest Plot of Phenothiazines vs Placebo for Clinical Success

Study or subgroup	Placebo Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI
Bigal et al 2002[6]	9	60	56	68	25.0%	26.44 [10.29-67.96]
Coppola et al 1995[7]	7	24	18	22	17.5%	10.93 [2.71-44.14]
Jones et al 1989[8]	18	40	37	42	21.7%	9.04 [2.94-27.79]
Jones et al 1996[9]	4	29	12	28	18.9%	4.69 [1.29-17.10]
McEwen 1987[10]	4	17	9	19	16.9%	2.92 [0.69-12.32]
Total (95% CI)		170		179	100.0%	8.92 [4.08-19.51]
Total events	42		132			

Heterogeneity: Tau² = 0.41; Chi² = 8.25, d.f. = 4 (*P* = .08); *I*² = 52%
Test for overall effect: Z = 5.48 (*P* < .00001)

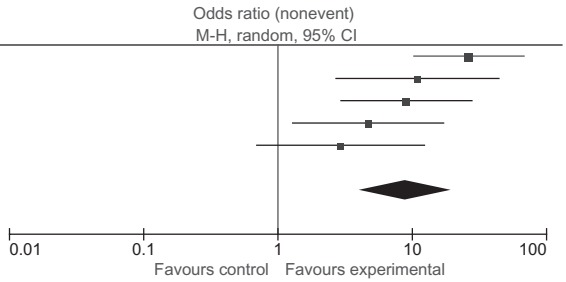
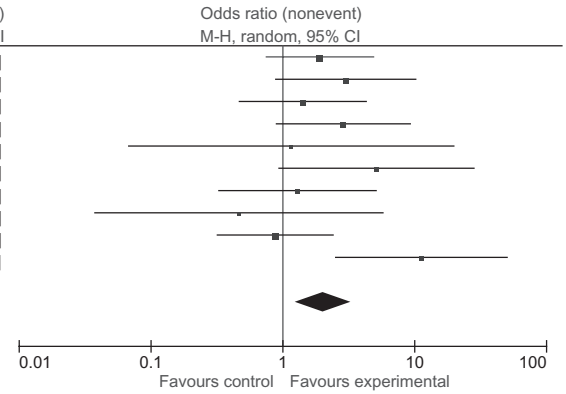


Table 6.—Forest Plot of Phenothiazines vs Active Agents for Clinical Success

Study or subgroup	Active agent Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI
Cameron et al 1995[11]	29	44	37	47	16.6%	1.91 [0.75-4.88]
Coppola et al 1995[7]	12	24	18	24	11.6%	3.00 [0.88-10.18]
Friedman et al 2008[12]	29	38	32	39	13.3%	1.42 [0.47-4.30]
Jones et al 1996[9]	6	29	12	28	12.3%	2.88 [0.89-9.26]
Kelly et al 1997[13]	19	20	22	23	2.7%	1.16 [0.07-19.80]
Lane et al 1989[14]	15	22	22	24	6.9%	5.13 [0.93-28.18]
Seim et al 1998[15]	29	35	25	29	9.7%	1.29 [0.33-5.11]
Shrestha et al 1996[16]	14	15	13	15	3.4%	0.46 [0.04-5.75]
Stiell et al 1991[17]	27	37	26	37	15.0%	0.88 [0.32-2.41]
Tanen et al 2003[18]	4	19	15	20	8.5%	11.25 [2.52-50.27]
Total (95% CI)		283		286	100.0%	2.04 [1.25-3.31]
Total events	184		222			

Heterogeneity: Tau² = 0.14; Chi² = 11.85, d.f. = 9 (*P* = .22); *I*² = 24%
Test for overall effect: Z = 2.87 (*P* = .004)

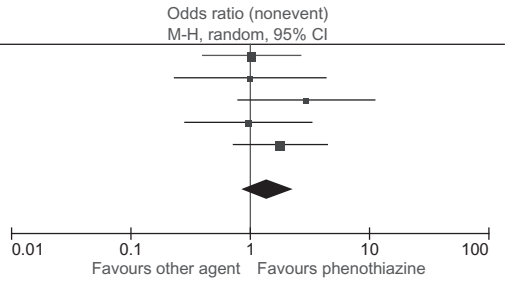


Note: Clinical success is the defined event.

Table 7.—Forest Plot of Phenothiazines vs Active Agents for Complete Headache Relief

Study or subgroup	Active agent Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI	Year
Cameron et al 1995[11]	11	44	12	47	27.6%	1.03 [0.40-2.65]	1995
Shrestha et al 1996[16]	9	15	9	15	11.6%	1.00 [0.23-4.31]	1996
Jones et al 1996[9]	4	29	9	28	14.2%	2.96 [0.79-11.09]	1996
Kelly et al 1997[13]	8	20	9	23	16.5%	0.96 [0.28-3.28]	1997
Friedman et al 2008[12]	15	38	21	39	30.2%	1.79 [0.72-4.42]	2008
Total (95% CI)		146		152	100.0%	1.39 [0.85-2.29]	
Total events	47		60				

Heterogeneity: Tau² = 0.00; Chi² = 2.49, d.f. = 4 (*P* = .65); I^2 = 0%
Test for overall effect: Z = 1.31 (*P* = .19)



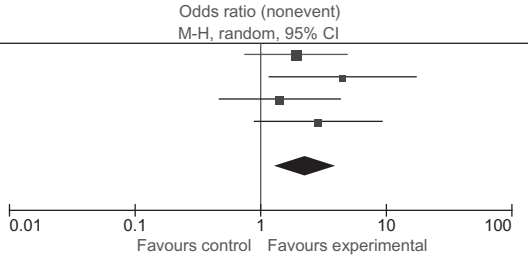
Note: Complete headache relief is the defined event.

arms that may themselves have had some activity thus influencing the results. For the primary analysis, a pooled active agents group was used. It is possible, if not likely, that the active agents varied in effectiveness. It is possible that one or more agents have similar effectiveness to phenothiazines; however, with the exception of the metoclopramide group, numbers were too small to detect anything other than a large treatment effect. This study did not address adverse events because of unacceptable heterogeneity in reporting of these in the papers studied; however, we recognize that adverse event profile is an important aspect of clinical decision making for individual patients.

Table 8.—Forest Plot of Phenothiazines vs Metoclopramide for Clinical Success

Study or subgroup	Metoclopramide Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI
Cameron et al 1995[11]	29	44	37	47	35.2%	1.91 [0.75-4.88]
Coppola et al 1995[7]	12	24	18	22	17.0%	4.50 [1.17-17.30]
Friedman et al 2008[12]	29	38	32	39	25.1%	1.42 [0.47-4.30]
Jones et al 1996[9]	6	29	12	28	22.6%	2.88 [0.89-9.26]
Total (95% CI)		135		136	100.0%	2.25 [1.29-3.92]
Total events	76		99			

Heterogeneity: Tau² = 0.00; Chi² = 1.97, d.f. = 3 (*P* = .58); I^2 = 0%
Test for overall effect: Z = 2.86 (*P* = .004)

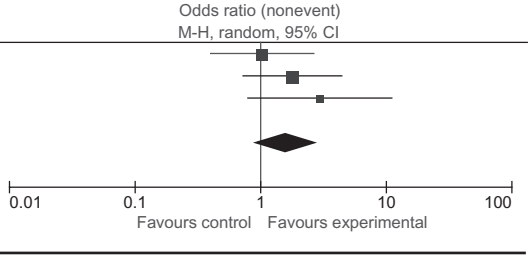


Note: Clinical success is the defined event.

Table 9.—Forest Plot of Phenothiazines vs Metoclopramide for Complete Headache Relief

Study or subgroup	Metoclopramide Events	Total	Phenothiazine Events	Total	Weight	Odds ratio (nonevent) M-H, random, 95% CI
Cameron et al 1995[11]	11	44	12	47	38.4%	1.03 [0.40-2.65]
Friedman et al 2008[12]	15	38	21	39	41.9%	1.79 [0.72-4.42]
Jones et al 1996[9]	4	29	9	28	19.7%	2.96 [0.79-11.09]
Total (95% CI)		111		114	100.0%	1.60 [0.89-2.87]
Total events	30		42			

Heterogeneity: Tau² = 0.00; Chi² = 1.73, d.f. = 2 (*P* = .42); I^2 = 0%
Test for overall effect: Z = 1.57 (*P* = .12)



Note: Complete headache relief is the defined event.

CONCLUSION

Phenothiazines are more effective than placebo for the treatment of migraine headache and have higher rates of clinical success than other agents against which they have been compared.

STATEMENT OF AUTHORSHIP

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(a) Conception and Design

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Tracy Walcynski; Barry Gunn

Category 3

(a) Final Approval of the Completed Article

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