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REVIEW

Systematic Review of Episodic Migraine Prophylaxis: Efficacy of Conventional Treatments Used in Comparisons with Acupuncture

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ABSTRACT

Objective: A Cochrane Systematic Review published by Linde et al. in 2016 found moderate evidence suggesting that acupuncture is ''at least non-inferior'' to conventional prophylactic drug treatments (flunarizine, metoprolol, and valproic acid) for episodic migraine prophylaxis. The evidence for the efficacy of these conventional treatments must be verified to strengthen and validate the original comparison made in Linde et al.'s 2016 review. The aim of the current authors' systematic review was to verify the efficacy of the conventional treatments used in Linde et al.'s 2016 comparison with acupuncture.

Materials and Methods: Search strategies were applied to find studies that could verify the efficacy of conventional treatments for treating episodic migraines. Relevant outcomes and dosages were extracted from the retrieved studies. Each study's quality was assessed, using the Cochrane's collaboration tool for assessing risk of bias and the Cochrane GRADE [Grading of Recommendations Assessment, Development, and Evaluation] scale.

Results: There is high-quality evidence suggesting that prophylactic drug treatment, at the treatment dosage ranges used in Linde et al.'s 2016 review, reduced headache frequency at a 3-month follow-up, compared to placebo. Headache frequency at a 6-month follow-up, and responses (at least 50% reduction of headache frequency) at 3-month and 6-month follow-ups could not be assessed.

Conclusions: These findings strengthened Linde et al.'s 2016 comparison of conventional treatments and acupuncture for reducing headache frequency at a 3-month follow-up. For episodic migraine prophylaxis, moderate evidence suggests that acupuncture is ''at least non-inferior,'' to now-*proven*, conventional treatments. This raises significant questions in the debate concerning claims that acupuncture is a placebo-based treatment and the prescriptions of proven conventional treatments that have similar effects as acupuncture.

Keywords: migraine prophylaxis, drug therapy, acupuncture

INTRODUCTION

The research base for alternative treatments, such as acupuncture, is rapidly increasing and is popular among healthcare consumers.[1] Notably, acupuncture is an alternative treatment to conventional prophylactic drug treatment used to reduce the frequency, duration, and intensity of migraine attacks.[2] Given that migraines are debilitating and highly prevalent, affecting $\sim$1 of every 7 Americans annually, it is essential that migraine treatments are both proven by accepted research methods and are justified.[3]

Controversies exist with respect to finding the appropriate comparisons to isolate the treatment effect of acupuncture. For instance, a systematic review of 38 trials revealed that acupuncture might work through nonspecific effects rather than by a treatment effect, given that the majority of trials

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did not report statistically significant differences between verum acupuncture and sham acupuncture for patient-important outcomes.[4] However, this is contrasted by a 2018 meta-analysis of 39 trials that found that acupuncture is effective for treating chronic pain and cannot be explained only by placebo effects.[5] To move beyond the debate, an alternative to sham acupuncture is to compare acupuncture with *proven* conventional treatments. There is substantial evidence supporting acupuncture's effectiveness, compared to conventional treatments, for addressing various conditions. However, it is unclear if the conventional treatment was *proven* to work.[6–10] Studies that include a conventional treatment arm often use research guideline–based dosages, whereas the dosages might or might not be based on evidence of efficacy.[7]

Notably, a systematic review, ''Acupuncture for the Prevention of Episodic Migraine,'' by Linde et al., was published by the Cochrane Library in 2016.[2] This 2016 article was an update of its previous version and is currently the latest review available in which 5 studies compared acupuncture with prophylactic drug treatment.[6–11] Qualitative analysis was performed on 2 studies,[6,10] 1 of which was in favor of conventional treatment, metoprolol, over acupuncture.[6] However, that study used a dummy–dummy design in favor of a metoprolol + sham acupuncture group over a metoprolol + verum acupuncture group and was found to have a skeptical needling technique, which could have accounted for the different outcome of that study, compared to the others in the review.[2,6] The other qualitatively analyzed study found acupuncture to be similar to valproic acid for migraine prophylaxis.[10] The remaining 3 studies compared acupuncture with metoprolol, flunarizine, and valproic acid, which were pooled and meta-analyzed together as ''prophylactic drug treatment.'' The pooled effect sizes estimated statistically significant results in favor of acupuncture (standardized mean difference: –0.25; 95% confidence interval [CI]: –0.39 to –0.10; 739 participants).[7–9]

Overall, in 2016, Linde et al. found moderate evidence that acupuncture is ''at least non-inferior'' to conventional treatment for episodic migraine prophylaxis.[2] There was also moderate evidence favoring acupuncture over conventional treatment for safety and tolerability, given that acupuncture produced a lower number of pooled adverse effects and had a lower likelihood of dropouts.[2]

In this systematic review by the current authors, the goal was to verify the efficacy of the *conventional* treatments used in Linde et al.'s 2016[2] comparisons with acupuncture. If there were strong evidence to support—or prove—the effectiveness of conventional treatment at the given dosages used in Linde et al.'s 2016 review,[2] then the validity of the overall comparison for acupuncture would be strengthened. The results could then support or discourage current practices further and shed light on potentially more-effective alternatives.

MATERIALS AND METHODS

Search Strategy

Separate search strategies were applied to identify the highest level of evidence regarding the efficacy of the dosages of flunarizine, metoprolol, and valproic acid as conventional treatments for episodic migraine prophylaxis. First, the Cochrane Library was searched to obtain the latest systematic reviews on the efficacy of flunarizine, metoprolol, and valproic acid for episodic migraine prophylaxis (Appendix A1). If no Cochrane Review was available, searches were conducted on Google Scholar and PubMed from their beginning to October 2018, using key terms including: flunarizine, metoprolol, valproic acid, valproate, randomized control trial, placebo, migraine, headache, and prophylaxis. References from included studies were also searched for any relevant studies.

Criteria for Considering Studies

Inclusion and exclusion criteria were all taken from Linde et al.'s 2016 review. Notably, these included studies, participants, interventions, and outcome measures, as noted in the next 4 subsections.

Types of studies. Any published quantitative study design in the English language was included. The study must have specifically investigated the intervention on episodic migraine prophylaxis.

Types of participants. Participants were all clinically diagnosed with episodic migraine with or without aura. *Episodic migraine* was defined as a recurrent headache disorder of at least 5 attacks lasting 4–72 hours.[12] Each attack had to have features of a migraine headache, including at least 2 of the following 4 characteristics: (1) unilateral location; (2) pulsating quality; (3) moderate-to-severe pain intensity; or (4) worsened by physical activity; as well as at least one of the following characteristics: nausea; vomiting; or photophobia.[12] Participants must have had the condition for at least 1 year to be included. Patients with chronic migraine were excluded. *Chronic migraine* was defined as a headache disorder occurring on 15 or more days per month for more than 3 months, which on at least 8 days per month has features of a migraine headache.[12]

Types of interventions. Studies were included if they used flunarizine, metoprolol, or valproic acid for the prevention of episodic migraine. The presence of a placebo group and reported between-group differences were also necessary for inclusion to allow for comparisons.

Types of outcome measures. Comparison had to be made in the studies between treatment and placebo groups

for the following outcomes: headache frequency at a 3-month follow-up; headache frequency at a 6-month follow-up; response (at least 50% frequency reduction) at a 3-month follow-up; and response (at least 50% frequency reduction) at a 6-month follow-up.

Study Selection

At least 2 of the current authors independently conducted citation identification, study selection, and data abstraction. Disagreements were resolved through consulting a third assessor.

Methodological Assessment

Two of the current authors independently assessed each selected study for methodological quality based on the Cochrane's collaboration tool for assessing risk of bias and the Cochrane GRADE [Grading of Recommendations Assessment, Development, and Evaluation] scale.[13,14] By convention, sensitivity analysis was performed separately for studies, based on risk of bias. The primary analysis only included studies with a low risk of bias, while the secondary analysis included studies with any risk of bias. Disagreements were resolved through consulting a third assessor.

Main Outcome Measures

Two of the current authors independently extracted relevant outcomes and dosages. Clinical judgment was used to assess homogeneity of dosage ranges used between the studies included in Linde et al.'s 2016 review[2] and the studies found in the current authors' review. The outcomes in this review matched the outcomes from the 2016 study by Linde et al.[2] All disagreements were resolved through a third assessor.

RESULTS

Included Studies and Characteristics

A total of 8 randomized controlled trials (RCTs) and 1 Cochrane Review were found.[15–23] The RCTs included 6 parallel and 2 crossover designs (Table 1). Each RCT included males and females and measured the outcome *headache frequency* (i.e., migraine days, attack frequency, or frequency of migraine attacks) after receiving treatment or placebo at a 3-month follow-up. Seven studies reported a significant reduction in headache frequency at a 3-month follow-up in a prophylactic drug treatment group, compared to a control group.[15–19,21–22]

Reductions in the frequency of migraine attacks were found by Frenken and Nuijten in 1984 ($P = 0.029$; flunarizine mean difference [MD]: 1.2; placebo MD: 0.4),[15] Louis in 1981 ($P < 0.001$; flunarizine pretreatment median: 7 [range: 6–14]; flunarizine post-treatment median: 2 [range: 0–5]; placebo pretreatment median: 7 [range: 6–12]; placebo post-treatment median: 3 [range: 2–5]),[16] Mendenopoulos et al. in 1985 ($P = 0.033$; number-needed-to-treat [NNT]: 1.23),[17] Sørenson et al. in 1986 ($P = 0.002$; NNT: 2.5),[18] Sorge et al. in 1988 ($P < 0.001$; flunarizine MD: 1.7; placebo MD: 0.7),[19] and Andersson et al. in 1983 ($P < 0.05$; flunarizine MD: 1.3; placebo MD: 0.53).[21]

Reductions in migraine days were found by Steiner et al. in 1988 ($P = 0.05$; metoprolol pretreatment mean: 7.1 [standard deviation (SD): 3.8]; metoprolol post-treatment mean: 5.2 [SD: 4.1]; placebo pretreatment mean: 6.5 [SD: 3.4]; and placebo post-treatment mean: 5.5 [SD: 2.7]).[22] However, 1 study (Lepcha et al., 2013) reported no significant between-group difference.[20]

Jensen et al. in 1994 reported a significant reduction in migraine days in a prophylactic drug–treatment group, compared to a control group ($P = 0.002$; pretreatment mean: 6.1 [range: 2–10]; sodium valproate post-treatment mean: 3.5 [CI: 2.7–4.3]; placebo post-treatment mean: 6.1 [CI: 4.8–7.4]).[25]

None of the included studies investigated headache frequency at a 6-month follow-up, or response (at least 50% reduction of headache frequency) at a 3-month and 6-month follow-up. Response could not be calculated, given that all included studies only provided mean or median values for control and intervention groups, and normal distribution could not be assumed.

Dosage Ranges

The dosage range for the RCTs involving flunarizine were 5–10 mg daily for 12–16 weeks.[15–20] Meanwhile, the dosage range for the study included in Linde et al.'s 2016 review[2] was 10 mg of flunarizine daily for 24 weeks.[9]

The dosage range for the RCTs involving metoprolol were 100–200 mg daily for 8–12 weeks.[21,22] Meanwhile, the dosage range for the studies included in Linde et al.'s 2016 review[2] were 50–200 mg of metoprolol daily for 6–17 weeks.[6–8]

The dosage range for the RCT involving sodium valproate was 1000–1500 mg daily for 12 weeks.[25] Meanwhile, the dosage range for the study included in Linde et al.'s 2016 review[2] was 600 mg of sodium valproate daily for 12 weeks, with the exception of taking 300 mg daily during the first week of the trial.[10]

Qualitative Assessment of Dosage and Duration Ranges

The studies included in Linde et al.'s 2016 review[2,6–10] and the studies found from the current authors' literature search[15–25] used treatment dosage ranges that were considered similar overall. In fact, with the exception of 1 study,[25] the dosage ranges in Linde et al.'s 2016 review[2,6–10] were typically greater than or equal to the dosage and duration ranges in the studies found from the current authors'

Table 1. Summary of Included Studies

Authors, year, and ref. #	*Design*	*Sample size*	*Participants*	*Main interventions*	*Outcome results*
Frenken & Nuijten, 1984[15]	Randomized, double-blinded placebo-controlled trial	35 participants; 17 in flunarizine group & 18 in placebo group	6 males & 29 females with either classic or common migraine and incidence of at least 1 attack per month during the 6 months preceding the study Adults ages 20–51 selected to participate Patients with cluster headaches, pregnant &/or nursing excluded	5 mg flunarizine or matching placebo twice daily for 3 months	Reduction of attack frequency in flunarizine group, compared to placebo group ($P = 0.029$)
Louis, 1981[16]	Randomized, double-blinded placebo-controlled trial	58 participants; 29 in flunarizine group & 29 in placebo group	29 males & 29 females with either classic or common migraine & an incidence of at least 6 attacks during the 6 months preceding the study Adults ages 20–51 selected to participate	5 mg flunarizine or matching placebo twice daily for 3 months	Reduction of attack frequency ($P < 0.001$) & increase in patient appreciation ($P < 0.0001$) in flunarizine group, compared to placebo group
Mendenopoulos et al., 1985[17]	Randomized, double-blinded placebo-controlled trial	20 participants; 9 in flunarizine group & 11 in placebo group	4 males &16 females with at least 1-year history of classic migraine & incidence of at least 4 severe attacks in the past 3 months Adults ages 20–65 selected to participate Patients with other types of headaches &/or pregnant excluded	10 mg flunarizine or matching placebo daily for 3 or 4 months	Reduction of attack frequency ($P = 0.033$), duration of attack ($P = 0.037$) & severity of attacks ($P = 0.006$) in flunarizine group, compared to the placebo group, at the 3rd month
Sørenson et al., 1986[18]	Randomized, double-blinded, placebo-controlled crossover trial	29 participants; 14 patients to the treatment sequence (flunarizine–placebo) & 15 patients to the baseline sequence (placebo–flunarizine)	6 males & 23 females with at least 1-year history of either common migraine & history of migraine of at least 1-year's duration & a frequency of attacks between 2 & 6 months Adults ages 18–65 selected to participate Patients with heart or brain diseases, arterial hypertension, &/or pregnant excluded	10 mg flunarizine or matching placebo daily for 4 months 4-week washout period before crossover for another 4 months	Reduction of attack frequency ($P = 0.001$) & duration of attacks ($P = 0.02$) in treatment sequence, compared to baseline sequence Severity of attacks unaffected for both groups
Sorge et al., 1988[19]	Randomized, double-blinded placebo-controlled crossover trial	63 participants; 33 patients to the treatment sequence (flunarizine–placebo) & 30 patients to the baseline sequence (placebo–flunarizine)	36 females & 34 males with at least 6-month history of common migraine 3 or more times/month Children ages 5–11 selected to participate Participants with past history of flunarizine use & objective neurologic or internal disorders excluded	5 mg flunarizine or matching placebo at bedtime for 12 weeks after a 4-week baseline period 4-week washout period with both groups on placebo before crossover for another 12 weeks	Reduction of attack frequency ($P < 0.001$) & duration of attacks ($P < 0.001$) in treatment-sequence, compared to baseline sequence from the 2nd to the 5th month

(*continued*)

TABLE 1. (CONTINUED)

Authors, year, and ref. #	*Design*	*Sample size*	*Participants*	*Main interventions*	*Outcome results*
Lepcha et al., 2013[20]	Randomized controlled trial	52 participants; 26 in Arm A (flunarizine) & 26 in Arm B (control); 4 lost to follow-up (1 from Arm A & 3 from Arm B)	18 males & 34 females with definitive migrainous vertigo Adults ages 18–75 selected to participate Participants excluded if they had benign paroxysmal positional vertigo, Meniere's disease, chronic discharging ear, past history of ear surgery, profound hearing loss, stroke, & intracranial tumors, or if they were taking calcium-channel blockers	10 mg flunarizine once daily, 16 mg beta-histine & 1 g paracetamol during episodes or just 16 mg beta-histine & 1 g paracetamol during episodes for 12 weeks	No statistically significant difference in flunarizine group in terms of frequency ($P = 0.38$) & severity ($P = 0.22$) of headache attacks
Andersson et al., 1983[21]	Randomized, double-blinded placebo-controlled trial	71 participants; 37 in placebo group & 34 in metoprolol group	11 males & 60 females with at least 2-year history of classical or non-classical migraine & an incidence of at least 3 attacks per month Individuals ages 16–65 selected to participate Patients excluded if they had prespecified contraindications or comorbidities	200 mg metoprolol or matching placebo every morning for 8 weeks after 4 weeks pretreatment period	Reduction in attack frequency ($P < 0.01$), number of migraine days ($P < 0.05$) & severity in metoprolol ($P < 0.05$) group, compared to placebo group
Steiner et al., 1988[22]	Randomized, double-blinded placebo-controlled trial	59 participants; 31 in placebo group & 28 in metoprolol group	14 males & 45 females with classical or common migraine for at least 2 years with 2-8 attacks per month Adults ages 18–64 selected to participate Patients excluded if they were pregnant, had previous experience in more than 1 clinical trial on migraine, had other headaches or hypertension, were taking other medications, or had other illness requiring regular medication	50 mg metoprolol or matching placebo b.i.d. for 8 weeks after a 4-week placebo period Responders to either placebo or metoprolol continued on their treatment for the next 12 weeks Nonresponders (NRs) from the metoprolol group were given 100 mg b.i.d. and NRs from the placebo group were given 50 mg metoprolol b.i.d. for up to 12 weeks	Reduction in migraine days in metoprolol group, compared to placebo group ($P = 0.05$) Mean attack frequency & mean severity of attacks did not change for either group in the first time period However, there was a significant reduction in attack frequency ($P < 0.05$ & $P < 0.01$) for those who were NRs & either switched from placebo to 50 mg metoprolol b.i.d. or switched their dosage from 50 mg to 100 mg metoprolol, respectively

TABLE 2. RISK OF BIAS OF INCLUDED STUDIES

Bias	*Frenken & Nuijten, 1984*[15]	*Louis, 1981*[16]	*Mendenopoulos et al., 1985*[17]	*Sørenson et al., 1986*[18]
Random sequence generation (selection bias)	Low risk ''randomly treated''	Low risk ''randomly assigned''	Low risk ''computer-drawn randomization list''	Low risk ''randomization assigned''
Allocation concealment (selection bias)	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Low risk ''member placed capsules in 2 different envelopes marked A or B, known only to this member''
Blinding (performance bias & detection bias) All outcomes—patients?	Low risk ''double-blind''	Low risk ''double-blind''	Low risk ''double blind''	Low risk ''double blind''
Blinding (performance bias & detection bias) All outcomes—providers?	Low risk ''double-blind''	Low risk ''double-blind''	Low risk ''double blind''	Low risk ''double blind''
Blinding (performance bias & detection bias) All outcomes—outcome assessors?	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed
Incomplete outcome data (attrition bias) All outcomes—drop-outs?	Low risk No dropouts	Low risk No dropouts	Low risk No dropouts	Low risk 2 dropouts, addressed & justified
Incomplete outcome data All outcomes—ITT analysis?	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Selective reporting (reporting bias)	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Similarity of baseline characteristics?	Low risk ''the 2 groups were comparable for all baseline values''	Low risk ''two groups were well matched for all patient and disease characteristics''	Low risk ''two study groups were comparable as to patient and migraine characteristics''	Low risk ''no significant clinical differences were found between the groups''
Co-intervention avoided or similar?	Low risk No co-intervention	Low risk No co-intervention	Low risk No co-intervention	Low risk Appropriate 4 weeks washout period between crossover
Compliance acceptable?	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable
Timing outcome assessments similar?	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups
Overall impression	Low risk	Low risk	Low risk	Low risk

(*continued*)

Table 2. (Continued)

Bias	*Sorge et al., 1988*[19]	*Lepcha et al., 2013*[20]	*Andersson et al., 1983*[21]	*Steiner et al., 1988*[22]
Random sequence generation (selection bias)	Low risk ''randomly assigned''	Low risk ''block randomized''	Low risk ''randomly allocated''	Low risk ''randomized''
Allocation concealment (selection bias)	Unclear risk Not addressed	Low risk ''allocation of patients was done by primary investigator based on computer-generated numbers''	Unclear risk Not addressed	Unclear risk Not addressed
Blinding (performance bias and detection bias) All outcomes—patients?	Low risk ''double blind''	High risk Not blinded	Low risk ''double-blind''	Low risk ''double-blind''
Blinding (performance bias & detection bias) All outcomes—providers?	High risk ''double blind''	High risk Not blinded	Low risk ''double-blind''	Low risk ''double-blind''
Blinding (performance bias & detection bias) All outcomes—outcome assessors?	Unclear risk Not addressed	High risk Not blinded	Unclear risk Not addressed	Unclear risk Not addressed
Incomplete outcome data (attrition bias) All outcomes—dropouts?	Low risk 7 dropouts, addressed & justified	High risk 4 dropouts, not justified	Low risk 9 dropouts, addressed & justified	Low risk 5 dropouts, addressed & justified
Incomplete outcome data All outcomes—ITT analysis?	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Selective reporting (reporting bias)	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Similarity of baseline characteristics?	Low risk ''two groups were similar with regard to age and sex and headache duration, type, frequency, and severity''	Low risk ''No statistical difference between two groups in terms of sex distribution and age distribution''	Unclear risk Patient demographics included; however, no analysis conducted to suggest homogeneity	Unclear risk Patient demographics included; however, no analysis conducted to suggest homogeneity
Co-intervention avoided or similar?	Low risk Crossover with adequate washout period	Low risk Co-intervention similar	Low risk No co-intervention	Low risk No co-intervention
Compliance acceptable?	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable
Timing outcome assessments similar?	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups
Overall impression	Low risk	High risk	Low risk	Low risk

ITT, intention-to-treat.

TABLE 3A. SUMMARY OF FINDINGS—PRIMARY ANALYSIS

Prophylactic Drug Treatment vs. Placebo
Study risk of bias: Low risk of bias
Patients or populations: Male & female participants with common or classic episodic migraine & no comorbidities
Settings: Neurologic, psychiatric, or migraine clinics
Interventions: Flunarizine, metoprolol, or valproic-acid capsule
Comparison: Placebo capsule

Outcomes	*Intervention* *Results with prophylactic drug treatment*	*# of participants & list of studies*	*Quality of the evidence per GRADE*[a–h]
Headache frequency at a 3-month follow-up	7 studies reported a significant reduction in headache frequency at a 3-month follow-up in the prophylactic drug treatment group, compared to the placebo group ***Reductions in frequency of migraine attacks:*** **Frenken & Nuijten, 1984**[15] ($P = 0.029$; flunarizine MD: 1.2; placebo MD: 0.4) **Louis, 1981**[16] ($P < 0.001$; flunarizine pretreatment median: 7 [range: 6–14]; flunarizine post-treatment median: 2 [range: 0–5]; placebo pretreatment median: 7 [range: 6–12]; placebo post-treatment median: 3 [range: 2–5]) **Mendenopoulos et al., 1985**[17] ($P = 0.033$; NNT: 1.23) **Sørenson et al., 1986**[18] ($P = 0.002$; NNT: 2.5) **Sorge et al., 1988**[19] ($P < 0.001$; flunarizine MD: 1.7; placebo MD: 0.7) **Andersson et al., 1983**[21] ($P < 0.05$; flunarizine MD: 1.3; placebo MD: 0.53) ***Reductions in migraine days*:** **Steiner et al., 1988**[22] ($P = 0.05$; metoprolol pretreatment mean: 7.1 [SD]: 3.8); metoprolol post-treatment mean: 5.2 [SD: 4.1]; placebo pretreatment mean: 6.5 [SD: 3.4]; placebo post-treatment mean: 5.5 [SD: 2.7])	335 (in 7 studies) Frenken & Nuijten, 1984[15] Louis, 1981[16] Mendenopoulos et al., 1985[17] Sørensen et al., 1986[18] Sorge et al., 1988[19] Andersson et al., 1983[21] Steiner et al., 1988[22]	**High** Limitations: 0 Imprecision: 0 Inconsistency: 0 Indirectness: 0 Other: 0A
Headache frequency at a 6-month follow-up	N/A	N/A	N/A
Response (at least 50% reduction of headache frequency) at a 3-months follow-up	N/A	N/A	N/A
Response (at least 50% reduction of headache frequency) at a 6-month follow-up	N/A	N/A	N/A

[a]Evidence from randomized controlled trials are initially classified as high quality and then downgraded based on five criteria: (1) limitations in design; (2) imprecision of results; (3) inconsistency of results; (4) indirectness of evidence; and (5) high probability of publication bias.

[b]Evidence from observational studies are initially classified as low quality and then upgraded based on three criteria: (1) large magnitude of effect; (2) all plausible confounders would reduce a demonstrated effect when results show no effect; (3) dose–response gradient.

[c]Evidence obtained from study designs with a high risk of bias.

[d]Evidence obtained from different study designs.

[e]No direct comparison of therapeutic dose with sham therapy.

[f]Lack of allocation concealment and blinding.

[g]Small study group.

[h]*GRADE Working Group grades of evidence:*

High quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and might change the estimate.

Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality: The reviewers are very uncertain about the estimate.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation scale; MD, mean difference; NNT, number needed to treat; SD, standard deviation; NA, not available (i.e., no available data).

TABLE 3B. SUMMARY OF FINDINGS—SECONDARY ANALYSIS

Prophylactic Drug Treatment vs. Placebo
Study risk of bias: Any risk of bias
Patients or populations: Male & female participants with common or classic episodic migraine & no comorbidities
Settings: Neurologic, psychiatric, or migraine clinics
Interventions: Flunarizine, metoprolol, or valproic-acid capsule
Comparison: Placebo capsule

Outcomes	*Intervention* *Results of prophylactic drug treatment*	*# of participants & list of studies*	*Quality of the evidence per GRADE*[a–h]
Headache frequency at a 3-month follow-up	8 studies reported a significant reduction in headache frequency at a 3-month follow-up in the prophylactic drug treatment group, compared to the placebo group.***Reductions in frequency of migraine attacks:*** **Frenken & Nuijten, 1984[15]** ($P = 0.029$; flunarizine MD: 1.2; placebo MD: 0.4) **Louis, 1981[16]** ($P < 0.001$; flunarizine pretreatment median: 7 [range: 6–14]; flunarizine post-treatment median: 2 [range: 0–5]; placebo pretreatment median: 7 [range: 6–12]; placebo post-treatment median: 3 [range: 2–5]) **Mendenopoulos et al., 1985[17]** ($P = 0.033$; NNT: 1.23) **Sørenson et al., 1986[18]** ($P = 0.002$; NNT: 2.5) **Sorge et al., 1988[19]** ($P < 0.001$; flunarizine MD: 1.7; placebo MD: 0.7) **Andersson et al., 1983[21]** ($P < 0.05$; flunarizine MD: 1.3; placebo MD: 0.53) ***Reductions in migraine days:*** **Steiner et al., 1988[22]** ($P = 0.05$; metoprolol pretreatment mean: 7.1 [SD: 3.8]; metoprolol post-treatment mean: 5.2 [SD: 4.1]; placebo pretreatment mean: 6.5 [SD: 3.4]; placebo post-treatment mean: 5.5 [SD: 2.7]) **Jensen et al., 1994[25]** ($P = 0.002$; pretreatment mean: 6.1 [range: 2–10]; sodium valproate post-treatment mean: 3.5 (CI: 2.7–4.3]; placebo post-treatment mean: 6.1 [CI: 4.8–7.4]) 1 study (Lepcha et al., 2013) did not report a significant difference in headache frequency between the prophylactic drug treatment group and the placebo group ($P = 0$ .38).	430 (9 studies) ΩΩ Frenken & Nuijten, 1984[15]Frenken & Nuijten, 1984[15] Louis, 1981[16] Mendenopoulos et al., 1985[17] Sørensen et al., 1986[18] Sorge et al., 1988[19] Lepcha et al., 2013[20] Andersson et al., 1983[21] Steiner et al., 1988[22] Jensen et al., 1994[25]	**Moderate**[a] Limitations: 1[c,f] Imprecision: 0 Inconsistency: 0 Indirectness: 0 Other: 0
Headache frequency at a 6-month follow-up	N/A	N/A	N/A
Response (at least 50% reduction of headache frequency) at a 3-month follow-up	N/A	N/A	N/A
Response (at least 50% reduction of headache frequency) at a 6-month follow-up	N/A	N/A	N/A

[a]Evidence from randomized controlled trials are initially classified as high quality and then downgraded based on five criteria: (1) limitations in design; (2) imprecision of results; (3) inconsistency of results; (4) indirectness of evidence, and (5) high probability of publication bias.

[b]Evidence from observational studies are initially classified as low quality and then upgraded based on three criteria: (1) large magnitude of effect; (2) all plausible confounders would reduce a demonstrated effect when results show no effect; (3) dose–response gradient.

[c]Evidence obtained from study designs with a high risk of bias.

[d]Evidence obtained from different study designs.

[e]No direct comparison of therapeutic dose with sham therapy.

[f]Lack of allocation concealment and blinding.

[g]Small study group.

[h]*GRADE Working Group grades of evidence:*

High quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and might change the estimate.

Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality: The reviewer are very uncertain about the estimate.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation scale; MD, mean difference; NNT, number needed to treat; SD, standard deviation; CI, confidence interval; NA, not available (i.e., no available data).

literature search.[15–25] Given that these drug pharmacodynamics might work through a dose–response relationship, it was likely based on evidence that the dosages of prophylactic drug treatment (i.e. flunarizine, metoprolol, and valproic acid)[26] were effective in Linde et al.'s 2016 review.[2]

DISCUSSION

All but 2 of the included studies from the current authors' literature search were assessed to have a low risk of bias (Table 2).[15–19,21–22] The first study was assessed to have a high risk of bias due to lack of blinding and incomplete outcome data that was unaddressed.[20] Thus, risk of performance bias, detection bias, and attrition bias were increased. This may explain why that was the only study to report no significant between-group differences. Meanwhile, the second study, by Jensen in 1994,[25] was determined by Linde et al.'s 2013 review[23] to have an unclear risk of selection bias because of the uncertainty concerning the random sequence generation and allocation concealment, and high risk of attrition bias as a result of incomplete outcome data.[25]

Linde et al.'s 2016 review found moderate evidence suggesting acupuncture is ''at least non-inferior'' to conventional treatment—prophylactic drug treatment (flunarizine, metoprolol, and valproic acid)—for migraine prophylaxis.[2] In the current authors' literature search, there were consistent findings in favor of conventional treatment over placebo.[15–22,25] Additionally, the treatment dosage ranges from the literature search were determined qualitatively to be similar with the treatment dosage ranges in the studies included in Linde et al.'s 2016 review.[2] In the primary analysis, there was a high quality of evidence suggesting that prophylactic drug treatment, at the treatment dosage ranges included in Linde et al.'s 2016 review,[2] reduced headache frequency at a 3-month follow-up, compared to placebo (Table 3A). The quality of evidence was downgraded in the secondary analysis to moderate due to the methodological limitations of the additional studies included (Table 3B).[20,25] However, in both analyses, there were no data for headache frequency at a 6-month follow-up, response at a 3-month follow-up, and response at a 6-month follow-up.

The current authors' approach to summarizing the literature had several strengths and limitations. Three systematic searches were conducted within the Cochrane Library to identify relevant reviews. Although key terms were only used to conduct searches in Google Scholar, the Cochrane Library, and PubMed, at least 2 people decided on article relevance based on set criteria. The quality of the current authors' findings was dependent on the quality of the trials and reviews that were included in the review. Additionally, the reliability of Cochrane's collaboration tool for assessing risk of bias is unclear, as we were unable to find any studies on the topic.[13]

Moreover, multiple implications arise considering the current authors' findings (i.e., moderate evidence suggesting acupuncture to be ''at least non-inferior'' to conventional treatments *proven* by multiple low-risk RCTs) and that some literature has suggested that acupuncture works through nonspecific effects (i.e., no statistically significant differences between verum acupuncture and sham acupuncture groups). First, the conditions set a strong precedent to re-evaluate the stigma on placebo-based treatments relative to the high standards the current authors set for conventional treatments. The conditions warrant the use of placebo-based treatments, despite the ethical dilemma of deception involved. Second, the conditions suggest that acupuncture might potentially be attributed to a unique or unexplored biologic mechanism that researchers still strive to understand.[27] Finally, if it is due to an enhanced placebo effect, then there might potentially be a fundamental methodological flaw or weakness in the randomized study design that has not yet been identified. To explore these implications further, perhaps the most appropriate study design should consist of a 3-arm RCT with acupuncture, sham acupuncture, and proven drug therapy; or a 4-arm RCT with acupuncture, sham acupuncture, drug therapy, and drug placebo therapy groups.

CONCLUSIONS

The current authors' findings strengthened Linde et al.'s 2016[2] comparisons of conventional treatments and acupuncture. For the treatment of episodic migraine prophylaxis, moderate evidence suggests that acupuncture is ''at least non-inferior'' to now-*proven*, conventional treatments to reduce headache frequency, at a 3-month follow-up, versus placebo. Given that there are ongoing debates of acupuncture as being merely placebo, this raises significant questions concerning the ethical dilemma involved in prescribing placebo-based treatments, and prescriptions of proven conventional treatments that have similar effects as acupuncture.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

REFERENCES

1. Astin JA. Why patients use alternative medicine: Results of a national study. *JAMA.* 1998;279(19):1548–1553.
2. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of episodic migraine. *Cochrane Database Syst Rev.* 2016;6:CD001218.
3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. *Headache*. 2015;55(1):21–34.
4. Moffet HH. Sham acupuncture may be as efficacious as true acupuncture: A systematic review of clinical trials. *J Altern Complement Med.* 2009;15(3):213–216.
5. Vickers AJ, Vertosick EA, MacPherson H, et al.; Acupuncture Trialists' Collaboration. Acupuncture for chronic pain: Update of an individual patient data meta-analysis. *J Pain.* 2018; 19(5):455–474.
6. Hesse J, Møgelvang B, Simonsen H. Acupuncture versus metoprolol in migraine prophylaxis: A randomized trial of trigger point inactivation. *J Intern Med.* 1994;235(5):451–456.
7. Streng A, Linde K, Hoppe A, et al. Effectiveness and tolerability of acupuncture compared with metoprolol in migraine prophylaxis. *Headache.* 2006;46(10):1492–1502.
8. Diener HC, Kronfeld K, Boewing G, et al.; GERAC Migraine Study Group. Efficacy of acupuncture for the prophylaxis of migraine: A multicentre randomised controlled clinical trial. *Lancet Neurol.* 2006;5(4):310–316.
9. Allais G, De Lorenzo C, Quirico PE, Airola G, Tolardo G, Mana O, Benedetto C. Acupuncture in the prophylactic treatment of migraine without aura: A comparison with flunarizine. *Headache.* 2002;42(9):855–861.
10. Facco E, Liquori A, Petti F, Fauci AJ, Cavallin F, Zanette G. Acupuncture versus valproic acid in the prophylaxis of migraine without aura: A prospective controlled study. *Minerva Anestesiol.* 2013;79(6):634–642.
11. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev.* 2009;1:CD001218.
12. Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders, 3rd edition* (beta version). *Cephalalgia.* 2013;33(9):629–808.
13. Higgins JP, Altman DG, Gøtzsche PC, et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
14. Guyatt G, Oxman AD, Akl EA., et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–394.
15. Frenken CW, Nuijten ST. Flunarizine, a new preventive approach to migraine: A double-blind comparison with placebo. *Clin Neurol Neurosurg.* 1984;86(1):17–20.
16. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. *Headache.* 1981; 21(6):235–239.
17. Mendenopoulos G, Manafi T, Logothetis I, Bostantjopoulou S. Flunarizine in the prevention of classical migraine: A placebo-controlled evaluation. *Cephalalgia.* 1985;5(1):31–37.
18. Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalalgia.* 1986;6(1):7–14.
19. Sorge F, De Simone R, Marano E, Nolano M, Orefice G, Carrieri P. Flunarizine in prophylaxis of childhood migraine: A double-blind, placebo-controlled, crossover study. *Cephalalgia.* 1988;8(1):1–6.
20. Lepcha A, Amalanathan S, Augustine A, Tyagi AK, Balraj A. Flunarizine in the prophylaxis of migrainous vertigo: A randomized controlled trial. *Eur Arch Otorhinolaryngol.* 2013; 271(11):2931–2936.
21. Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Kristensen TN, de Fine Olivarius B. Prophylactic treatment of classical and non-classical migraine with metoprolol—a comparison with placebo. *Cephalalgia.* 1983;3(4):207–212.
22. Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: Parallel-groups comparison with placebo and dose-ranging follow-up. *Headache.* 1988;28(1): 15–23.
23. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev.* 2013;6: CD010611.
24. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: A double-blind study versus placebo. *Cephalalgia.* 1992;12(2):81–84.
25. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. *Neurology.* 1994;44(4): 647–651.
26. Porter RS, Kaplan JL; Merck & Co. *Merck Manual of Diagnosis and Therapy, 19th ed.* Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2011.
27. Zheng YC, Yuan TT, Liu T. Is acupuncture a placebo therapy? *Complement Ther Med.* 2014;22(4):724–730.

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(Appendix follows→)

Appendix

Appendix Table A1. Search Strategies

Cochrane Library <Beginning to 2016 July 11>
Acupuncture vs. Conventional Treatment Search Strategy:

D	Search	Hits
#1	MeSH descriptor: [Acupuncture Therapy] explode all trees	3787
#2	MeSH descriptor: [Migraine Disorders] explode all trees	1832
#3	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	39
#4	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	28
#5	headach*	21148
#6	conventional treatmen*	21120
#7	MeSH descriptor: [Drug Therapy] explode all trees	126895
#8	MeSH descriptor: [Drug Therapy, Combination] explode all trees	40281
#9	migraine frequenc*	907
#10	migraine attac*	1398
#11	#2 or #3 or #4 or #5	21633
#12	#6 or #7 or #8	144326
#13	#9 or #10	1849
#14	#1 and #11 and #12 and #13 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	8

Cochrane Library <Beginning to 2016 July 11>
Flunarizine vs. Placebo Search Strategy:

D	Search	Hits
#1	MeSH descriptor: [Migraine Disorders] explode all trees	1832
#2	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	39
#3	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	28
#4	headach*	21148
#5	MeSH descriptor: [Flunarizine] explode all trees	127
#6	placebo	180379
#7	migraine frequenc*	907
#8	migraine attac*	1398
#9	#1 or #2 or #3 or #4	21633
#10	#7 or #8	1849
#11	#5 and #6 and #9 and #10 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	21

Cochrane Library <Beginning to 2016 July 11>
Metoprolol vs. Placebo Search Strategy:

D	Search	Hits
#1	MeSH descriptor: [Migraine Disorders] explode all trees	1832
#2	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	39
#3	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	28
#4	headach*	21148
#5	MeSH descriptor: [Metoprolol] explode all trees	1419
#6	placebo	180379
#7	migraine frequenc*	907
#8	migraine attac*	1398
#9	#1 or #2 or #3 or #4	21633
#10	#7 or #8	1849
#11	#5 and #6 and #9 and #10 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	7

Cochrane Library <Beginning to 2016 July 11>
Valproic Acid vs. Placebo Search Strategy:

D	Search	Hits
#1	MeSH descriptor: [Migraine Disorders] explode all trees	1832
#2	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	39
#3	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	28
#4	headach*	210148
#5	MeSH descriptor: [Valproic Acid] explode all trees	734
#6	placebo	180379
#7	migraine frequenc*	907
#8	migraine attac*	1398
#9	#1 or #2 or #3 or #4	21633
#10	#7 or #8	1849
#11	#5 and #6 and #9 and #10 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	16

MeSH, Medical Subject Headings.
*A symbol used to broaden the search by obtaining variations of words that have the same letters prior to it.