Systematic Review and Meta-Analysis

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Flunarizine as prophylaxis for episodic migraine: a systematic review with meta-analysis

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Abstract

Based on few clinical trials, flunarizine is considered a first-line prophylactic treatment for migraine in several guidelines. In this meta-analysis, we examined the pooled evidence for its effectiveness, tolerability, and safety. Prospective randomized controlled trials of flunarizine as a prophylaxis against migraine were identified from a systematic literature search, and risk of bias was assessed for all included studies. Reduction in mean attack frequency was estimated by calculating the mean difference (MD), and a series of secondary outcomes—including adverse events (AEs)—were also analyzed. The database search yielded 879 unique records. Twenty-five studies were included in data synthesis. We scored 31/175 risk of bias items as "high," with attrition as the most frequent bias. A pooled analysis estimated that flunarizine reduces the headache frequency by 0.4 attacks per 4 weeks compared with placebo (5 trials, 249 participants: MD −0.44; 95% confidence interval −0.61 to −0.26). Analysis also revealed that the effectiveness of flunarizine prophylaxis is comparable with that of propranolol (7 trials, 1151 participants, MD −0.08; 95% confidence interval −0.34 to 0.18). Flunarizine also seems to be effective in children. The most frequent AEs were sedation and weight increase. Meta-analyses were robust and homogenous, although several of the included trials potentially suffered from high risk of bias. Unfortunately, reporting of AEs was inconsistent and limited. In conclusion, pooled analysis of data from partially outdated trials shows that 10-mg flunarizine per day is effective and well tolerated in treating episodic migraine—supporting current guideline recommendations.

Keywords: Migraine, Headache, Flunarizine, Sibelium, Pharmacological prophylaxis, Pooled analysis, Systematic review, Meta-analysis

1. Introduction

Flunarizine is one of many prophylactic treatment options for episodic migraine. The drug is a nonselective calcium entry blocker acting on slow calcium channels.[1,46] It was presented some 30 years ago as a prophylactic drug in migraine treatment[3] but has not attained the same popularity as other cardiovascular drugs prescribed for migraine prophylaxis. Still, flunarizine is largely regarded as effective, inexpensive, and easy to use with its once-daily dosing. Adverse events (AEs) are regarded as infrequent, with weight increase and somnolence as the most common, whereas depression and extrapyramidal symptoms are the most feared.[50,63] Flunarizine is recommended in headache treatment guidelines in several countries[12,41,57] and is also considered a first treatment choice by the European Federation of Neurologic Societies.[17] However, despite these recommendations, flunarizine is not readily available in many countries.[62]

In addition to the limited availability of the drug, the guidelines recommending flunarizine are primarily based on individual clinical trials.[4–7,9,13–15,19,22,35,44,52] All but one of these trials are over 20 years old and many of them do not adhere to current guidelines of clinical trials and migraine diagnosis.[25,59,60] To address this problem, we believe that there is a need for a systematic review of the topic—providing pooled estimates on effectiveness, tolerability, and safety, and describing the quality of trials and their risk of bias.

The primary aims of this meta-analysis are: (1) to retrieve and describe the scientific quality of randomized controlled trials (RCTs) investigating flunarizine as migraine prophylaxis; and (2) to assess the pooled evidence of effectiveness, tolerability, and safety in these trials.

2. Methods

2.1. Protocol

A protocol for the systematic review was registered at PROSPERO international prospective register of systematic reviews. Protocol number: CRD42017057670, available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017057670.

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2.2. Criteria for considering studies for this review

2.2.1. Types of studies

Eligible studies were required to be prospective, randomized, or pseudo-RCTs, evaluating the use of flunarizine as a prophylactic drug for episodic migraine. Studies without an explicit description as randomized were excluded. Studies were also required to be published in papers and available in typing with Latin alphabet.

2.2.2. Types of participants

Included studies were not required to have strictly applied the International Headache Society diagnostic criteria[24,25] as long as the migraine diagnoses were based on their list of distinctive features, such as nausea/vomiting, severe pain, pulsating pain, unilaterality, photophobia/phonophobia, or aura. Trials combining migraine and other headache types were excluded.

2.2.3. Types of interventions

The included studies were required to have at least one treatment arm where participants received flunarizine regularly during headache-free intervals to reduce the migraine burden. Acceptable comparison groups included placebo or other pharmacological and nonpharmacological treatments with proven efficacy. Overuse of acute medication among trial participants led to exclusion of said trial.

2.2.4. Types of outcomes

The primary outcome of interest was mean reduction in migraine frequency. Secondary outcomes included proportion of responders (≥50% reduction in migraine frequency), intensity and duration of migraine headache, doses of acute medication, disability, quality of life, and AEs.

2.3. Search strategies

We conducted a database search across the databases MEDLINE, Embase, and CENTRAL with assistance of a medical research librarian.[48] The query involved a combination of thesaurus and free-text terms optimized to identify RCTs on patients with migraine receiving flunarizine treatment (Supplemental digital content 1, available at http://links.lww.com/PAIN/A702). A search filter optimized for detecting clinically sound treatment studies was used when searching in MEDLINE[23] and Embase.[67] To identify other potentially relevant studies, references listed in reviews on flunarizine were also hand searched.

2.4. Data collection and management

Two of the authors independently screened the search results through titles and abstracts and compared their finding. Full-text files of the potentially eligible references were retrieved and reviewed for inclusion. Near-eligible studies were reported with reasons for exclusion. Two of the reviewers extracted data independently (using data collection forms from previous Cochrane reviews on antiepileptics in migraine[32–34]), before comparing and reconciling their findings. Disagreements were resolved through discussion.

Migraine frequency was converted to number of days or attacks per 28-day (4-week) period, and migraine intensity scores were converted to a 4-point scale to facilitate comparison across studies. We extracted data from tables and figures, and converted precision and variance data where appropriate and possible. We anticipated that endpoints such as "headache index"[60] would be reported in a variety of ways—often by combining outcomes. We used such endpoints only if they could be converted to one of our desired outcomes. We chose to focus analyses on the third month of treatment and onwards as recommended by guidelines.[60] For continuous data, we preferred end-of-treatment values over change scores, and extracted change scores only if final values were unavailable.[26] From cross-over trials, we extracted data from the pre–cross-over period to analyze these as parallel group trials. In cases where data on variance were still unavailable after attempts to calculate estimated variances based on primary data, we imputed variance data as the median value of variance data from the other studies. Sensitivity analyses were conducted by excluding studies with missing data. In cases where different studies reported AE synonyms, these were pooled into preferred-term categories as defined in the Medical Dictionary for Regulatory Activities (MedDRA) by the World Health Organization. Characteristics of included studies were summarized with description of the study design, interventions, participants, outcomes, and risk of bias assessments.

2.5. Data synthesis

Meta-analyses and figures were made using Review Manager (RevMan 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For continuous outcome data, the mean difference (MD) with 95% confidence intervals (CIs) was calculated using an inverse variance fixed-effects model. In cases where outcome scales varied within the same analysis, and were not feasible to convert, the standardized MD (SMD) was used. For dichotomous data, we calculated odds ratios (ORs) with 95% CI, using a fixed-effects Mantel–Haenszel model. For AEs, we calculated the risk difference (RD) with 95% CI. We additionally computed numbers needed to treat to benefit and numbers needed to treat for an additional harmful outcome (NNTH) for dichotomous data. Subgroup analyses were made of different drug doses. Statistical heterogeneity was also calculated for each meta-analysis and addressed in cases where it was deemed problematic.

In cases where only one study was available, we calculated the MD in migraine frequency or OR for response to treatment (in case migraine frequency was not reported).

2.6. Risk of bias assessment

All included studies were evaluated for risk of bias. We used the Cochrane Collaboration risk assessment tool, assigning bias categories to "low," "unclear," or "high" risk. The bias categories were: sequence generation/randomization; allocation concealment; blinding; blinding of outcome assessment; reporting of incomplete outcome data; evidence of selective outcome reporting; and other potential risks of bias.

We also planned for creating and analyzing funnel plots, but such analyses were not deemed appropriate, as the number of studies for each analysis was too low.

3. Results

3.1. Search results

Figure 1 shows the flow of study selection. The database search updated to November 13, 2017, yielded 879 records after

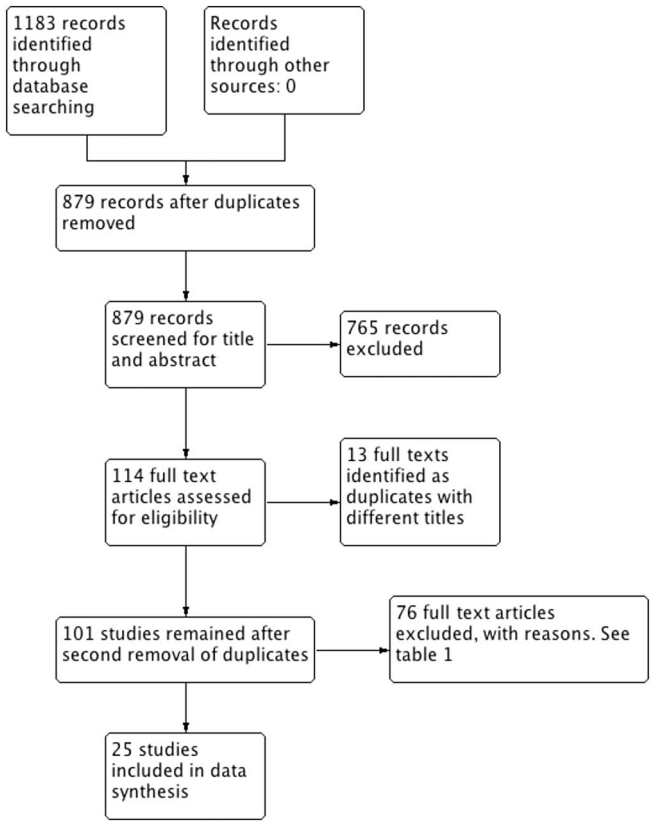

Figure 1. Study flow diagram.

removal of duplicates. Of these, 765 were excluded through screening of titles and abstracts. After reviewing the remaining 114 full texts, 13 were identified as duplicates with different titles. Twenty-five of the 101 unique studies met all the eligibility criteria and were included in data synthesis, whereas the remaining 76 were excluded with stated reason (Supplemental digital content 2, available at http://links.lww.com/PAIN/A702). A summary of the characteristics of the included studies is presented in **Table 1** (comprehensive characteristics in Supplemental digital content 3, available at http://links.lww.com/PAIN/A702).

3.2. Risk of bias

Of 175 risk of bias items scored, 34.3% were deemed as low, 48.0% as unclear, and 17.7% as high (**Fig. 2**). At least one "high risk" score was assigned to 19 of the 25 studies (**Fig. 3**). A "low risk" of selection bias score was assigned to 6 studies[2,15,42,47,65,66] providing a description of a computer-generated randomization and 2 studies[15,66] providing a description of appropriate allocation concealment—the remaining selection bias judgments were of "unclear risk." "Low risk" of performance bias was assigned to 3 studies[52,54,66] providing an accurate description of blinding procedures, whereas 6 studies[2,37,38,43,53,65] were deemed to have insufficient blinding of participants and personnel, and thus a "high risk" of bias. Three studies provided sufficient description of blinding of outcome assessors.[2,37,66] Ten studies[8,13,22,38,42,47,53–56] assigned a "high risk" of attrition bias because they made completers-only analyses without reporting reasons for withdrawals, or because reasons for withdrawal were associated with the outcome. Five additional studies[2,10,36,43,58] provided completers-only analyses with limited attrition, or the reported reasons for attrition were not associated with the outcome—these bias categories were rated as "unclear risk." Furthermore, 12 of the studies were assigned a "high risk" of selective reporting. Finally, 2 studies were assigned a "high risk" of other bias—one for only including women and[2] the other for only including previous responders to migraine prophylactics.[13]

3.3. Data analysis

Frequency data were extracted from figures in 3 publications[22,54,58] and converted to 28-day periods in 4 studies.[13,35,45,53] Data for responders to treatment were extracted from figures in 4 studies.[20,35,37,42] Data on headache intensity were required to be extracted from a figure in one study[2] and converted to a 4-point Likert-scale (0-3) in 3 other studies.[22,37,66] Use of abortive medication was reported as number of attacks treated with abortive medication in one study[15] and as number of analgesic doses in another study.[37] This necessitated estimating the SMD. On the other hand, 2 trials comparing flunarizine with acupuncture[2,66] reported drug consumption as number of participants stopping abortive drug use, allowing for estimation of OR. Quality-of-life measures were analyzed as SMD because the 2 studies that reported quality of life used different scales.[65,66]

Eighteen of 25 studies provided 10-mg doses of flunarizine; 3 used different doses at 5,[38] 15,[10] and 20 mg[65]; one[15] investigated 5 mg vs 10 mg; whereas the 3 pediatric studies[39,53,54] provided 5-mg doses. All the placebo-controlled trials in adults used 10-mg doses. Propranolol doses varied throughout studies. Subgroup analyses depending on dosage of propranolol were made for migraine frequency to ensure detailed analyses of the primary outcome. On the other hand, propranolol doses were merged for analyses of headache intensity, headache duration, and drug consumption, as fewer studies reported these outcomes.

3.4. Results of analyses

3.4.1. Flunarizine vs placebo

Flunarizine was superior to placebo in reducing migraine frequency after 3 months of active treatment (MD −0.44; 95% CI −0.61 to −0.26; **Fig. 4**) in the pooled analysis of 5 studies (249 participants[13,20,35,45,58]). A sensitivity analysis ignoring trials with imputed data[20,58] produced a similar estimate (MD −0.43; 95% CI −0.60 to −0.25). Flunarizine also showed higher responder proportion than placebo (OR 8.86; 95% CI 3.57-22.0; **Fig. 5**) in the pooled analysis of 3 studies (113 participants[20,35,42]). The number needed to treat to benefit was 3 (95% CI 2-4), based on an assumed control risk of 0.28 calculated from the baseline migraine frequency of the control groups.

3.4.2. Flunarizine direct dose comparisons

A single study (524 participants[15]) comparing 5-mg vs 10-mg doses of flunarizine revealed no difference in effect on headache frequency after 4 months of active treatment (MD 0.20; 95% CI −0.08 to 0.48).

3.4.3. Flunarizine vs propranolol

No difference between 10-mg flunarizine and all doses of propranolol (60-160 mg) was observed after 4 months of active treatment (MD −0.08; 95% CI −0.34 to 0.18; **Fig. 6**) in the pooled analysis of 7 studies (1151 participants[8,15,22,37,51,55,56]). A sensitivity analysis ignoring trials with imputed data[8,22,51] showed

Table 1

Characteristics of included studies in summary.

Allais et al.[2]	Methods	Prospective, open RCT.
	Participants	Migraine without aura diagnosis according to IHS criteria. 160 participants; 150 completers; mean age 37.8 years; 160 females.
	Interventions	Flunarizine 10 mg/day vs acupuncture.
	Outcomes	1, 3, 5, and 8.
Bordini et al.[8]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 45 participants; 38 completers; mean age 31.2 years; 41 females and 4 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 60 mg/day vs flunarizine + propranolol 10 mg/day + 60 mg/day.
	Outcomes	1 and 8.
Cerbo et al.[10]	Methods	Prospective, double-blind RCT.
	Participants	Characteristic migraine symptoms. 30 participants; 27 completers; age range 23 to 54 years; 14 females and 16 males.
	Interventions	Flunarizine 15 mg/day vs pizotifen 1.5 mg/day.
	Outcomes	8.
Diamond and Freitag[13]	Methods	Prospective, double-blind RCT.
	Participants	Two-year migraine history. 143 participants; 101 completers; mean age 35 years; 75 females and 26 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Diener et al.[15]	Methods	Prospective, double-blind RCT.
	Participants	Inclusion criteria: migraine as defined by IHS. 810 participants; 783 included in intention to treat analysis; median age 37 years; 658 females and 150 males.
	Interventions	Flunarizine 5 mg/day vs flunarizine 10 mg/day vs propranolol 160 mg/day.
	Outcomes	1, 2, 4, 5, and 8.
Frenken and Nuijten[20]	Methods	Prospective, double-blind RCT.
	Participants	Common or classic migraine as defined by IHS. 35 participants; 35 completers; age range 20 to 51 years; 29 females and 6 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1, 2, and 8.
Gawel et al.[22]	Methods	Prospective, double-blind RCT.
	Participants	Migraine headache as defined by the World Federation of Neurology Research Group. 94 participants; 89 completers; mean age 35.7 years; 85 females and 9 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 160 mg/day.
	Outcomes	1, 3, 4, and 8.
Louis[35]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with throbbing or pulsating attacks. 58 participants; 58 completers; mean age 29 years; 29 females and 29 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1, 2, and 8.
Louis and Spierings[36]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine diagnosed according to IHS criteria. 75 participants; 72 completers; mean age 37 years; 40 females and 32 males.
	Interventions	Flunarizine 10 mg/day vs pizotifen 2 to 3 mg/day.
	Outcomes	1 and 8.
Ludin[37]	Methods	Prospective, double-blind RCT.
	Participants	Headache attacks with characteristic features of migraine. 71 participants; 48 completers; mean age 34.3 years; 51 females and 20 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 2, 3, 4, 5, and 8.
Luo et al.[38]	Methods	Prospective, open RCT.
	Participants	Migraine diagnosis according to IHS criteria. 150 participants; 126 completers; mean age 43 years; 90 females and 36 males.
	Interventions	Flunarizine 5 mg/day vs topiramate 25 to 100 mg/day vs flunarizine + topiramate 5 mg/day + 25 to 100 mg/day.
	Outcomes	1 and 8.
Lutschg and Vassella[39]	Methods	Prospective, double-blind RCT.
	Participants	Children with classic or common migraine with characteristic migraine symptoms. 33 participants; 32 completers; mean age 10.5 years; 17 females and 16 males.
	Interventions	Flunarizine 5 to 10 mg/day vs propranolol 30 to 120 mg/day.
	Outcomes	1 and 8.

(*continued on next page*)

Table 1 (*continued*)

Mentenopoulos et al.[42]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 30 participants; 15 completers; median age 44 years; 16 females and 4 males.
	Interventions	Flunarizine 10 mg/day vs placebo
	Outcomes	2 and 8.
Mitsikostas and Polychronidis[43]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 44 participants; 41 completers; mean age 36.1 years; 31 females and 13 males.
	Interventions	Flunarizine 10 mg/day vs sodium valproate 1000 mg/day.
	Outcomes	2 and 8.
Pini et al.[45]	Methods	Prospective, double-blind RCT.
	Participants	Diagnosis of classic or common migraine. 20 participants; 29 completers; mean age 39.5 years; 24 females and 5 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Rascol et al.[47]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 35 participants; 32 completers; median age 38 years; 25 females and 10 males.
	Interventions	Flunarizine 10 mg/day vs pizotifen 2.19 mg/day.
	Outcomes	1 and 8.
Shimell et al.[51]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 58 participants; 49 completers; mean 34.5 years; 40 females and 17 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 180 mg/day.
	Outcomes	1 and 8.
Sorge and Marano[53]	Methods	Prospective, double-blind RCT.
	Participants	Children with migraine diagnosed according to the Valquist criteria. 48 participants; 42 completers; mean age 10.6 years; 27 females and 21 males.
	Interventions	Flunarizine 5 mg/day vs placebo.
	Outcomes	1, 4, and 8.
Sorge et al.[54]	Methods	Prospective, double-blind cross-over trial.
	Participants	Children with migraine diagnosed according to the Valquist criteria. 70 participants; 63 completers; mean age 10.6 years; 36 females and 34 males.
	Interventions	Flunarizine 5 mg/day vs placebo.
	Outcomes	1, 4, and 8.
Soyka and Oestreich[55]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with characteristic features. 87 participants; 69 completers; mean age 42.5 years; 51 females and 18 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 4, and 8.
Soyka and Oestreich[56]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with characteristic features. 434 participants; 336 completers; mean age 42 years; 265 females and 61 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 4, and 8.
Sørensen et al.[58]	Methods	Prospective, double-blind cross-over trial.
	Participants	Migraine diagnosis according to IHS criteria, modified by Olesen et al. 29 participants; 27 completers; median age 40 years; 23 females and 6 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Sørensen[52]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 149 participants; 127 completers; median age 42 years; 118 females and 31 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1 and 8.
Vijayalakshmi et al.[65]	Methods	Prospective, open RCT.
	Participants	Migraine diagnosis according to IHS criteria. 60 participants.
	Interventions	Flunarizine 20 mg/day vs acupuncture.
	Outcomes	6.
Wang et al.[66]	Methods	Prospective single-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 140 participants; 120 completers; mean age 39.5 years; 119 females and 21 males.
	Interventions	Flunarizine 10 mg/day vs acupuncture.
	Outcomes	1, 3, 5, 6, and 8.

1 = migraine frequency; 2 = responders to treatment; 3 = migraine intensity; 4 = headache duration; 5 = drug consumption; 6 = quality of life; 7 = disability; 8 = adverse events.
IHS, International Headache Society; RCT, randomized controlled trial.

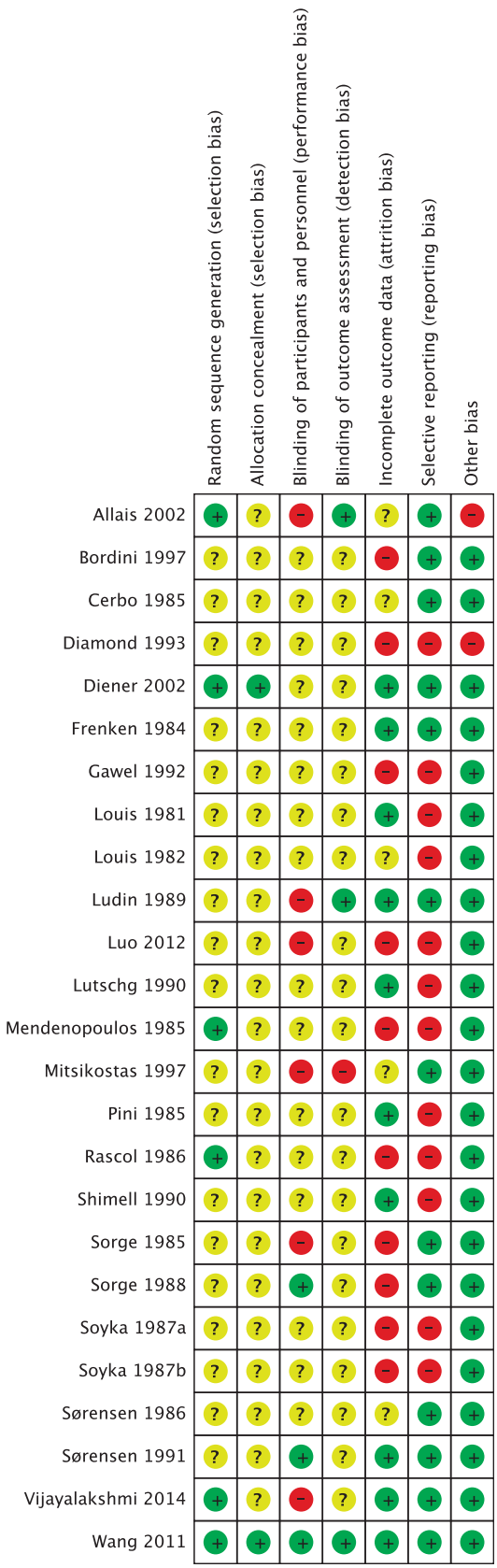

Figure 2. Distribution of risk of bias assessments, presented as percentages across all included studies.

a similar result (MD −0.07; 95% CI −0.33 to 0.20). **Figure 6** shows the effect estimates for different doses of propranolol. A pooled analysis of 2 trials comparing responders to treatment (581 participants[15,37]) revealed no difference between the 2 drugs (OR 1.19; 95% CI 0.86-1.64). Using an assumed control risk from the control groups in the included studies, at 0.19, the number needed to treat to benefit in favor of flunarizine was 36 (CI not defined).

For secondary outcomes in flunarizine vs propranolol trials, 2 studies (135 participants[22,37]) showed no difference in intensity of migraine attacks after 4 months of treatment (MD 0.22; 95% CI −0.12 to 0.57); 5 studies (1063 participants[15,22,37,55,56]) showed no difference in headache duration after 4 months of treatment (MD 0.60; 95% CI −1.48 to 2.69); and 2 studies (583 participants[15,37]) demonstrated no difference in use of abortive drugs between the groups (SMD 0.07; 95% CI −0.09 to 0.23).

3.4.4. Flunarizine vs pizotifen

Flunarizine was superior to pizotifen, with a larger percentage reduction in migraine frequency after 4 months of treatment (MD −7.86; 95% CI −22.82 to 7.11) in the pooled analysis of 2 studies.[36,47] A third[10] study was excluded from the analysis due to difference in flunarizine dosage and time point for data reporting.

3.4.5. Flunarizine vs drugs other than propranolol or pizotifen

A single trial (127 participants[52]) comparing flunarizine with metoprolol found no difference in migraine frequency after 3 months of treatment (MD −0.10; 95% CI −1.08 to 0.88). One study (41 participants[43]) comparing flunarizine with sodium valproate found no difference between the drugs (OR 1.07; 95% CI 0.28-4.12). A third parallel design and open trial (83 participants[38]) compared flunarizine with topiramate. At 3 months, no significant difference was found between the 2 treatments with respect to migraine frequency (MD −0.30; 95% CI −0.97 to 0.37).

3.4.6. Flunarizine vs acupuncture

Acupuncture was superior to flunarizine in reducing migraine frequency after 3 months of active treatment (MD 1.01; 95% CI 0.48-1.54) in the pooled estimate of 2 studies (290 participants[2,66]). Acupuncture treatment also had a better effect on migraine intensity (MD 0.26; 95% CI 0.06-0.46) and drug consumption (OR 0.41; 95% CI 0.21-0.77).

Pooled analysis of 2 studies (200 participants[65,66]) showed higher quality of life after one month of treatment in the acupuncture group compared with the flunarizine group with respect to both psychological (SMD 0.79; 95% CI 0.50-1.09) and physical domains (SMD 0.76; 95% CI 0.45-1.06).

3.4.7. Flunarizine in children

Two placebo-controlled trials (105 participants[53,54]) of flunarizine in children showed a reduction in migraine frequency after 3 months of active treatment (MD −1.14; 95% CI −1.51 to −0.77). The same 2 studies (105 participants) also found a shorter duration of headache in the flunarizine group (MD −0.46; 95% CI −0.77 to −0.16).

A single study (32 participants[39]) found flunarizine to be more efficient than propranolol in reducing migraine frequency in children after 3 months of treatment (MD −2.00; 95% CI −3.05 to −0.95). However, after 4 months of treatment, the children responded better to propranolol (MD 0.96; 95% CI 0.53-1.39).

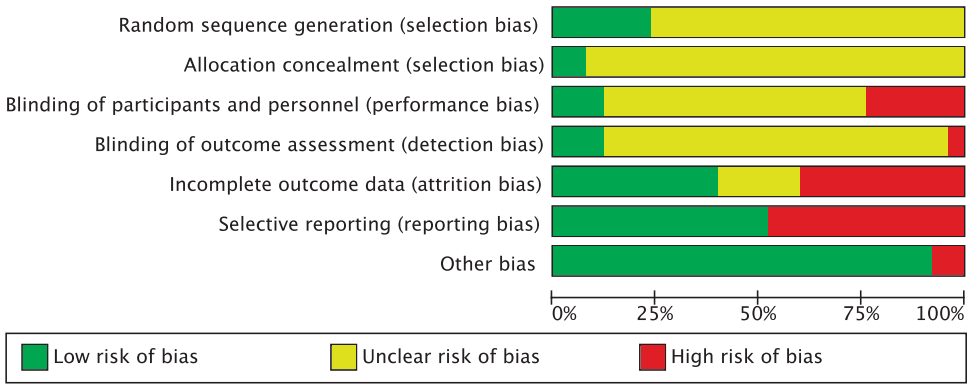

Figure 3. Judgment for each risk of bias item for each included study.

3.4.8. Safety and tolerability

Adverse events were reported in 3 of 6 placebo-controlled trials. Flunarizine users did not have higher risk of experiencing any one or more AEs, compared with placebo (RD 0.04; 95% CI −0.08 to 0.17; **Fig. 7**) in the pooled analyses of these trials.[20,35,42] The following mild-to-moderate AEs were reported in the placebo-controlled trials: Weight gain (NNTH 6; CI not defined); daytime sedation (NNTH 8; 95% CI 4-50); stomach complaints (NNTH not defined); and dry mouth (NNTH not defined).

No serious AEs were reported in any of the placebo-controlled trials and only one flunarizine-treated participant withdrew due to AEs.[58] The single study[15] comparing doses of flunarizine found that 88 of 263 (33.5%) participants in the 5-mg group experienced one or more AEs, whereas 88 of 275 (32%) participants in the 10-mg group experienced one or more AEs.

None of the trials comparing flunarizine with active treatment reported any serious AEs. Six studies (1133 participants[8,15,22,51,55,56]) of flunarizine vs propranolol found no difference in the occurrence of any AEs (RD −0.04; 95% CI −0.09 to 0.02). **Figure 8** gives a summary of the frequency of AEs reported in more than one of the flunarizine vs propranolol trials. Two combined AE categories were created, the first including synonyms for sedation and somnolence, and the second including synonyms for fatigue and asthenia. The flunarizine vs pizotifen trials had insufficient reporting of AEs to allow for meta-analysis. Finally, 2 trials of flunarizine vs acupuncture (270 participants[2,66]) found a higher proportion of AEs among flunarizine users (RD 0.15; 95% CI 0.07-0.23).

Depression was only reported in 3 of 25 studies[2,15,52]—in total 2.9% (20/683) of the flunarizine users. In one of these studies, a flunarizine vs propranolol trial,[15] 7/263 of 5-mg dose flunarizine users and 2/275 of 10-mg flunarizine users experienced depression. Extrapyramidal symptoms were reported in 1 of 25 studies[52]—among 2.7% (2/74) of the flunarizine users during the run-in phase. No extrapyramidal symptoms were observed during or after flunarizine treatment in any of the included studies.

The reported data on AEs in the 2 placebo-controlled trials of flunarizine in children were insufficient for meta-analysis. One of these (48 participants[53]) reported that 3 of 24 participants discontinued due to AEs, whereas the other study (70 participants[54]) reported weight gain in 14 and drowsiness in 6 of all analyzed participants.

4. Discussion

Our meta-analysis shows that active flunarizine treatment reduces the migraine frequency by approximately 0.4 attacks per month compared with placebo (results from 5 studies with a median baseline migraine frequency of 3.4 attacks per month). To confirm our assumptions on imputing data, a sensitivity analysis was conducted, which showed no significant alteration in the result of the analysis. Migraine sufferers treated with flunarizine were also more likely to experience a 50% or greater reduction in headache frequency compared with placebo—one out of every 3 participants showed this response. Neither 5-mg nor 10-mg doses of flunarizine were superior in terms of effectiveness and tolerability. Flunarizine seems to be noninferior to propranolol, pizotifen, metoprolol, valproate, and topiramate in reduction in migraine frequency, but acupuncture seems to be more effective. Flunarizine seems to have the same risk of AEs as placebo, but the pooled data for this analysis were limited and included trials with potential bias. The most prominent AEs from the placebo-controlled trials were weight increase and daytime sedation, with NNTHs at 6 and 8, respectively.

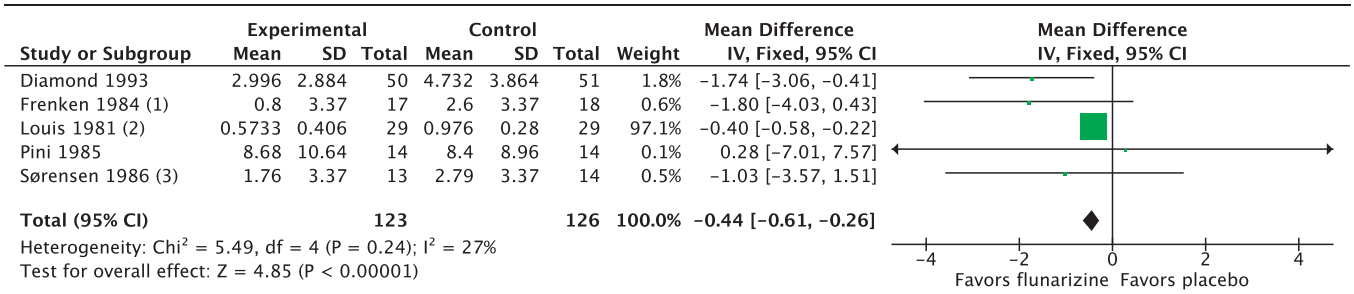

Figure 4. Forest plot of flunarizine vs placebo for migraine frequency. 95% CI, 95% confidence interval; (1), SDs imputed; (2), SD calculated from individual patient data; (3), point estimates extracted from figures; IV, inverse variance; SD, standard deviation.

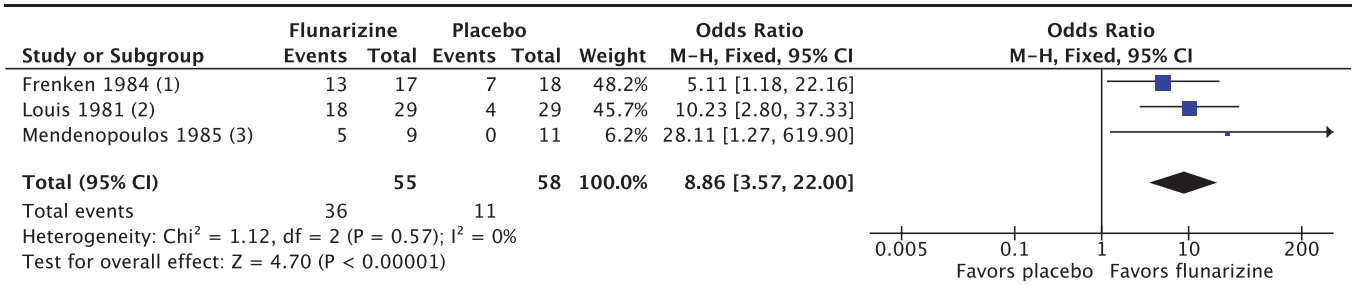

Figure 5. Forest plot of flunarizine vs placebo for responders to treatment (≥50% reduction in migraine frequency). 95% CI, 95% confidence interval; (1), data extracted from figures; (2), data extracted from figures; (3), data extracted from figures; M-H, Mantel-Haenszel.

Our main findings are in line with those of other systematic reviews. A Spanish meta-analysis from 2003,[49] including 4 RCTs, found that flunarizine reduced monthly migraine frequency with 0.55 compared with placebo. A network meta-analysis from 2015[28] also found an advantage of flunarizine over placebo, but because this study combined data on migraine frequency and headache index these findings are not directly comparable with ours. In addition, the meta-analysis also included a nonrandomized trial.[61]

Despite positive findings, most of the placebo-controlled trials currently available lack sufficient power to properly assess the effect size of the intervention. In fact, several of the studies are underpowered in their sample size, and none provides sample size calculations. A power analysis reveals that a sample size of 64 participants is required in each treatment arm to identify a significant difference given an effect size of 0.5 and a power of 0.8 at the 0.05 significance level.[27] Only one of the placebo-controlled parallel trials recruited more participants.[13] Similarly, the sample sizes for most individual trials investigating flunarizine vs active comparators were far too low, for noninferiority analysis.[30] Only one study[15] provided sample size calculations, concluding with a necessary sample size of over 260 participants per arm to prove that flunarizine was at least as effective as propranolol. Consequently, this study was weighed at 87.0% in the meta-analysis for headache frequency and highlights the importance of conducting sufficiently powered studies.

Flunarizine has acquired a reputation to induce depression and extrapyramidal symptoms.[11,16,18] Despite this, depression was rarely reported and extrapyramidal symptoms were not reported in any included studies during or after flunarizine treatment. We found daytime sedation and weight increase to be the most common AEs. This is in line with the results of a large open study with 1435 participants.[40] However, of the 6 placebo-controlled trials, only one reported weight increase[20] and 2 reported daytime sedation[20,35]—it is therefore possible that similar AEs may have gone unreported in other studies. In the propranolol analyses, we decided to analyze AEs reported by 2 or more trials. According to the hierarchical categorization of the MedDRA, several low-level term synonyms for AEs were reported in the included studies. We therefore chose to pool these into categories encompassing preferred terms within the same high-level categories. This resulted in 2 combined preferred-term categories. The first included somnolence and sedation synonyms representing AEs related to disturbances in consciousness, and the other included fatigue and asthenia synonyms representing asthenic conditions. Together, this serves to give a direct comparison of flunarizine

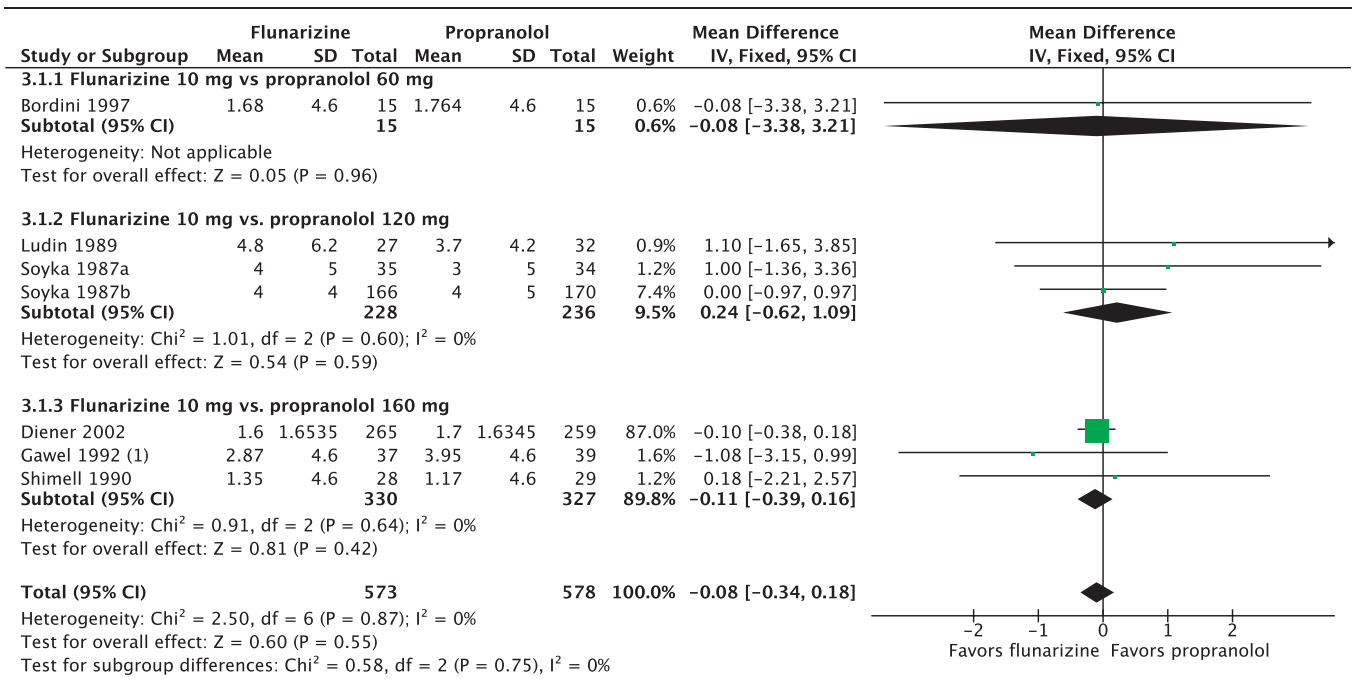

Figure 6. Forest plot of flunarizine vs propranolol for migraine frequency. 95% CI, 95% confidence interval; (1), data extracted from figures; IV, inverse variance; SD, standard deviation.

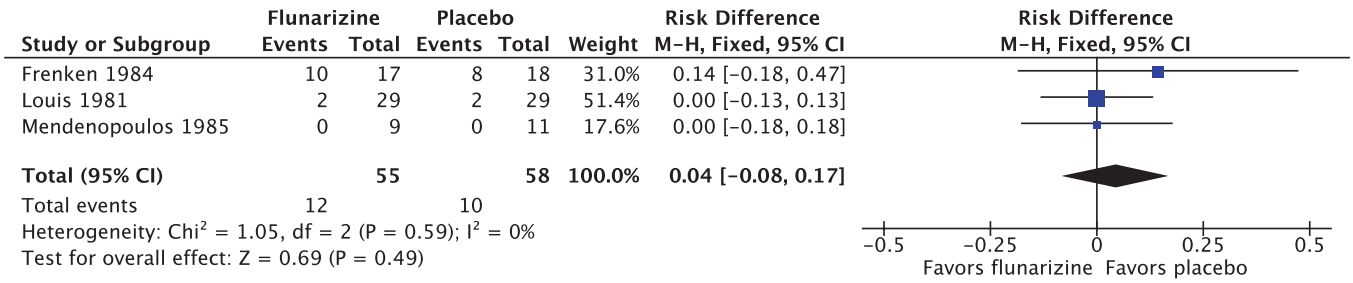

Figure 7. Forest plot of flunarizine vs placebo for adverse events. 95% CI, 95% confidence interval; M-H, Mantel-Haenszel.

AEs with those of the commonly used propranolol. Interestingly, flunarizine gives a higher risk of fatigue, whereas propranolol gives a higher risk of somnolence. Ultimately, flunarizine seems to be a well-tolerated alternative for patients with contraindications for beta blockers, such as obstructive pulmonary disease and bradyarrhythmias, but such diagnoses were excluded from several flunarizine vs propranolol trials.

Data on AEs in the pediatric trials were limited and lacked transparency. This makes us reluctant to draw conclusions and compare it with AE findings in the adult trials. Still, the most frequent AEs in children were, similarly as for adults, weight gain and drowsiness. Furthermore, many earlier systematic reviews and guidelines recommend flunarizine for children, with the same source of tolerability findings as we present in this article.[17,31,63,64] On the other hand, it is possible that these estimates are somewhat high as a recent retrospective study observed AEs in 10/166 (6.0%) pediatric flunarizine users.[29]

We took several steps to reduce between-study heterogeneity issues in this study. First, we used strict criteria for inclusion and avoided merging different drugs, populations, interventions, comparisons, and outcomes. We made the choice to strictly compare flunarizine to treatments with proven efficacy, which excluded studies with comparators such as dihydroergocryptine, dihydroergotamine, and calcium channel blockers.[17] In addition, the use of pragmatic criteria to define migraine in included studies, despite the fact that specific diagnose criteria have changed over the years, justifies pooling studies. Another strength is also that we translated papers from several other languages than English (16 different countries). Only a few Chinese papers were not translated, yet none of these studies had placebo or active drugs as controls, and we can conclude that the pooled estimates were unaffected. Finally, we have made comprehensive reviews, descriptions, and thorough assessments of risk of bias for all included studies.

A limitation of this review is the variability and incompleteness of data in the included studies. This required us to complete a series of conversions and calculations from scarce primary data to allow for pooled analysis of the eligible studies. In some studies, we also had to impute missing variance data. This is hypothesized not to introduce bias[21] but still makes the pooled estimate less certain. Nonetheless, omitting all studies with missing variance data could have yielded a biased point estimate because these studies may not be a random subset of all studies.[21] However, the sensitivity analyses indicate that the assumptions made on imputing data are valid. One should also keep in mind the limitations of the AE analyses due to heterogeneous and often incomplete reporting in many studies. For example, 2 studies[55,56] analyzed effectiveness of data only from participants with "accepted rating sheets" but still reported AEs from all participants. If we assume all dropouts were due to ineffectiveness, there could potentially be a large mismatch between the reported effect and the number of AEs. Similar attrition bias might also have been present in several of the included studies.

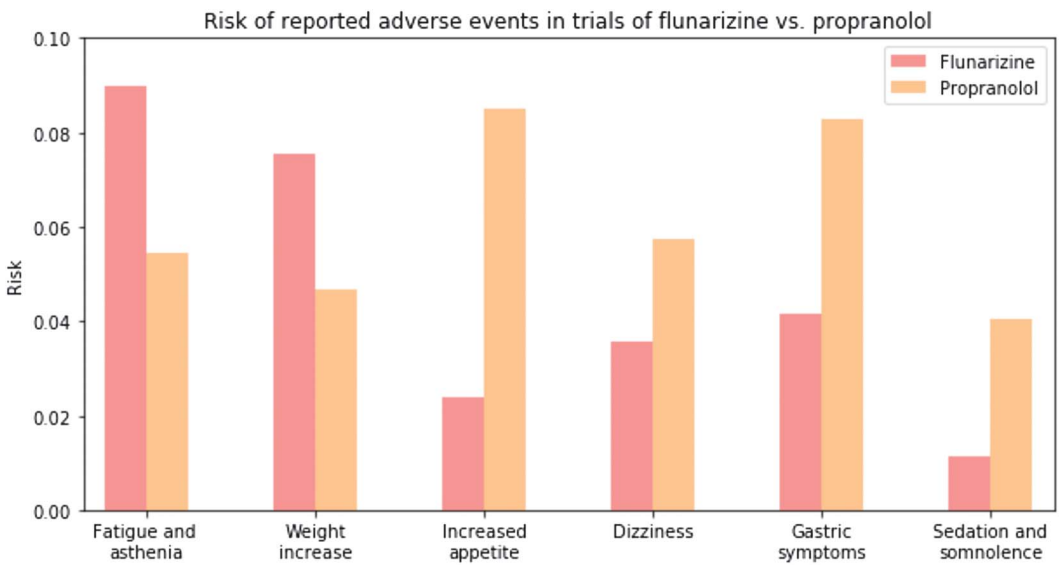

Figure 8. Distribution of adverse events reported in more than one study for trials of flunarizine vs propranolol. AEs, adverse events.

Current evidence indicates that 10-mg flunarizine is as effective as other well-established alternatives, such as propranolol, but with an AE profile focused on fatigue, somnolence, and weight increase. Guidelines give grade A recommendation to flunarizine as migraine prophylaxis, derived from results presented in individual and, to a large extent, old studies. This review supports this recommendation, but our conclusion is mainly based on the same sources. Methodological quality issues in the included studies—several of them involves substantial risks of bias—hamper us from concluding whether today's limited use of flunarizine represents healthy skepticism or a neglect of a subgroup of patients in need of additional prophylactic drug options. To avoid simply putting a new timestamp on something that is outdated, new placebo-controlled RCTs meeting the latest methodological standards are required.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A702.

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