# Flunarizine as Prophylaxis for Episodic Migraine: A Systematic Review with Meta-Analysis

**Authors**:

Anker Stubberud[1], Nikolai Melseth Flaaen[1], Douglas C. McCrory[2], MD, MHS, Sindre Andre Pedersen[3], PhD and Mattias Linde[1,4], MD, PhD

**Affiliations**:

[1]Department of Neuromedicine and Movement Sciences, NTNU Norwegian University of Science and Technology, Trondheim, Norway

[2]Duke Evidence Synthesis Group, Duke Clinical Research Institute; Department of Medicine, Duke University School of Medicine; and Center for Health Services Research in Primary Care, Durham Veterans Affairs Medical Center, Durham, North Carolina

[3]Library Section for Medicine and Health Sciences, NTNU University Library, NTNU Norwegian University of Science and Technology, Trondheim, Norway

[4]Norwegian Advisory Unit on Headaches, St. Olavs Hospital, Trondheim, Norway

**Corresponding Author**:

Anker Stubberud

Department of Neuroscience, Norwegian University of Science and Technology, Nevro Øst, Edvard Griegs gt 8, NO-7030, Trondheim, Norway

Telephone number: 004745229174

Email: ankers@stud.ntnu.no

Manuscript pages: 18

Number of figures: 8

Number of tables: 1

# Introduction

Flunarizine is one of many prophylactic treatment options for episodic migraine. The drug is a non-selective 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 are regarded as infrequent, with weight increase and somnolence as the most common, while depression and extrapyramidal symptoms are the most feared [50,64]. 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 [63].

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 [25,60,61]. 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 investigating flunarizine as migraine prophylaxis; and (2) assess the pooled evidence of effectiveness, tolerability and safety in these trials.


# Methods

### 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

**Criteria for considering studies for this review**

*Types of studies*

Eligible studies were required to be prospective, randomized or pseudo-randomized controlled trials (RCT) 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.

*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, photo-/phonophobia, or aura. Trials combining migraine and other headache types were excluded.

*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 non-pharmacological treatments with proven efficacy. Overuse of acute medication among trial participants led to exclusion of said trial.

*Types of outcomes*

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

**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 randomized

control trials (RCTs) on migraine patients receiving flunarizine treatment (Supplemental digital content 1). A search filter optimized for detecting clinically sound treatment studies was used when searching in MEDLINE [23] and Embase [68]. To identify other potentially relevant studies, references listed in reviews on flunarizine were also hand searched.

**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 (four-week) period, and migraine intensity scores were converted to a 4-point scale in order 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' [61] would be reported in a variety of ways – often by combining outcomes. We used such endpoints only if they could be convert to one of our desired outcomes. We chose to focus analyses on the third month of treatment and onwards as recommended by guidelines [61]. For continuous data we preferred end-of-treatment values over change scores, and extracted change scores only if final values were unavailable [26]. From crossover trials we extracted data from the pre-cross-over period to analyze these as parallel group trials. In cases where data on variance was 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 of analyses with imputed data were conducted by excluding studies with missing data. In cases were different studies reported AE synonyms these were pooled into preferred term categories as defined in the Medical Dictionary for Regulatory Activities (MedDRA) by the WHO. Characteristics of included studies were summarized with description of the study design, interventions, participants, outcomes and risk of bias assessments.

**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 (CI) 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 mean difference (SMD) was used. For dichotomous data, we calculated odds ratios (OR) 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. Sub-group 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).

**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.

# Results

**Search results**

Figure 1 shows the flow of study selection. The database search updated to November 13th 2017 yielded 879 records after 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, while the remaining 76 were excluded with stated reason (Supplemental digital content 2). A summary of the characteristics of the included studies is presented in Table 1 (comprehensive characteristics in Supplemental digital content 3).

**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 (Figure 2). At least one 'high risk' score was assigned to 19 of the 25 studies (Figure 3). A 'low risk' of selection bias score was assigned to six studies [2,15,42,47,66,67] providing a description of a computer-generated randomization, and two studies [15,67] providing a description of appropriate allocation concealment – the remaining selection bias judgments were of 'unclear risk'. 'Low risk' of performance bias was assigned to three studies [54,59,67] providing an accurate description of blinding procedures, while six studies [2,37,38,43,53,66] 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 [2,37,67]. 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 to the outcome – these bias categories were rated as 'unclear risk'. Furthermore, 12 of the studies were assigned a 'high risk' of selective reporting. Finally, two studies were assigned a 'high risk' of other bias – one for only including women [2], the other for only including previous responders to migraine prophylactics [13].

**Data analysis**

Frequency data were extracted from figures in three publications [22,54,58], and converted to 28-day periods in four studies [13,35,45,53]. Data for responders to treatment were extracted from figures in four 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 three other studies [22,37,67]. Use of abortive medication was reported as number of attacks treated with abortive medication in one

study [15], and as number of analgesics doses in another study [37]. This necessitated estimating the SMD. On the other hand, two trials comparing flunarizine to acupuncture [2,67] reported drug consumption as number of participants stopping abortive drug use, allowing estimation of OR. Quality of life measures were analyzed as SMD as the two studies that reported quality of life used different scales [66,67].

Eighteen of 25 studies provided 10 mg doses of flunarizine; three used different doses at 5mg [38], 15mg [10] and 20mg [66]; one [15] investigated 5 mg vs. 10 mg; while the three 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. Sub-group 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.

**Results of analyses**

*Flunarizine versus placebo*
Flunarizine was superior to placebo in reducing migraine frequency after three months of active treatment (MD -0.44; 95% CI -0.61 to -0.26; Figure 4) in the pooled analysis of five studies ([13,20,35,45,58]; 249 participants). 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 to 22.0; Figure 5) in the pooled analysis of three studies ([20,35,42]; 113 participants). The number needed to treat to benefit was three (95% CI 2 to 4), based on an assumed control risk of 0.28 calculated from the baseline migraine frequency of the control groups.

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

*Flunarizine versus propranolol*
No difference between 10 mg flunarizine and all doses of propranolol (60-160 mg) was observed after four months of active treatment (MD -0.08; 95% CI -0.34 to 0.18;

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Figure 6) in the pooled analysis of seven studies ([8,15,22,37,51,55,56]; 1,151 participants). A sensitivity analysis ignoring trials with imputed data [8,22,51] showed 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 two trials comparing responders to treatment ([15,37]; 581 participants) revealed no difference between the two drugs (OR 1.19; 95% CI 0.86 to 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 versus propranolol trials, two studies ([22,37]; 135 participants) showed no difference in intensity of migraine attacks after four months of treatment (MD 0.22; 95% CI -0.12 to 0.57); five studies ([15,22,37,55,56]; 1063 participants) showed no difference in headache duration after four months of treatment (MD 0.60; 95% CI -1.48 to 2.69); and two studies ([15,37]; 583 participants) demonstrated no difference in use of abortive drugs between the groups (SMD 0.07; 95% CI -0.09 to 0.23).

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

*Flunarizine versus drugs other than propranolol or pizotifen*
A single trial ([59]; 127 participants) comparing flunarizine to metoprolol found no difference in migraine frequency after three months of treatment (MD -0.10; 95% CI -1.08 to 0.88). One study ([43]; 41 participants) comparing flunarizine to sodium valproate found no difference between the drugs (OR 1.07; 95% CI 0.28 to 4.12). A third parallel design and open trial ([38]; 83 participants) compared flunarizine to topiramate. At three months, no significant difference was found between the two treatments with respect to migraine frequency (MD -0.30; 95% CI -0.97 to 0.37).

*Flunarizine versus acupuncture*
Acupuncture was superior to flunarizine in reducing migraine frequency after three months of active treatment (MD 1.01; 95% CI 0.48 to 1.54) in the pooled estimate of

two studies ([2,67]; 290 participants). Acupuncture treatment also had a better effect on migraine intensity (MD 0.26; 95% CI 0.06 to 0.46) and drug consumption (OR 0.41; 95% CI 0.21 to 0.77).

Pooled analysis of two studies ([66,67]; 200 participants) showed higher quality of life after one month of treatment in the acupuncture group compared to the flunarizine group with respect to both psychological (SMD 0.79; 95% CI 0.50 to 1.09) and physical domains (SMD 0.76; 95% CI 0.45 to 1.06).

*Flunarizine in children*
Two placebo-controlled trials ([53,54]; 105 participants) of flunarizine in children showed a reduction in migraine frequency after three months of active treatment (MD -1.14; 95% CI -1.51 to -0.77). The same two 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 ([39]; 32 participants) found flunarizine to be more efficient than propranolol in reducing migraine frequency in children after three months of treatment (MD -2.00; 95% CI -3.05 to -0.95). However, after four months of treatment, the children responded better to propranolol (MD 0.96; 95% CI 0.53 to 1.39).

*Safety and tolerability*
Adverse events (AEs) were reported in three of six placebo-controlled trials. Flunarizine users did not have higher risk of experiencing any one or more AEs, compared to placebo (RD 0.04; 95% CI -0.08 to 0.17; Figure 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 to 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, while 88 of 275 (32%) participants in the 10 mg group experienced one or more AEs.

None of the trials comparing flunarizine to active treatment reported any serious AEs. Six studies ([8,15,22,51,55,56]; 1133 participants) of flunarizine versus 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 versus 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 versus pizotifen trials had insufficient reporting of AEs to allow meta-analysis. Finally, two trials of flunarizine versus acupuncture ([2,67]; 270 participants) found a higher proportion of AEs among flunarizine users (RD 0.15; 95% CI 0.07 to 0.23).

Depression was only reported in three of 25 studies [2,15,59] – in total 2.9% (20/683) of the flunarizine users. In one of these studies, a flunarizine versus propranolol trial [15], 7/263 5 mg dose flunarizine users and 2/275 10 mg flunarizine users experienced depression. Extrapyramidal symptoms was reported in one of 25 studies [59] – 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 two placebo-controlled trials of flunarizine in children was insufficient for meta-analysis. One of these ([53]; 48 participants) reported that three of 24 participants discontinued due to AEs, while the other study ([54]; 70 participants) reported weight gain in 14 and drowsiness in 6 of all analyzed participants.

## Discussion

Our meta-analysis shows that active flunarizine treatment reduces the migraine frequency by approximately 0.4 attacks per month compared to placebo (results from five 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 to placebo – one out of every three

participant showed this response. Neither 5 mg nor 10 mg doses of flunarizine were superior in terms of effectiveness and tolerability. Flunarizine seems to be non-inferior 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 adverse events from the placebo-controlled trials was weight increase and daytime sedation, with NNTHs at 6 and 8, respectively.

Our main findings are in line with those of other systematic reviews. A Spanish meta-analysis from 2003 [49], including four RCTs, found that flunarizine reduced monthly migraine frequency with 0.55 compared to placebo. A network meta-analysis from 2015 [28] also found an advantage of flunarizine over placebo, but since this study combined data on migraine frequency and headache index these findings are not directly comparable to ours. In addition, the meta-analysis also included a non-randomized trial [62].

In spite of 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 in order 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 versus active comparators were far too low, for non-inferiority 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 1,435 participants [40]. However, of the six placebo-controlled trials, only one reported weight increase [20], and two 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 two 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 two 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 AEs to those of the commonly used propranolol. Interestingly, flunarizine gives a higher risk of fatigue, while 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 versus 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 paper [17,31,64,65]. 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. Firstly, 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 dihydroergocriptine, 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 has 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 in order to allow 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 as 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, two studies [55,56] analyzed effectiveness 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.

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 sub-group 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.

## Acknowledgements

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**Figure Legends**

Figure 1. Study flow diagram.

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

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

Figure 4. Forest plot of flunarizine versus placebo for migraine frequency. SD = standard deviation; 95% CI = 95% confidence interval; (1) = SDs imputed; (2) = SD calculated from individual patient data; (3) Point estimates extracted from figures. SDs imputed

Figure 5. Forest plot of flunarizine versus placebo for responders to treatment (≥50% reduction in migraine frequency). SD = standard deviation; 95% CI = 95% confidence interval; (1) = Data extracted from figures; (2) = Data extracted from figures; (3) = Data extracted from figures

Figure 6. Forest plot of flunarizine versus propranolol for migraine frequency. SD = standard deviation; 95% CI = 95% confidence interval; (1) = Data extracted from figures

Figure 7. Forest plot of flunarizine versus placebo for adverse events. SD = standard deviation; 95% CI = 95% confidence interval

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