A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache

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Abstract

Objective
To compare the effectiveness and side effects of migraine prophylactic medications.

Design
We performed a network meta-analysis. Data were extracted independently in duplicate and quality was assessed using both the JADAD and Cochrane Risk of Bias instruments. Data were pooled and network meta-analysis performed using random effects models.

Data Sources
PUBMED, EMBASE, Cochrane Trial Registry, bibliography of retrieved articles through 18 May 2014.

Eligibility Criteria for Selecting Studies
We included randomized controlled trials of adults with migraine headaches of at least 4 weeks in duration.

Results
Placebo controlled trials included alpha blockers (n = 9), angiotensin converting enzyme inhibitors (n = 3), angiotensin receptor blockers (n = 3), anticonvulsants (n = 32), beta-blockers (n = 39), calcium channel blockers (n = 12), flunarizine (n = 7), serotonin reuptake inhibitors (n = 6), serotonin norepinephrine reuptake inhibitors (n = 1) serotonin agonists (n = 9)
and tricyclic antidepressants (n = 11). In addition there were 53 trials comparing different drugs. Drugs with at least 3 trials that were more effective than placebo for episodic migraines included amitriptyline (SMD: -1.2, 95% CI: -1.7 to -0.82), flunarizine (-1.1 headaches/month (ha/month), 95% CI: -1.6 to -0.67), fluoxetine (SMD: -0.57, 95% CI: -0.97 to -0.17), metoprolol (-0.94 ha/month, 95% CI: -1.4 to -0.46), pizotifen (-0.43 ha/month, 95% CI: -0.6 to -0.21), propranolol (-1.3 ha/month, 95% CI: -2.0 to -0.62), topiramate (-1.1 ha/month, 95% CI: -1.9 to -0.73) and valproate (-1.5 ha/month, 95% CI: -2.1 to -0.8). Several effective drugs with less than 3 trials included: 3 ace inhibitors (enalapril, lisinopril, captopril), two angiotensin receptor blockers (candesartan, telmisartan), two anticonvulsants (lamotrigine, levetiracetam), and several beta-blockers (atenolol, bisoprolol, timolol). Network meta-analysis found amitriptyline to be better than several other medications including candesartan, fluoxetine, propranolol, topiramate and valproate and no different than atenolol, flunarizine, clomipramine or metoprolol.

**Conclusion**

Several drugs good evidence supporting efficacy. There is weak evidence supporting amitriptyline’s superiority over some drugs. Selection of prophylactic medication should be tailored according to patient preferences, characteristics and side effect profiles.

**Introduction**

Migraine headaches are common, with a worldwide prevalence ranging between 8 and 18% [1–7]. Migraines cause significant disability [8–11], even during periods between attacks [12], and are responsible for $1 billion in medical costs and $16 billion in lost productivity per year [13,14] in the US alone. The diagnostic criteria for migraine headaches have evolved over time. Currently, the International Headache Society (IHS) diagnostic criteria for migraine includes having at least 5 attacks that last 4–72 hours, that are unilateral, pulsating, moderate or severe in intensity and aggravated by or cause avoidance of routine physical activity and are also accompanied by nausea and/or vomiting, photophobia or phonophobia [15]. IHS further classifies migraine as with or without an aura and as episodic or chronic. Chronic migraine is defined as more than 15 migraine headaches per month for more than 3 months. Chronic migraines result in significantly greater disability than episodic migraines[16].

Treatment of headaches can be either abortive or prophylactic. Abortive treatment provides symptom relief for the acute headache [17,18], while prophylactic treatment aims to reduce the frequency or severity of headaches over time. We focus on prophylactic migraine headache treatment in this manuscript. There are a large number of prophylactic treatment options available; common ones include alpha antagonists, anti-convulsants [19], beta-blockers [20], botulinum-A [21], calcium channel blockers [22], serotonin agonists[23], serotonin reuptake inhibitors (SSRIs) [24] and tricyclic antidepressants (TCAs) [25]. Two emerging prophylactic candidates are angiotensin converting enzymes (ACE) and angiotensin receptor antagonists (ARB). Unfortunately nearly half of males and a third of females who are candidates for prophylactic therapy do not receive it [26]. Selection of prophylactic treatment is tailored on individual patient characteristics, costs and side effects of the available options. However, for patients and their providers, the decision about which prophylactic regimen to use is hampered by the lack of head to head trials comparing the different classes of medications. In addition,
previous systematic reviews have focused on single classes of drugs. Two recent systematic reviews that looked more broadly at different drug options have been published. One only included studies since 1999 and did not pool any results, providing qualitative statements about relative treatment effectiveness [27]. Another review analyzed focused only on dichotomous outcomes among patients with episodic migraines and found no difference in likelihood of experiencing at least 50% improvement in headaches between different classes of oral medications [28]. Previous systematic reviews have also had methodological problems. Some combine outcomes from the end of the study, regardless of study duration. This inappropriately combines study results at markedly different time points. This also tends to overstate the strength of the evidence by making it appear that there are more studies contributing data to the results and produces inappropriately narrow confidence intervals. We conducted a meta-analysis asking what is the comparative effectiveness and side effects of the prophylactic treatment of migraine headaches in adults using oral pharmacological medications.

**Materials and Methods**

This report closely adheres to the PRISMA guidelines for conducting a systematic review [29]. We searched MEDLINE, EMBASE, the bibliographies of all retrieved articles, published systematic reviews and the Cochrane Database of Clinical Trials for each of the classes of medications (Table 1) through 7 November 2014. The search was conducted independently in duplicate. We included published, randomized clinical trials that evaluated efficacy in reducing the frequency or severity of migraine headaches that were at least 4 weeks in duration among adults. These comparisons could be between active treatment with placebo controls or comparative trials comparing two or more active treatments. We did not include unpublished data as there is no systematic means of searching for it. Because the classification of headache has changed over time [30,31], two authors independently reviewed each included article’s headache definition and, where possible, classified it according to the 3rd edition of the International Headache Society (IHS) criteria (ICDH-III) and included only those that could reasonably be defined based on these diagnostic criteria [15]. For headache trials before 2004, we classified trials as focusing on episodic or chronic migraine based on the number of headaches experienced by participants at baseline.

Two authors independently abstracted data. Because measures of headache outcomes varied, a priori we followed International Headache Society outcome recommendations by prioritizing abstraction and analysis in this order: 1) headache frequency, 2) a headache index that included frequency, 3) severity or 4) duration [32]. Headache frequency was standardized to number of headaches per month. Whenever possible, we pooled frequency as the number of headaches/month. When not possible, we pooled standardized mean differences between studies, a measure also known as an effect size. By convention, effect sizes greater than 0.8 are considered to be large effect sizes, 0.5 – 0.8 moderate and 0.2 – 0.5 small [33]. When missing, variances were calculated from reported mean, sample size and p values [34]; for one non-placebo comparison trial [35] variance was imputed based on sample size and the reported effect size ($r^2 = 0.76$) When not explicitly reported, to verify we were using the proper variance, we tested the abstracted data for each article to ensure that the p value reported in the article matched our analysis. This helped insure that standard errors weren’t abstracted as standard deviations, a common error in systematic reviews [36]. In addition, because of reports on the potential for misleading data [37,38], we only accepted data that was unadjusted and that was either based on a true intention to treat analysis or based on the subjects remaining in the trial. We rejected any “modified intention to treat” analyses or analyses subject to other adjustments. We assessed article quality independently and in duplicate, using both component and scales
approaches using the Cochrane Risk of Bias Tool [39] and the Jadad scale [40] with good inter-rater agreement (Cochrane ICC: 0.83; Jadad kappa: 0.85). Disagreements were resolved by consensus.

For studies with more than one arm or using a cross-over design, we followed the recommendations of the Cochrane collaboration by pooling the arms into a single arm (if the study

| Search Purpose                                      | Search Strategy                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------|
| Headaches                                           | (headache OR headache disorders OR migraine OR headache OR cephalgia OR cephalalgia OR tension) |
| Randomized controlled trials                        | (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial” [tw]) OR ((singl* [tw] OR double* [tw] OR trбл* [tw]) AND (mask* [tw] OR blind* [tw]) OR placebo [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh]) |
| Alpha blockers                                       | (“Adrenergic alpha-Antagonists”[MeSH Terms] OR clonidine OR tizanidine)          |
| Angiotension converting enzyme inhibitor            | (“Angiotenin-Converting Enzyme Inhibitors” [mh] OR benzapril OR captopril OR enalapril OR lisinopril OR moxipril OR perindopril OR quinapril OR ramipril OR trandolapril) |
| Angiotension receptor blockers                      | (“Angiotensin Receptor Antagonists” [mh] OR losartan OR irbesartan OR olmesartan OR candesartan OR valsartan OR telmisartan) |
| Anticonvulsants                                      | ((anticonvulsants [mh] OR anticonvulsant* OR antiepileptic* OR acetazolamide OR carbamazepine OR chlormethiazole OR clonazepam OR clorazepate OR divalproex OR ethosuximide OR felbamate OR fosphenytoin OR gabapentin OR lamotrigine OR levetiracetam OR meprobamate OR methsuximide OR midazolam OR oxcarbazepine OR paraldehyde OR pentobarbital OR phenobarbital OR phenytoin OR pramipexole OR valproate OR tiagabine OR topiramate OR valproic* OR vigabatrin OR zonisamide) |
| Beta-blocker                                         | adrenergic beta receptor blockers [mh] OR (alprenolol OR bucindolol OR carteolol OR carvedilol OR labetalol OR nadolol OR penbutolol OR pindolol OR propranolol OR Sotalol OR timolol OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR celipril OR esmolol OR metoprolol OR nebivolol) |
| Calcium channel blocker                              | (calcium channel blockers/therapeutic use*[mh] OR (amlodipine OR arandipine OR azelnidine OR bamilnide OR benidpine OR bepridil OR cilnidipine OR clevidipine OR diltazem OR enidipine OR felodipine OR fendline OR flunarizine OR fluspireline OR gallopamil OR isradipine OR lacidipine OR lercanidipine OR manidipine OR mibefradil OR nicardpine OR nifedipine OR nilvadipine OR nimodpine OR nisoldipine OR nitrendipine OR prandpine OR verapamil)) |
| Selective serotonin reuptake inhibitor               | serotonin Uptake Inhibitors/therapeutic use [MH] OR (citalopram OR dapoxetine OR escitalopram OR fluoxetine OR fluvoxamine OR indapine OR paroxetine OR sertraline OR vilazodone OR zimelidine OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR sibutramine OR bicalutamide) |
| Serotonin agonist (Pizotifen)                        | Pizotyline [mh] OR pizotifen OR sandomigran                                      |
| Tricyclic antidepressant                              | antidepresive agents, tricyclic OR antidepresive$ OR tricyclc$ OR amitriptyline OR amoxapine OR clomipramine OR desipramine OR dibenzepin OR dothiepin OR doxepin OR imipramine OR lófepramine OR nortripryline OR opipramol OR protriptyline OR trimipramine |

* (is the symbol for wild-card in MEDLINE)
reported no differences between arms) or by reducing the sample sizes for cross-over trials by 50% [41]. We abstracted data from each trial at the following time points: baseline, 4, 8, 12, 24, 30 and 36 weeks using the DerSimonian and Laird random effects model [42]. Because of controversy about the accuracy of reporting of off-label use of one of gabapentin [37,38], we relied on data in McCrory’s reanalysis of misleading data presented in one of the studies [43] based on drug company trial data.

The main focus of our analysis is between active treatment and placebo controls. We also included data from comparative effectiveness trials. In addition to direct comparisons between drugs, we also conducted a network meta-analysis [44–47]. In brief, network meta-analysis asks if one drug has a pooled efficacy compared to placebo of X and another drug has a pooled efficacy compared to placebo of Y, are X and Y statistically different? We only included drugs with at least 2 clinical trials and at least 8 weeks in duration, adjusting for duration and for correlation between outcomes reported from the same trial. Because these studies did not always report their outcomes in frequency of headaches, the network meta-analysis was done using standardized mean differences (SMD) rather than weighted mean differences.

Heterogeneity was assessed visually using Galbraith plots [48], and I-square [49]. We assessed for small study effects (publication bias) using the methods of Peters [50] for dichotomous outcomes and Eggers [51] for continuous ones. We explored the potential source of heterogeneity using stratified analysis and random-effects meta-regression [52]. These analyses included assessment of the impact of quality, study duration, percentage women, losses to follow-up, and drug dose. All analyses were done using STATA (v 13.1, College Station TX). There was no external funding for this study.

Results

Individual searches yielded 4789 unique articles: 138 ACE, 195 alpha blockers, 109 ARB, 139 anticonvulsants, 654 beta blockers, 711 calcium channel blockers, 279 serotonin agonists, 363 SSRI and 876 TCA publications. Application of inclusion criteria (Fig 1) resulted in selecting 179 randomized clinical trials. These included the following placebo controlled trials: 9 alpha blockers [53–61], 3 ACE trials [62–64] 3 ARB [65–67], 33 anticonvulsants [43,68–99], 39 beta-blockers [66,73,100–136], 12 calcium channel blocker [106,137–147], 7 flunarizine [148–154], 6 SSRI [155–160], 1 SNRI [161], 9 serotonin agonists [162–170] and 9 TCA [118,136,171–177] trials. Fifteen of these placebo-controlled trials included more than one active treatment [66,74,106,116,118,131,136,141,163,167,169,170,175,178,179]. In addition, we also include 53 non-placebo controlled comparative effectiveness trials [178–230].

Placebo Comparisons

Table 2 provides study characteristics of trials investigating prophylactic treatment of episodic migraine (< 15 headaches/month), Table 3 provides details about studies of chronic migraine (>15 headaches/month) and chronic daily headache. There were a total of 15,493 participants in the placebo controlled trials. Studies averaged 112 participants, ranging from 9 to 783. The average patient was 39.2 years old and 78% of subjects were women. Included studies averaged 12 weeks in duration (range 4–82) and had a mean dropout rate of 24%. Thirty nine trials used the 1962 Ad Hoc Committee criteria, seven used the 1969 World Federation of Neurology criteria, forty seven studies used the 1988 International Headache Society criteria, and sixteen the 2004 IHS criteria. Among included trials, most (n = 120) studied episodic migraine headaches with subjects averaging 5.6 headaches per month (range 1.2–11.7). Ten studies focused on subjects with chronic migraine with an average of 18.6 (range 12–24) headaches a month. Six studied chronic daily headaches; the majority of participants (73%) had chronic migraine. Ninety
Records identified through database searching
Ace Inhibitors (n= 197)
Alpha blockers (278)
Angiotensin Receptor Blockers (n= 155)
Anticonvulsants (n= 1982)
Beta Blockers (n= 933)
Calcium Channel Blockers (n= 1014)
Pizotifen (n=398)
Selective Serotonin Reuptake Inhibitors (n= 518)
Tricyclic Antidepressants (n= 1249)

Records screened
Ace Inhibitors (n= 138)
Alpha Blockers (195)
Angiotensin Receptor Blockers (n= 109)
Anticonvulsants (n=1390)
Beta Blockers (n=654)
Calcium Channel Blockers (n=711)
Pizotifen (n=279)
Selective Serotonin Reuptake Inhibitors (n=363)
Tricyclic Antidepressants (n= 876)

Additional records identified through other sources
Ace Inhibitors (n=0)
Alpha Blockers (n=2)
Angiotensin Receptor Blockers (n=1)
Anticonvulsants (n=12)
Beta Blockers (n=12)
Calcium Channel Blockers (n=7)
Pizotifen (n=8)
Selective Serotonin Reuptake Inhibitors (n=2)
Tricyclic Antidepressants (n= 11)

Records excluded
Ace Inhibitors (n=73)
Alpha Blockers (n=148)
Angiotensin Receptor Blockers (n=77)
Anticonvulsants (n=632)
Beta Blockers (n=709)
Calcium Channel Blockers (n=910)
Pizotifen (n=13)
Selective Serotonin Reuptake Inhibitors (n=278)
Tricyclic Antidepressants (n= 802)

Full-text articles assessed for eligibility
Ace Inhibitors (n=9)
Alpha blockers (n=22)
ARB (n= 22)
Anticonvulsants (n=719)
Beta Blockers (n=128)
Calcium Channel Blockers (n= 153)
Pizotifen (n=79)
SSRI (n=80)
Tricyclic Antidepressants (n= 165)

Records excluded after full review

|               | ACE (n=8) | ARB (n=20) | AC (n=689) | BB (n=91) | CCB (n=124) | Pizotifen (n=54) | SSRI (n=74) | TCA (n=154) |
|---------------|----------|------------|------------|-----------|-------------|-----------------|-------------|-------------|
| Acute Migraine| 23       | 4          | 5          |           |             |                 |             |             |
| Case Series   | 2        | 1          | 3          | 148       | 66          | 8               | 26          | 20          |
| Data not extractable | 78 | 3 | 3 | 3 | | | | |
| Duplicate Data| 2        | 2          | 1          | 2         | 2           | 8               |             |             |
| IV treatment  | 1        | 1          |            |           |             |                 |             |             |
| Not RCT       | 1        | 32         | 2          | 5         | 24          |                 |             |             |
| Pediatric     | 1        | 78         | 17         | 11        | 18          | 2               |             |             |
| Review        | 6        | 10         | 17         | 300       | 1           | 87              | 24          | 39          | 7           |

Studies included in quantitative synthesis (meta-analysis)
Ace Inhibitors (n=3)
Alpha blockers (n=9)
Angiotensin Receptor Blockers (n=3)
Anticonvulsants (n=32)
Beta blockers (n=39)
Calcium Channel Blockers (n=12)
Flunarizine (n=7)
Pizotifen (n=9)
TCA (n=11)
SSRI/SNRI (n=7)
Direct comparison (n=48)

Fig 1. PRISMA Flowchart of study selection.
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Table 2. Study characteristics of included randomized trials of treatment of episodic (<15 headaches/month) migraine headaches.

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|-----------------------|---------------|-----------------------------|------------|------------------|------------------------|----------------|-------------|----------|-----|-------|
| **ALPHA BLOCKER**     |               |                             |            |                  |                        |                |             |          |     |       |
| Adam [53], 1978, UK   | Episodic      | ns                          | Clonidine (0.15) | Frequency        | Crossover (0)         | 24             | 96          | 27%      | 37.5| 84%  |
| Boison [54], 1978, Denmark | Episodic  | ns                          | Clonidine (0.1) | Frequency        | Crossover (0)         | 8              | 71          | 31%      | ns  | ns   |
| Bredfield [55], 1989, USA | Episodic  | ns                          | Clonidine (0.2) | Frequency        | Crossover             | 6              | 43          | 30%      | ns  | 80%  |
| Lynggaard [56], 1975, Denmark | Episodic  | ns                          | Clonidine (0.1) | Frequency        | Crossover (1)         | 12             | 37          | 26%      | 34.1| 95%  |
| Mondrup [57], 1977, Denmark | Episodic  | ns                          | Clonidine (0.1) | Frequency        | Crossover (4)         | 12             | 32          | 34%      | 35  | 76%  |
| Ryan [58], 1975, USA  | Episodic      | ns                          | Clonidine (0.15) | Frequency        | Crossover (2 days)    | 8              | 133         | ns       | 41  | 78%  |
| Shafar [60], 1972, UK  | Episodic      | 8.4                         | Clonidine (0.1) | Frequency        | Crossover             | 8              | 65          | 23%      | 47.4| 84%  |
| Stensrud, 1976, Norway | Episodic      | 5.8                         | Clonidine (0.15) | Frequency        | Crossover (0)         | 7              | 29          | 7%       | 43.3| 83%  |
| **ANGIOTENSIN ENZYME CONVERTING INHIBITORS** |               |                             |            |                  |                        |                |             |          |     |       |
| Paterna [62], 1992, Italy | Episodic  |                             | Captopril (75) | Headache Index   | Crossover              | 16             | 20          | 23%      | 37  | 81%  |
| Schrader [63], 2001, Norway | Episodic  | 2.3                         | Lisinopril (20) | Frequency        | Parallel               | 12             | 30          | 5%       | 41  | 81%  |
| Sonbolotestan [64], 2013, Iran | Episodic  | 11.3                        | Enalapril (10) | Frequency        | Parallel               | 8              | 34          | 0%       | 34.4| 825  |
| **ANGIOTENSIN RECEPTOR BLOCKER** |               |                             |            |                  |                        |                |             |          |     |       |
| Diener [65], 2009, Germany | Episodic  | 6.9                         | Telmisartan (80) | Frequency        | Parallel               | 12             | 95          | 5%       | 47  | 85%  |
| Stovner [66], 2013, Norway | Episodic  | 4.8                         | Candesartan (16), Propranolol (160) | Frequency | Crossover | 12 | 61 | 15% | 37 | 82% |
| Tronvik [67], 2003 Norway | Episodic    | 5.7                         | Candesartan (16) | Frequency | Parallel | 12 | 57 | 5% | 43.2 | 79% |
| **ANTICONVULSANTS**   |               |                             |            |                  |                        |                |             |          |     |       |
| Brandes [69], 2004, Canada/USA | Episodic | 5.7                         | Topiramate, (50,100,200) | Frequency | Parallel | 26 | 483 | 46% | 38.9 | 87% |
| Cady [70], 2009, USA | Episodic      | 4.4                         | Carisbamate (100,300,600) | Frequency | Parallel | 14 | 318 | 30% | 41.3 | 85% |
| de Tommaso [71], 2007, Italy | Episodic | 10.9                        | Topiramate (100), Levitracetam (1000) | Frequency | Parallel | 8 | 45 | 16% | 37.8 | 78% |
| Di Trapani [72], 2000, Italy | Episodic | 5.2                         | Gabapentin (1200) | Frequency | Parallel | 12 | 63 | 0% | ns  | 52% |
| Diener [73], 2004 Europe | Episodic     | 5.1                         | Topiramate (100, 200), Propranolol (160) | Frequency | Parallel | 20 | 568 | 37% | 40.8 | 80% |
| Edwards [75], 2003, USA | Episodic      | 4.5                         | Topiramate (200) | Frequency | Parallel | 4 | 70 | 0% | 41.4 | 97% |
| Freitag [76], 2002 USA | Episodic      | 4.2                         | Divalproex (1000) | Frequency | Parallel | 12 | 237 | 15% | 40.5 | 79% |
| Ghose [77], 2002, New Zealand | Episodic | 7.6                         | Vigabatrin (2000) | Frequency | Crossover (4) | 12 | 23 | 17% | 43.6 | 74% |

(Continued)
| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|-----------------------|--------------|----------------------------|-----------|-----------------|----------------------|----------------|------------|----------|-----|--------|
| Gupta [78], 2007, India | Episodic     | 7.0                        | Topiramate (50), Lamotrigine (50) | Frequency | Crossover () | 4             | 60         | 7%       | 30  | 78%    |
| Hering [79], 1992, Israel | Episodic     | 7.7                        | Valproate (800) | Frequency | Crossover (0) | 8             | 32         | 9%       | 34  | 79%    |
| Jensen [80], 1994, Denmark | Episodic     | 6.6                        | Valproate (1500) | Frequency | Crossover (4) | 12            | 43         | 21%      | 46  | 86%    |
| Klapper [81], 1997, USA | Episodic     | 5.0                        | Divalproex (500,100,1500) | Frequency | Parallel | 12            | 176        | 22%      | 40.8| 89%    |
| Lipton [82], 2011, USA | Episodic     | 11.7                       | Topiramate (100) | Frequency | Parallel | 26            | 385        | 14%      | 40.3| 89%    |
| Mathew [83], 1995, USA | Episodic     | 6.2                        | Valproate (750) | Frequency | Parallel | 12            | 107        | 16%      | 45.6| 78%    |
| Mathew [43], 2001, USA | Episodic     | 4.9                        | Gabapentin (2400) | Frequency | Parallel | 12            | 143        | 39%      | 40  | 83%    |
| Rompel [85], 1970, S Africa | Episodic    | 3.0                        | Carbamazepin (ns) | Frequency | Crossover () | 6             | 48         | 2%       | 60  | 69%    |
| Silberstein [87], 2004, USA | Episodic | 5.5                        | Topiramate (50,100,200) | Frequency | Parallel | 24            | 487        | 46%      | 40.4| 89%    |
| Silberstein [88], 2006, USA | Episodic | 4.9                        | Topiramate (200) | Frequency | Parallel | 20            | 211        | 27%      | 40.8| 86%    |
| Silberstein [90], 2008, USA | Episodic | 3–9                       | Oxcarbazepine(1200) | Frequency | Parallel | 15            | 170        | 26%      | 40.5| 85%    |
| Silberstein [91], 2013, USA | Episodic | 9.2                       | Gabapentin (1200,1800,2400,3000) | Frequency | Parallel | 20            | 263        | 29%      | 39.3–40.6| 83% |
| Steiner [94], 1997, UK | Episodic     | 4.1                        | Lamotrigine (200) | Frequency | Parallel | 12            | 77         | 31%      | 37.2| 82%    |
| Stensrud [86], 1979, Norway | Episodic    | 6.3                        | Clonazepam (1) | Frequency | Crossover () | 4             | 38         | 11%      | ns  | 71%    |
| Storey [88], 2001, USA | Episodic     | 4.7                        | Topiramate (200) | Frequency | Parallel | 16            | 40         | 13%      | 38.3| 98%    |
| Vahedi [87], 2002, France | Episodic | 5.0                        | Acetazolamide (500) | Frequency | Parallel | 12            | 53         | 34%      | 39.2| 75%    |
| Verma [98], 2013, India | Episodic     | 5.7                        | Levetiracetam  | Frequency | Parallel | 12            | 65         | 20%      | 31.1| 73%    |
| **Beta Blockers** | | | | | | | | | |
| Ahuja [100], 1985, India | Episodic     | 7.2                        | Propranolol (120) | Frequency | Crossover | 8             | 26         | ns       | ns  | 46%    |
| Al-Qassab [101], 1993, UK | Episodic     | 4                         | Propranolol (80, 160) | Frequency | Crossover | 8             | 45         | 33%      | 36  | 80%    |
| Andersson [102], 1983, Denmark | Episodic | 4.9                        | Metoprolol (200) | Frequency | Parallel | 8             | 71         | 13%      | 39.6| 85%    |
| Borgesen [103], 1974, Denmark | Episodic | 1.8                        | Propranolol (120) | Frequency | Crossover | 12            | 45         | 33%      | 37.6| 83%    |
| Briggs [104], 1979, UK | Episodic     | 6.9                        | Timolol (20) | Frequency | Crossover | 6             | 24         | 4%       | ns  | 71%    |
| Dahlof [105], 1987, Sweden | Episodic | 4.3                        | Propranolol (120) | Frequency | Crossover | 4             | 29         | 0%       | ns  | 83%    |
| Diener [106], 1996, Germany | Episodic     | 4                         | Propranolol (120) | Duration | Parallel | 20            | 214        | 19%      | 39  | 78%    |

(Continued)
| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|------------------------|---------------|-----------------------------|------------|-----------------|-----------------------|----------------|-------------|----------|-----|--------|
| Diener [73], 2004, Germany | Episodic | 5.1 | Propranolol (160) | Frequency | Parallel | 20 | 568 | 37% | 40.8 | 80% |
| Ekbom [107], 1972, Sweden | Episodic | 11.7 | Pindolol (7.5, 15) | Frequency | Parallel | 4 | 30 | 13% | 33.7 | 87% |
| Ekbom [108], 1975, Sweden | Episodic | 2.2 | Alprenolol (400) | Frequency | Parallel | 6 | 33 | 15% | 41.3 | 82% |
| Ekbom [109], 1977, Sweden | Episodic | >3 | Oxprenolol | Headache Index | Crossover (1) | 12 | 34 | 46% | 41.8 | 89% |
| Forssman [110], 1976, Sweden | Episodic | 6.9 | Propranolol (240) | Frequency | Crossover | 12 | 40 | 20% | 37.4 | 97% |
| Forssman [111], 1983, Sweden | Episodic | >3 | Atenolol (100) | Frequency | Crossover | 12 | 24 | 17% | 40 | 80% |
| Freitag [112], 1984, USA | Unclear ns | Nadolol (160, 240) | Frequency | Parallel | ns | 32 | ns | ns | 81% |
| Holroyd [113], 2010, USA | Episodic | 5.4 | Propranolol (180) | Frequency | Parallel | 64 | 232 (35%) | 35% | 38.2 | 78% |
| Johannsson [114], 1987, Sweden | Episodic | >2 | Atenolol (100) | Frequency | Crossover | 12 | Ns | 14% | 43 | 70% |
| Johnson [115], 1986, New Zealand | Episodic | 5 | Propranolol (240) | Frequency | Crossover | 12 | 29 | 41% | 42 | 69% |
| Kangasniemi [116], 1987, Norway | Episodic | 4.3 | Metoprolol (200) | Frequency | Crossover (4) | 8 | 74 | 1% | 37.5 | 79% |
| Langohr [175], 1985, Germany | Episodic | | Propranolol (Clomipramine) | Frequency | Crossover (4) | 12 | 36 | 43% | 44 | 74% |
| Malvea [117], 1973, USA | Episodic | >4 | Propranolol (?) | Headache Index | Crossover | 6 | 31 | 6% | ns | 87% |
| Mathew [118], 1981, USA | Unclear ns | Propranolol (75) | Headache Index | Parallel | 24 | 554 | 22% | 38 | 95% |
| Mikkelsen [119], 1986, Denmark | Episodic | >3 | Propranolol (120) | Frequency | Crossover (0) | 12 | 39 | 21% | ns | 84% |
| Nadelmann [120], 1986, USA | Unclear ns | Propranolol (240) | Headache Index | Crossover (0) | 6 | 64 | 36% | ns | 86% |
| Nanda [121], 1977, Scotland | Episodic | 4.8 | Acebutolol (800) | Frequency | Crossover (4) | 12 | 43 | 24% | ns | 74% |
| Pita [123], 1977, Spain | Episodic | 5.5 | Propranolol (160) | Headache Index | Crossover (0) | 8 | 9 | 11% | 32 | 78% |
| Pradalier [124], 1989, France | Episodic | 6.1 | Propranolol (160) | Frequency | Parallel | 12 | 74 | 25% | 37.5 | 76% |
| Sargent [125], 1985, USA | Episodic | >2 | Propranolol (120) | Frequency | Parallel | 16 | 161 | 13% | 30 | 79% |
| Sjaastad [126], 1972, Norway | Episodic | 7.5 | Pindolol (7.5) | Frequency | Crossover (3) | 4 | 24 | 17% | 35.3 | 75% |
| Standnes [127], 1982, Norway | Episodic | 6.7 | Propranolol (160) Timolol (20) | Frequency | Crossover | 0 | 25 | 28% | ns | 80% |
| Steiner [128], 1988, UK | Episodic | 4 | Metoprolol (100) | Frequency | Parallel | 8 | 59 | 19% | 37.6 | 76% |

(Continued)
| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|-----------------------|--------------|-----------------------------|------------|------------------|------------------------|-----------------|-------------|----------|-----|-------|
| Stellar [129], 1984, USA | Episodic | 6.8 | Timolol (30) | Frequency | Crossover | 6 | 107 | 8% | 43 | 72% |
| Stensrud [130], 1976, Norway | Episodic | 6.1 | Propranolol (160) Inderal (160) | Headache Index | Crossover (1) | 4 | 20 | 5% | ns | 70% |
| Stensrud [131], 1980, Norway | Episodic (n = 21) | <15>15 | Atenolol (100) Propranolol (160) | Frequency | Crossover (1) | 6 | 21 | 20% | ns | 69% |
| Tfelt-Hansen [132], 1984, Scandinavia | Episodic | 6.0 | Timolol (20)Propranolol (160) | Frequency | Crossover (2) | 10 | 96 | 10% | 39.5 | 74.5% |
| Van de Ven [133], 1997, Denmark | Episodic | 5.5 | Bisoprolol (10) | Frequency | Parallel | 8 | 226 | 14% | 38.7 | 82% |
| Weber [134], 1972, USA | Unclear ns | Propranolol (80) | Headache Index | Crossover (0) | 12 | 25 | 24% | 40.5 | 52% |
| Wideroe [135], 1974, Norway | Episodic | 3 | Propranolol (160) | Headache Index | Crossover (0) | 12 | 30 | 13% | 38 | 87% |
| Zeigler [136], 1987, USA | Episodic ≥2 | Propranolol (240) | Headache Index | Crossover (4) | 4 | 30 | ns | 38 | 73% |

**Calcium Channel Blockers**

| Nimodipine European Migraine (with aura) Trial [137], 1989, EU | Episodic | 3.3 | Nimodipine (120) | Frequency | Parallel | 12 | 89 | 19% | 33.8 | 79% |
| Nimodipine European Migraine (Without aura) trial (1989) [138], EU | Episodic | 4.4 | Nimodipine (120) | Frequency | Parallel | 12 | 192 | 16% | 38.1 | 78% |
| Ansell [139], 1988, UK | Episodic >2 | Nimodipine (120) | Headache Index | Parallel | 12 | 68 | 16% | ns | 71% |
| Gelmers [140], 1983, Netherlands | Episodic | 9.1 | Nimodipine (120) | Headache Index | Parallel | 12 | 60 | 17% | 30 | 62% |
| Havanka-Kanniainen [141], 1985, Finland | Episodic | 7.9 | Nimodipine (120) | Frequency | Crossover (0) | 8 | 33 | 12% | 33 | 85% |
| Leandri [142], 1990, Italy | Episodic | 4.3 | Nifedipine (40) | Frequency | Crossover (ns) | 8 | 35 | 15% | ns | ns |
| Markley [143], 1984, USA | Episodic | 3.4 | Verapamil (240) | Frequency | Crossover (ns) | 8 | 20 | 30% | 33 | 86% |
| McArthur [144], 1989, USA | Episodic | 2.3 | Nifedipine (90) | Frequency | Crossover (1) | 12 | 24 | 42% | ns | ns |
| Shukla [145], 1995, UK | Episodic | 10.4 | Nifedipine (15) | Frequency | Crossover (ns) | 6 | 36 | 22% | 22.8 | 50% |
| Solomon [146], 1983, USA | Episodic | 6.7 | Verapamil (320) | Frequency | Crossover (ns) | 6 | 12 | 52% | 38 | 78% |
| Stewart [147], 1988, Canada | Episodic | 6.3 | Nimodipine (120) | Frequency | Parallel | 8 | 37 | 19% | ns | ns |

**Flunarizine**

(Continued)
### Table 2. (Continued)

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|-----------------------|---------------|-----------------------------|------------|------------------|------------------------|----------------|-------------|----------|-----|--------|
| Diamond [148], 1992, USA | Episodic | 4.3 | Flunarizine (10) | Frequency | Parallel | 20 | 143 | 8% | 34.8 | 74% |
| Frenken [149], 1984, Netherlands | Episodic | 3.6 | Flunarizine (10) | Frequency | Parallel | 12 | 35 | 0% | NS | 83% |
| Louis [150], 1981, Belgium | Episodic | 1.2 | Flunarizine (10) | Frequency | Parallel | 12 | 58 | 0% | 29 | 50% |
| Mendenopoulos [151], 1985, Greece | Episodic | 4 | Flunarizine (10) | Headache Index | Parallel | 12 | 20 | 0% | 44 | 80% |
| Pini [152], 1986, Italy | Episodic | 9.9 | Flunarizine (20) | Headache Index | Parallel | 4 | 18 | 0% | 40.2 | 83% |
| Sorensen [153], 1986, Denmark | Episodic | 3 | Flunarizine (10) | Frequency | Crossover (4) | 16 | 29 | 7% | 40 | 79% |
| Thomas [154], 1991, India | Episodic | 6.7 | Flunarizine (10) | Headache Index | Crossover (2) | 12 | 29 | 48% | 30.5 | 87% |

#### Selective Serotonin Reuptake Inhibitor

| Adly [155], 1993, USA | Episodic | >4 | Fluoxetine (40) | Headache Index | Parallel | 10 | 32 | 44% | 37.5 | 83% |
| d’Amato [156], 1999, Italy | Episodic | 1–4 | Fluoxetine (20) | Headache Index | Parallel | 20 | 52 | 0% | 37.6 | 63% |
| Landy [157], 1998, USA | Episodic | >2 | Sertraline (50) | Headache Index | Parallel | 8 | 27 | 41% | 36 | 93% |
| Steiner [159], 1998, UK | Episodic | 3.9 | s-Fluoxetine (40) | Frequency | Parallel | 12 | 53 | 32% | 37 | 75% |
| Zeeberg [160], 1981, Sweden | Episodic | 3.5 | Femoxetine (300) | Headache Index | Parallel | 12 | 59 | ns | ns | ns |

#### Serotonin Norepinephrine Reuptake Inhibitor

| Ozycalin [161], 2004, Turkey | Episodic | 2.3 | Venlafaxine (75, 150) | Frequency | Parallel | 8 | 60 | 17% | 36.5 | 83% |

#### Serotonin Agonist

| Arthur [162], 1971, New Zealand | Episodic | 8.1 | Pizotifen (3.0) | Frequency | Crossover (ns) | 4 | 63 | 17% | ns | ns |
| Bellavance [163], 1990, Canada | Episodic | 6.7 | Pizotifen (1.5) | Frequency | Parallel | 12 | 176 | 14% | 32.5 | 79% |
| Carroll [164], 1975, UK | Episodic | >3 | Pizotifen (3.0) | Headache Index | Crossover (2) | 4 | 27 | 48% | ns | ns |
| Cleland [165], 1997, UK | Episodic | 3.4 | Pizotifen (2.0) | Frequency | Crossover (ns) | 12 | 130 | 32% | 40.5 | 63% |
| Hughes [166], 1971, UK | Episodic | 9.1 | Pizotifen (0.5) | Frequency | Crossover (ns) | 12 | 26 | 0% | ns | 81% |
| Kangasniemi [167], 1979, Finland | Episodic | 4.3 | Pizotifen (1.5) | Frequency | Crossover (0) | 7 | 50 | 22% | 36 | 80% |
| Lance, 1968 | Pizotifen | | | | | | | | |
| Lawrence [168], 1977, UK | Episodic | >4 | Pizotifen (1.5) | Headache Index | Parallel | 12 | 36 | 14% | ns | 79% |
| Osterman [169], 1977, Sweden | Episodic | 5.1 | Pizotifen (0.5) | Frequency | Crossover (2) | 8 | 30 | 10% | 37 | 70% |
| Ryan [170], 1968, USA | Episodic | 8.9 | Pizotifen (4) | Frequency | Crossover (ns) | 4 | 62 | ns | ns | ns |

(Continued)
trials (57%) used a parallel-group design, while sixty-six used a crossover design. There were 23 countries contributing studies. Fifty-one trials (46%) were sponsored by industry. Most studies (82%) used frequency as their outcome measure, nineteen (13.7%) used a headache index, two used headache duration and three headache intensity. Overall, the studies varied in quality. Quality ratings for placebo controlled trials are given in Table 4. By Jadad criteria, 34% of studies had scores ≤ 3.0, suggesting low quality, 39% had scores between 3 and 5 consistent with modest quality and only 37% had scores ≥ 5 suggesting high quality. Only 36% used an intention to treat analysis, 27% assessed compliance, 26% had concealed allocation, and 51% had adequate blinding. There was no difference in the overall effect sizes for placebo controlled trials using Jadad criteria as a scale (p = 0.44) or when coded as high, modest or low quality (p = 0.37), or when assessed by most of the specific Jadad or Cochrane Risk of Bias quality characteristics (compliance p = 0.59; blinding p = 0.36; adequacy of blinding p = 0.50, industry sponsorship p = 0.52; incomplete outcome reporting p = 0.96; reporting of withdrawals p = 0.24). However, trials which had inadequate concealed allocation had significantly higher reported effects (SMD: -0.52, 95% CI: -0.63 to -0.41) than those who had concealed allocation (SMD: -0.26, 95% CI: -0.34 to 0.17).

**Alpha-blockers.** There were 9 trials comparing alpha blockers to placebo with a total of 4590 participants who averaged 39.3 (range 12–76) years in age with 84% women (Table 2). All of the studies measured headache frequency. Eight of these trials focused on episodic migraine headaches; all studied clonidine. One trial focused on chronic migraines using tizanidine. The average rate of withdrawals was 32%. Studies averaged 11 weeks (range 4–82) with a mean of 71.3 participants (range 11–67). At no time point was clonidine more effective than placebo for episodic migraines (Table 5, Fig 2) and tizanidine was no more effective than placebo for chronic migraine headaches (Table 6). None of these trials reported on the likelihood of a 50% reduction in headaches.

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Drugs (mg) | Headache Measure | Study design (washout) | Duration, weeks | Sample size | Dropouts | Age | Female |
|------------------------|--------------|-----------------------------|------------|------------------|------------------------|----------------|------------|----------|-----|-------|
| **Tricyclic Antidepressants** | | | | | | | | | | |
| Couch [241], 1976, USA | Episodic | 6.9 | Amitriptyline (100) | Headache Index | Parallel | 4 | 73 | 36% | NS | 64% |
| Couch [171], 1979 | Episodic | 6.9 | Amitriptyline (100) | Frequency | Parallel | 8 | 162 | 38% | NS | 85% |
| Couch [172], 2011, USA | Episodic | 7.6 | Amitriptyline (100) | Frequency | Parallel | 16 | 391 | 51% | 34.9 | 81% |
| Gomersall [173], 1973, UK | Episodic | 2.7 | Amitriptyline (60) | Frequency | Crossover (0) | 26 | 20 | 20% | 42 | 75% |
| Jacobs [174], 1972, UK | Episodic | 3.3 | Opipramol (75) | Frequency | Parallel | 12 | 27 | 43% | 42 | 78% |
| Langohr [175], 1985, Germany | Episodic | >4 | Clomipramine (100) | Frequency | Crossover (4) | 4 | 36 | 43% | 44 | 67% |
| Mathew [118], 1981, USA | Unclear | Unclear | Amitriptyline (75) | Headache Index | Parallel | 24 | 554 | 22% | 38 | 95% |
| Noone [177], 1980, UK | Episodic | 6 | Clomipramine (30) | Frequency | Crossover | 4 | 10 | 50% | Ns | 70% |
| Ziegler [136], 1987, USA | Episodic | 2–12 | Amitriptyline (100) | Headache Index | Crossover (1) | 8 | 30 | 0% | 38 | 73% |

**Table 2. (Continued)**
Angiotensin Converting Enzyme Inhibitors (ACE)/ Angiotensin Receptor Blockers (ARB). There were three ACE (captopril, enalapril, lisinopril) and three ARB (candesartan x2, telmisartan) placebo-controlled trials, all focusing on episodic migraines (Table 2). The ACE studies were 8, 12 and 16 weeks in duration with 120 participants who averaged 7.3 headaches per month. All three ARB studies were 12 weeks in duration with a total of 231 participants, averaging 6.5 headaches/month. One of the ACE trials suggested no benefit at 4 or 8 weeks (enalapril), another found benefit at 12 weeks (lisinopril) and a third benefit at 16 weeks (captopril, Table 5, Fig 3); none of the trials reported outcomes at a common time-point. At twelve weeks, ARBs were better than placebo in reducing the frequency of headaches (Table 5, Fig 3). The likelihood of experiencing at least 50% improvement was not reported in all clinical trials. One of the ACE trials (captopril) was more likely than placebo to achieve at least a 50% reduction in headache frequency (Table 7). This was not found in the trial studying lisinopril or for two of the ARB trials.

Anticonvulsants. There were 32 trials comparing anticonvulsants to placebo with a total of 8529 participants who averaged 41 years (range 12–76) in age; 81% of participants were women (Table 2). Twenty-seven of these trials focused on episodic migraine headaches (Table 2), five evaluated chronic migraine and four chronic daily headaches (Table 3). The
Table 4. Quality Ratings of included placebo controlled trials.

| Study | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of "other" bias | Industry sponsored |
|-------|-------------------|--------------------|-------------------------------|-------------------------------|-------------------|-----------------------------------|-----------------------------------|-------------------|--------------------|
| Adam, 1978, UK | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | No |
| Boison, 1978, Sweden | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | No |
| Bredfeldt, 1989, USA | 5 | No | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Yes |
| Lynggaard, 1975, Denmark | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Mondrup, 1977, Denmark | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Unclear |
| Ryan, 1975, USA | 1 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | No |
| Shafar, 1972, UK | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| Stensrud, 1976, Norway | 0 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| **Antiogensin Enzyme Converting Inhibitors** | | | | | | | | | |
| Schrader (2001), Norway, Lisinopril | 6 | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Yes |
| **Angiotensin Receptor Blocker** | | | | | | | | | |
| Diener (2009), Germany, Telmisartan | 3 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| Trovnik (2003), Norway, Candesartan | 8 | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| **Anticonvulsants** | | | | | | | | | |
| Brandes, 2004, Canada/USA, Topiramate | 8 | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes |
| Cady, 2009, USA, Carisbamate | 8 | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| de Tommaso, 2007, Italy, Topiramate, Levitracetam | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Di’ Trapani, 2000, Italy, Gabapentin | 4 | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Unclear | Unclear |
| Diener, 2004 Europe, Topiramate, Propranolol | 6 | Yes | Unclear | Unclear | Unclear | Yes | Yes | Unclear | Yes |
| Diener, 2007, Italy, Topiramate | 8 | No | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear |
| Edwards, 2003, USA, Topiramate | 4 | Yes | Unclear | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| Freitag, 2002, USA, divalproex | 8 | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes |
| Gupta, 2007, India, Topiramate | 8 | Yes | Yes | Yes | Yes | Yes | Unclear | No | Unclear |
| Herling 1992, Israel, Valproate | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Jensen, 1994, Denmark, Valproate | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Yes |

(Continued)
| Study | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|-------|-------------------|--------------------|-----------------------------|-------------------------------|------------------|-------------------------------|-------------------------------|-----------------|------------------|
| Klapper, 1997, USA, Divalproex | 4 | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Lipton, 2011, USA, Topiramate | 8 | Yes | Yes | Yes | Yes | Yes | No | Unclear | Yes |
| Mathew, 1995, USA, Valproate | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | No | Yes |
| Mathew, 2001, USA, Gabapentin | 6 | Yes | Yes | Unclear | Unclear | Unclear | Unclear | No | Yes |
| Rompel, 1970, South Africa, Carbamazepine | 5 | No | Yes | Yes | Yes | Yes | Yes | Unclear | Yes |
| Silberstein, 2004, USA, Topiramate | 6 | Yes | Yes | Yes | Unclear | Yes | Unclear | Unclear | Yes |
| Silberstein, 2006, USA, Topiramate | 4 | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Silberstein, 2008, USA, Oxcarbazepine | 8 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Steiner, 1997, UK, Lamotrigine | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Yes |
| Stensrud, 1979, Norway, Clonazepam | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Storey, 2001, USA, Topiramate | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Vahedi, 2002, France, Acetazolamide | 6 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Beta Blockers**

| Study | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|-------|-------------------|--------------------|-----------------------------|-------------------------------|------------------|-------------------------------|-------------------------------|-----------------|------------------|
| Ahuja, 1985, India, Propanolol | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Al-Qassab, 1993, England, Propanolol | 3 | No | Unclear | Unclear | Yes | Unclear | Unclear | Yes | Yes |
| Andersson, 1983, Denmark, Metoprolol | 2 | Yes | Unclear | Unclear | Yes | No | Unclear | Unclear | Yes |
| Borgesen, 1974, Denmark, Propranolol | 4 | No | Unclear | Unclear | Yes | No | No | No | Yes |
| Dahlof, 1987, Sweden, Propranolol | 5 | Yes | Unclear | Unclear | Yes | No | No | No | Yes |
| Dierer, 1996, Germany, Propranolol, Cycloleucate | 4 | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Dierer, 2004, Germany, Propranolol | 6 | Yes | Unclear | Unclear | Unclear | Yes | Yes | Unclear | Yes |
| Ekblom, 1972, Sweden, Pindolol | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |
| Ekblom, 1975, Sweden, Alprenolol | 2 | No | Unclear | Unclear | Unclear | Yes | Unclear | Yes | Yes |
| Forssman, 1976, Sweden, Propranolol | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Yes | Yes |
| Forssman, 1983, Sweden, Atenolol | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes |

(Continued)
### Table 4. (Continued)

| Study                           | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|--------------------------------|-------------------|--------------------|------------------------------|--------------------------------|-------------------|----------------------------------|-------------------------------------|---------------------|-------------------|
| Freitag, 1984, USA, Nadolol     | 3                 | Yes                | Unclear                      | Unclear                        | Yes               | Unclear                          | Unclear               | Unclear            | Unclear           |
| Holroyd, 2010, USA, Propanolol  | 6                 | Yes                | Yes                          | Yes                            | Yes               | Yes                              | Yes                   | Unclear            | Unclear           |
| Johannsson, 1987, Sweden, Atenolol | 2              | No                 | Unclear                      | Unclear                        | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Johnson, 1986, New Zealand, Propanolol | 3             | No                 | Unclear                      | Yes                            | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Kangasniemi, 1987, Norway, Metoprolol | 0           | 4                  | Yes                          | Unclear                        | Unclear           | Unclear                          | Yes                   | Unclear            | Unclear           |
| Malvea, 1973, USA, Propanolol   | 4                 | Yes                | Unclear                      | Unclear                        | Yes               | Unclear                          | Unclear               | Unclear            | Unclear           |
| Mathew, 1981, USA, Propanolol, Amiltriptiline | 2       | No                 | Unclear                      | Unclear                        | No                | No                              | No                    | Yes                | Unclear           |
| Mikkelsen, 1986, Denmark, Propanolol | 6         | No                 | Unclear                      | Unclear                        | Unclear           | Unclear                          | Unclear               | Unclear            | Yes               |
| Nadelmann, 1986, USA, Propanolol | 6                 | No                 | Unclear                      | Unclear                        | No                | Unclear                          | No                    | Unclear            | Yes               |
| Nanda, 1977, Scotland, Acebutolol | 2             | No                 | Unclear                      | Unclear                        | No                | Unclear                          | Unclear               | Yes                | Yes               |
| Pita, 1977, Spain, Propranolol  | 6                 | No                 | No                           | Unclear                        | Yes               | Yes                             | Unclear               | Unclear            | Yes               |
| Pradalier, 1989, France, Propranolol | 5           | Yes                | Unclear                      | Unclear                        | Yes               | Unclear                          | Unclear               | Unclear            | Unclear           |
| Sargent, 1985, USA, Propranolol  | 4                 | No                 | Unclear                      | Unclear                        | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Sjaastad, 1972, Norway, Pindolol | 5                 | No                 | Unclear                      | Yes                            | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Standnes, 1982, Norway, Propranolol, Timolol | 4      | No                 | Unclear                      | Yes                            | Unclear           | Unclear                          | Unclear               | Yes                | Yes               |
| Steiner, 1988, UK, Metoprolol   | 6                 | No                 | Unclear                      | Yes                            | No                | No                              | Unclear               | Unclear            | Unclear           |
| Stellar, 1984, USA, Timolol     | 7                 | No                 | Yes                          | Unclear                        | Yes               | No                              | Unclear               | Unclear            | Unclear           |
| Stensrud, 1976, Norway, Propranolol, Inderal | 5      | No                 | Unclear                      | Yes                            | Unclear           | Unclear                          | Unclear               | Unclear            | Yes               |
| Tfelt-Hansen, 1984, Scandinavia, Timolol, Propranolol | 6   | No                 | Unclear                      | Yes                            | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Van de Ven, 1997, Denmark, Bisoprolol | 4           | Yes                | Unclear                      | Unclear                        | Unclear           | Unclear                          | Unclear               | Unclear            | Unclear           |
| Wideroe, 1974, Norway, Propranolol | 4           | No                 | Unclear                      | Yes                            | No                | Unclear                          | Unclear               | Unclear            | Yes               |
| Zeigler, 1987, USA, Propranolol  | 3                 | No                 | Unclear                      | Yes                            | Yes               | Unclear                          | Unclear               | Unclear            | No                |

**Calcium Channel Blockers**

(Continued)
Table 4. (Continued)

| Study                                      | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|--------------------------------------------|-------------------|--------------------|------------------------------|------------------------------|-------------------|-----------------------------------|------------------------------------|---------------------|-------------------|
| Ansell, 1988, UK, Nimodipine               | 3                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Gelmers, 1983, Netherlands, Nimodipine     | 4                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Havanka-Kanniainen, 1985, Finland, Nimodipine | 4               | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Yes               |
| Leandri, 1990, Italy, Nicardipine          | 3                 | No                 | Unclear                     | Unclear                      | Yes               | Unclear                           | Unclear               | Unclear             | Yes               |
| Markley, 1984, USA, Verapamil              | 3                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| McArthur, 1989, USA, Nifedipine            | 3                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Yes               |
| Nimodipine European Migraine (with aura) trial, 1989, EU, Nimodipine | 2 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Nimodipine European Migraine (Without aura) trial (1989), EU, Nimodipine | 5 | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Unclear |
| Shukla, 1995, UK, Nifedipine               | 5                 | No                 | Unclear                     | Unclear                      | Yes               | Unclear                           | Unclear               | Unclear             | Yes               |
| Solomon, 1983, USA, Verapamil              | 5                 | No                 | Unclear                     | Unclear                      | Yes               | No                               | No                   | Yes                 |
| Stewart, 1988, Canada, Nimodipine          | 2                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Flunarazine                                |                   |                    |                              |                              |                   |                                   |                      |                    |
| Diamond, 1993, USA, Flunarazine            | 2                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Frecken, 1984, Netherlands, Flunarizine    | 6                 | Yes                | Unclear                     | Unclear                      | Yes               | Yes                              | Yes                   | Yes                 |
| Louis, 1981, Belgium, Flunarizine          | 5                 | Yes                | Unclear                     | Unclear                      | Yes               | Yes                              | Yes                   | Yes                 |
| Mendenopoulos, 1985, Greece, Flunarizine   | 7                 | Yes                | Yes                         | Yes                          | Yes               | Yes                              | Unclear               | No                  |
| Pini, 1986, Italy, Flunarizine             | 2                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Sorensen, 1986, Denmark, Flunarizine       | 4                 | No                 | Unclear                     | Unclear                      | Unclear           | Unclear                           | Unclear               | Unclear             | Unclear           |
| Thomas, 1991, India, Flunarizine           | 3                 | No                 | Unclear                     | Unclear                      | Yes               | Unclear                           | Unclear               | Unclear             | Unclear           |
| Selective Serotonin Reuptake Inhibitors    |                   |                    |                              |                              |                   |                                   |                      |                    |
| Adly, 1993, USA, Fluoxetine                | 2                 | No                 | Unclear                     | Yes                          | Unclear           | No                               | No                   | Unclear             | Unclear           |
| d'Amato, 1999, Italy, Fluoxetine           | 5                 | No                 | Unclear                     | Yes                          | Unclear           | No                               | No                   | Unclear             | Unclear           |

(Continued)
## Table 4. (Continued)

| Study                                                                 | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|----------------------------------------------------------------------|------------------|-------------------|------------------------------|------------------------------|------------------|-----------------------------------|-----------------------------------|-------------------|--------------------|
| Landy, 1998, USA, Sertaline                                           | 3                | No                | Unclear                      | Unclear                      | Unclear          | No                                | No                                | Unclear           | No                 |
| Steiner, 1998, UK, s-Fluoxetine                                      | 6                | No                | Unclear                      | Unclear                      | Yes              | No                                | No                                | Unclear           | Unclear            |
| Zeeberg, 1981, Sweden, Fenoxetine                                    | 2                | No                | No                           | No                           | No               | Unclear                           | Unclear                           | Unclear           | Unclear            |
| **Serotonin Norepinephrine Reuptake Inhibitor**                       |                  |                   |                              |                              |                  |                                   |                                   |                   |                    |
| Ozyalcin, 2004, Turkey, Venlafaxine                                    | 3                | No                | Unclear                      | Unclear                      | Unclear          | No                                | No                                | Unclear           | Yes                |
| **Serotonin Agonist (Pizotifen)**                                     |                  |                   |                              |                              |                  |                                   |                                   |                   |                    |
| Arthur, 1971, New Zealand, Pizotifen                                  | 2                | No                | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Yes               | Yes                |
| Bellavance, 1990, Canada, Pizotifen                                  | 4                | No                | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Carroll, 1975, UK, Pizotifen                                          | 4                | No                | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Cleland, 1997, UK, Pizotifen                                          | 4                | No                | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Hughes, 1971, UK, Pizotifen                                           | 4                | Yes               | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Kangasniemi, 1979, Finland, Pizotifen                                  | 4                | Yes               | Unclear                      | Unclear                      | Unclear          | Yes                               | Unclear                           | Unclear           | Unclear            |
| Lance, 1968, Pizotifen                                                |                  |                   |                              |                              |                  |                                   |                                   |                   |                    |
| Lawrence, 1977, UK, Pizotifen                                          | 4                | No                | Unclear                      | Unclear                      | Yes              | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Osterman, 1977, Sweden, Pizotifen                                     | 5                | No                | Unclear                      | Unclear                      | Yes              | Unclear                           | Unclear                           | Unclear           | Unclear            |
| Ryan, 1968, USA, Pizotifen                                            | 5                | No                | Unclear                      | Unclear                      | Unclear          | Unclear                           | Unclear                           | Unclear           | Unclear            |
| **Tricyclic Antidepressants**                                         |                  |                   |                              |                              |                  |                                   |                                   |                   |                    |
| Couch, 1976, USA, Amitriptyline                                       | 3                | No                | Unclear                      | Unclear                      | Yes              | No                                | Unclear                           | Yes               | Yes                |
| Couch, 1979, Amitriptyline                                            | 6                | No                | Unclear                      | Unclear                      | Yes              | No                                | Unclear                           | Yes               | Yes                |
| Couch, 2011, USA, Amitriptyline                                       | 8                | No                | Yes                          | Yes                          | Yes              | No                                | Unclear                           | Yes               | Yes                |
| Gomersall, 1973, UK, Amitriptyline                                    | 3                | No                | Unclear                      | Unclear                      | Unclear          | No                                | No                                | Yes               | Yes                |
| Jacobs, 1972, UK, Opipramol                                           | 4                | No                | Unclear                      | Yes                          | Yes              | No                                | No                                | Yes               | Yes                |
| Langohr, 1985, Germany, Clomipramine                                   | 4                | No                | Unclear                      | Unclear                      | Unclear          | No                                | No                                | Yes               | Yes                |
| Morland, 1979, Norway, Doxepin                                         | 3                | No                | Unclear                      | Unclear                      | Unclear          | No                                | Unclear                           | Yes               | Unclear            |
| Noone, 1980, UK, Clomipramin                                          | 4                | No                | Yes                          | Yes                          | Unclear          | No                                | Unclear                           | Yes               | Yes                |
| Ziegler, 1987, USA, Amitriptyline                                     | 3                | No                | Unclear                      | Yes                          | Yes              | Yes                               | Unclear                           | Unclear           | No                 |

(Continued)
| Study | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|-------|-------------------|-------------------|-----------------------------|-----------------------------|------------------|-------------------------------|-------------------------------|-------------------|-----------------|
| **CHRONIC MIGRAINES** | | | | | | | | | |
| **Alpha-blockers** | | | | | | | | | |
| Saper, 2002, USA | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| **Anticonvulsants** | | | | | | | | | |
| Dieren, 2007, Italy, Topiramate | 8 | No | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes |
| Mei, 2006, Italy, Topiramate | 4 | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| Silberstein, 2007, USA, Topiramate | 8 | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes |
| Silvestrini, 2003, Italy, Topiramate | 4 | Yes | Unclear | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| **Beta Blockers** | | | | | | | | | |
| Palferman, 1983, UK, Propranolol | 3 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| **CHRONIC DAILY HEADACHE** | | | | | | | | | |
| **Anticonvulsants** | | | | | | | | | |
| Beran, 2010, Australia, Levetiracetam | 5 | No | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Spira, 2003, Australia, Gabapentin | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| Yurekli, 2008, Turkey, Valproate | 4 | No | Unclear | Unclear | Yes | Yes | Unclear | Unclear | Yes |
| **Selective Serotonin Reuptake Inhibitors** | | | | | | | | | |
| Saper, 1994, USA, Fluoxetine | 8 | No | Yes | Yes | Yes | Unclear | Unclear | Yes |
| **MIXED (CHRONIC + EPISODIC)** | | | | | | | | | |
| **Anticonvulsants** | | | | | | | | | |
| Ghose, 2002, New Zealand, Vigabatrin | 4 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| **Beta Blockers** | | | | | | | | | |
| Stensrud, 1980, Norway, Atenolol | 5 | No | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| **Unclear Migraine Headache Type** | | | | | | | | | |
| **Beta Blockers** | | | | | | | | | |
| Freitag, 1984, USA, Nadolol | 3 | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| Mathew, 1981, USA, Propranolol, Amtriptyline | 2 | No | Unclear | Unclear | No | No | No | Yes | Unclear |
| Nadelmann, 1986, USA, Propranolol | 6 | No | Unclear | Unclear | Yes | Unclear | Unclear | Yes |
| Weber, 1972, USA, Propranolol | 3 | No | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| **Selective Serotonin Reuptake Inhibitors** | | | | | | | | | |

(Continued)
The average rate of withdrawals was 23%. Studies averaged 15 weeks (range 4–82) with a mean of 153 participants (range 23–487). All of the studies reported headache frequency as their outcome. The two most commonly tested anticonvulsants were topiramate (n = 12) and valproate (n = 6). Other anticonvulsants tested included acetazolamide (n = 1), carbamazepine (n = 1), carisbamate (n = 1), clonazepam (n = 1), gabapentin (n = 4), lamotrigine (n = 1), levetiracetam (n = 3), oxcarbazepine (n = 1), and vigabatrin (n = 1).

In single trials, several anticonvulsants were no better than placebo for episodic migraines including acetazolamide, carbamazepine, carisbamate, clonazepam, oxcarbazepine and vigabatrin (Table 5). In single trials, gabapentin was not superior to placebo (Table 5). Several of these anticonvulsants were assessed for ability to reduce headaches by 50% (Table 7). Carisbamate was less effective than placebo and anticonvulsants no more likely than placebo to reduce headaches by at least 50% included acetazolamide, gabapentin, lamotrigine, levetiracetam and oxcarbazepine.

Anticonvulsants that were found to be more effective than placebo for episodic migraine included levetiracetam (Table 6), topiramate (Fig 4) and valproate (Fig 5). Both topiramate and valproate had numerous trials demonstrating benefit at multiple time points (Table 5).

**Topiramate.** Topiramate has been evaluated in twelve placebo-controlled trials that reported outcomes at numerous time points and different doses (50, 100 and 200mg). Pooled results suggest that topiramate was more effective than placebo at all time points (4–24 weeks, Table 5) and at all doses assessed. There was evidence that higher doses of topiramate was more effective than lower ones, with a stepwise increase as the dose increased from 50 to 100 to 200mg (Fig 6). For chronic migraine, 2 studies of topiramate suggested effectiveness for up to 16 weeks (Table 6). In several studies (n = 8) topiramate was also demonstrated to be more effective than placebo at reducing migraine by more than 50% (Table 7).

**Valproate.** Valproate also had been compared to placebo in six trials with multiple time points and varying doses (500-1500mg). Valproate was found to be more effective than placebo for episodic migraine at all time points assessed including 4, 8 and 12 weeks (Table 5, Fig 5). However, unlike topiramate there was no evidence of a difference in response to increased doses (dose-response p = 0.83). Valproate was also found in numerous trials (n = 5) to reduce headaches by more than 50% (Table 7).

**Beta Blockers.** There were 38 trials comparing beta-blockers to placebo with a total of 2019 participants, 37 focusing on episodic (Table 2) and 1 on chronic migraine headaches (Table 3). The average rate of withdrawals was 18%. Study duration averaged 11 weeks (range 4–64) with a mean of 64 participants (range 20–568). The majority (82%) reported headache frequency, four trials used headache index, and one duration. There were a variety of beta-
| Drug                        | Time Point (weeks) | Metric                | Study (Year)  | Pooled Mean Difference (95% CI) | Heterogeneity |
|-----------------------------|-------------------|-----------------------|---------------|---------------------------------|---------------|
| **Alpha Blockers**          |                   |                       |               |                                 |               |
| Clonidine                   | 8                 | Headaches/month       | Boisen (1978) | -0.09 (-0.99 to 0.80)           |               |
|                             | 8                 | Headaches/month       | Bredfeldt (1989) | -0.96 (-2.6 to 0.64) |               |
|                             | 8                 | Headaches/month       | Ryan (1975)   | -0.46 (-2.7 to 1.8)            |               |
|                             | 8                 | Headaches/month       | Shafar (1972) | -0.72 (-1.6 to 0.14)           |               |
|                             | 8                 | Headaches/month       | Stensrud (1976) | -1.0 (-3.1 to 1.1)            |               |
|                             |                   | **Pooled (HA/Month):** |               | **-0.52 (-1.06 to 0.02)**      | **Q = 1.57, df = 4, I² = 0.0%** |
|                             | 12                | Headaches/month       | Lynggaard (1975) | -0.37 (-3.4 to 2.0)  |               |
|                             | 12                | Headaches/month       | Mondrup (1977) | 1.1 (-2.5 to 4.8)             |               |
|                             |                   | **Pooled (HA/Month):** |               | **0.24 (-2.1 to 2.6)**         | **Q = 0.38, df = 1, I² = 0.0%** |
|                             | 24                | Headaches/month       | Adam (1978)   | 0.00 (-0.47 to 0.47)           |               |
| **Angiotensin Converting Enzyme Inhibitors** | |                       |               |                                 |               |
| Enalapril                   | 4                 | Headaches/month       | Sonbolestan (2013) | -2.4 (-7.5 to 2.7)  |               |
| Enalapril                   | 8                 | Headaches/month       | Sonbolestan (2013) | -0.83 (-6.2 to 4.5) |               |
| Lisinopril                  | 12                | Headaches/month       | Schrader (2001) | -1.4 (-2.6 to -0.2)           |               |
| Captopril                   | 16                | Headache Index        | Paterna (1992) | -0.86 (-1.5 to -0.21)         |               |
| **Angiotensin Receptor Blockers** | |                       |               |                                 |               |
| Candesaran                  | 12                | Headaches/month       | Stovner (2013) | -0.58 (-1.4 to 0.23)          |               |
|                             | 12                | Headaches/month       | Trovnik (2003) | -1.6 (-3.0 to -0.16)          |               |
|                             |                   | **Pooled (HA/Month):** |               | **-0.9 (-1.8 to 0.03)**       | **Q = 1.46, df = 1, I² = 31.7%** |
| Telmisartan                 | 12                | Headaches/month       | Diener (2009) | -1.9 (-3.6 to -0.23)          |               |
|                             |                   | **Pooled (HA/Month):** |               | **-1.1 (-1.9 to -0.27)**      | **Q = 2.82, df = 3 I² = 29.1%** |
| **Anticonvulsants**         |                   |                       |               |                                 |               |
| Acetazolamide               | 12                | Headaches/month       | Vahedi (2002) | 0.5 (-1.7 to 2.7)             |               |
| Carbamazepine               | 6                 | Headaches/month       | Rompel (1970) | -3.2 (-6.6 to 0.20)           |               |
| Carbiramate                 | 14                | Headaches/month       | Cady (2009)   | -0.09 (-0.34 to 0.17)         |               |
| Clonazepam                  | 4                 | Headaches/month       | Stensrud (1979) | -3.6 (-7.2 to 0.03) |               |
| Gabapentin                  | 4                 | Headaches/month       | Di' Trapani   | -0.2 (-1.6 to 1.2)           |               |
|                             | 12                | Headaches/month       | Di' Trapani   | -1.1 (-2.5 to 0.34)           |               |
|                             | 12                | Headaches/month       | Di’ Trapani   | -1.9 (-3.4 to -0.41)          |               |
|                             |                   | **Pooled (HA/Month):** |               | **-0.92 (-2.6 to 0.74)**      | **Q = 4.1, df = 2, I² = 75.6%** |
| Lamotrigine                 | 20                | Headaches/month       | Silberstein (2013) | -0.33 (-0.71 to 0.04) |               |
|                             | 4                 | Headaches/month       | Gupta (2006)  | -1.2 (-2.2 to -0.18)          |               |
|                             | 12                | Headaches/month       | Steiner (1997) | 0.20 (-0.36 to 0.76)          |               |
| Levetiracetam               | 8                 | Headaches/month       | De Tommaso (2007) | -4.2 (-7.2 to -1.3) |               |
|                             | 12                | Headaches/month       | Verma (2013)  | -2.2 (-3.0 to -1.3)           |               |
|                             |                   | **Pooled (HA/Month):** |               | **-2.7 (-4.4 to -0.97)**      | **Q = 1.69, df = 1 I² = 40.9%** |
| Oxcarbazepine               | 15                | Headaches/month       | Silberstein (2008) | 0.17 (-0.13 to 0.47) |               |
| Topiramate                  | 4                 | Headaches/month       | Brandes (2004) | -0.75 (-1.4 to -0.06)         |               |
|                             | 4                 | Headaches/month       | Gupta (2006)  | -2.1 (-3.0 to -1.1)           |               |
|                             | 4                 | Headaches/month       | Silberstein (2004) | -1.0 (-1.9 to -0.13) |               |
|                             | 4                 | Headaches/month       | Silvestrini (2003) | -5.0 (-9.2 to -0.8)          |               |
|                             | 4                 | **Pooled (HA/Month):** |               | **-1.4 (-2.2 to -0.5)**       | **Q = 7.81, df = 3, I² = 43.0%** |

(Continued)
| Drug          | Time Point (weeks) | Metric         | Study (Year)          | Pooled Mean Difference (95% CI) | Heterogeneity |
|---------------|--------------------|----------------|-----------------------|--------------------------------|---------------|
| Topiramate    | 4 (100 mg/day)     | Headaches/month| Brandes (2004)        | -0.80 (-1.4 to -0.18)          |               |
|               | 4 (100 mg/day)     | Headaches/month| Diener (2004)         | -1.1 (-1.9 to -0.2)            |               |
|               | 4 (100 mg/day)     | Headaches/month| Silberstein (2004)    | -0.9 (-1.7 to -0.14)           |               |
|               | 4 (100 mg/day)     | Pooled (HA/Month)| -0.89 (-1.3 to -0.48) | Q = 0.23, df = 2, I^2 = 0.0%  |               |
|               | 4 (200 mg/day)     | Headaches/month| Brandes (2004)        | -1.9 (-2.4 to -1.3)            |               |
|               | 4 (200 mg/day)     | Headaches/month| Edwards (2003)        | -0.60 (-1.1 to -0.13)          |               |
|               | 4 (200 mg/day)     | Headaches/month| Silberstein (2004)    | -1.4 (-2.2 to -0.62)           |               |
|               | 4 (200 mg/day)     | Headaches/month| Silberstein (2006)    | -0.9 (-2.3 to 0.55)            |               |
|               | 4 (200 mg/day)     | Pooled (HA/Month)| -0.91 (-1.3 to -0.48) | Q = 12.07, df = 3, I^2 = 75.1% |               |
|               | 4 (all doses)      | Pooled (HA/Month)| -1.1 (-1.5 to -0.79)  | Q = 21.3, df = 10, I^2 = 53%  |               |
|               | 8 (50 mg/day)      | Headaches/month| Brandes (2004)        | -0.50 (0.12 to 0.19)           |               |
|               | 8 (50 mg/day)      | Headaches/month| Silberstein (2004)    | -0.80 (-1.4 to -0.20)          |               |
|               | 8 (50 mg/day)      | Headaches/month| Silberstein (2006)    | -12.5 (-17.1 to -7.9)          |               |
|               | 8 (50 mg/day)      | Pooled (HA/Month)| -2.3 (-4.4 to -0.23)  | Q = 25.56, df = 2, I^2 = 92.2% |               |
|               | 8 (100 mg/day)     | Headaches/month| Brandes (2004)        | -0.8 (-1.4 to -0.18)           |               |
|               | 8 (100 mg/day)     | Headaches/month| De Tammossa (2007)    | -5.2 (-7.8 to -2.5)            |               |
|               | 8 (100 mg/day)     | Headaches/month| Diener (2004)         | -0.85 (-2.1 to 0.39)           |               |
|               | 8 (100 mg/day)     | Headaches/month| Silberstein (2004)    | -1.1 (-1.7 to -0.53)           |               |
|               | 8 (100 mg/day)     | Pooled (HA/Month)| -1.3 (-2.2 to -0.43)  | Q = 10.18, df = 3, I^2 = 70.5% |               |
|               | 8 (200 mg/day)     | Headaches/month| Brandes (2004)        | -1.8 (-2.3 to -1.3)            |               |
|               | 8 (200 mg/day)     | Headaches/month| Silberstein (2004)    | -1.5 (-2.1 to -0.9)            |               |
|               | 8 (200 mg/day)     | Headaches/month| Silberstein (2006)    | -0.30 (-1.7 to 1.1)            |               |
|               | 8 (200 mg/day)     | Pooled (HA/Month)| -1.5 (-2.1 to -0.87)  | Q = 3.68, df = 2, I^2 = 45.7%  |               |
|               | 8 (All Doses)      | Pooled (HA/Month)| -1.3 (-1.9 to -0.7)   | Q = 46.42, df = 9, I^2 = 80.6% |               |
|               | 12 (50 mg/day)     | Headaches/month| Brandes (2004)        | -0.40 (-1.1 to 0.29)           |               |
|               | 12 (50 mg/day)     | Headaches/month| Silberstein (2004)    | -0.70 (-1.4 to 0.02)           |               |
|               | 12 (50 mg/day)     | Pooled (HA/Month): -0.54 (-1.0 to -0.05) | Q = 0.39, df = 2, I^2 = 0.0%  |               |
|               | 12 (100 mg/day)    | Headaches/month| Brandes (2004)        | -0.75 (-1.4 to -0.13)          |               |
|               | 12 (100 mg/day)    | Headaches/month| Diener (2004)         | -0.90 (-2.2 to 0.39)           |               |
|               | 12 (100 mg/day)    | Headaches/month| Silberstein (2004)    | -1.1 (-2.0 to -0.19)           |               |
|               | 12 (100 mg/day)    | Pooled (HA/Month): -0.87 (-1.3 to -0.39) | Q = 1.52, df = 2, I^2 = 0.0%  |               |
|               | 12 (200 mg/day)    | Headaches/month| Brandes (2004)        | -1.7 (-2.2 to -1.1)            |               |
|               | 12 (200 mg/day)    | Headaches/month| Silberstein (2004)    | -1.4 (-2.2 to -0.59)           |               |
|               | 12 (200 mg/day)    | Headaches/month| Silberstein (2006)    | -0.70 (-2.1 to 0.75)           |               |
|               | 12 (200 mg/day)    | Pooled (HA/Month): -1.5 (-1.9 to -1.1) | Q = 0.35, df = 1, I^2 = 0.0%  |               |
|               | 12 (All doses)     | Pooled (HA/Month): -0.99 (-1.3 to -0.64) | Q = 0.04, df = 1, I^2 = 0.0%  |               |
|               | 16 (50 mg/day)     | Headaches/month| Brandes (2004)        | -0.50 (-1.2 to 0.19)           |               |
|               | 16 (50 mg/day)     | Headaches/month| Silberstein (2004)    | -0.40 (-1.1 to 0.33)           |               |
|               | 16 (50 mg/day)     | Pooled (HA/Month): -0.45 (-0.95 to 0.05) | Q = 0.04, df = 1, I^2 = 0.0%  |               |
|               | 16 (100 mg/day)    | Headaches/month| Brandes (2004)        | -0.70 (-1.3 to -0.08)          |               |
|               | 16 (100 mg/day)    | Headaches/month| Diener (2004)         | -1.1 (-2.4 to 0.24)            |               |
|               | 16 (100 mg/day)    | Headaches/month| Silberstein (2004)    | -1.2 (-2.0 to -0.38)           |               |
|               | 16 (100 mg/day)    | Headaches/month| Silberstein (2007)    | -1.5 (-3.1 to 0.06)            |               |
|               | 16 (100 mg/day)    | Pooled (HA/Month): -0.95 (-1.4 to -0.51) | Q = 1.51, df = 3, I^2 = 0.0%  |               |
|               | 16 (200 mg/day)    | Headaches/month| Brandes (2004)        | -1.6 (-2.1 to -1.1)            |               |
| Drug        | Time Point (weeks) | Metric         | Study (Year) | Pooled Mean Difference (95% CI) | Heterogeneity   |
|-------------|--------------------|----------------|--------------|---------------------------------|-----------------|
| 16 (200 mg/day) | Headaches/month   | Silberstein (2004) | -1.3 (-2.2 to -0.45) |                                 |                 |
| 16 (200 mg/day) | Headaches/month   | Silberstein (2006) | -0.05 (-1.5 to 1.4) |                                 |                 |
| 16 (200 mg/day) | Headaches/month   | Storey (2001)    | -0.52 (-1.67 to 0.63) |                                 |                 |
| 16 (200 mg/day) | Headaches/month   | Pooled (HA/Month): | -1.0 (-1.7 to -0.44) | Q = 5.76, df = 3, I² = 47.9% |                 |
| 16 (All doses)   | Headaches/month   | Pooled (HA/Month): | -0.92 (-1.2 to -0.59) | Q = 13.41, df = 9, I² = 32.9% |                 |
| 20 (50mg/day)    | Headaches/month   | Brandes (2004)   | -0.50 (-1.2 to 0.19) |                                 |                 |
| 20 (50mg/day)    | Headaches/month   | Silberstein (2004) | -0.55 (-1.5 to 0.40) |                                 |                 |
| 20 (50mg/day)    | Headaches/month   | Pooled (HA/Month): | -0.52 (-1.1 to -0.04) | Q = 0.01, df = 1, I² = 0.0% |                 |
| 20 (100 mg/day)  | Headaches/month   | Brandes (2004)   | -0.70 (-1.3 to -0.08) |                                 |                 |
| 20 (100 mg/day)  | Headaches/month   | Diener (2004)    | -1.2 (-2.6 to 0.17) |                                 |                 |
| 20 (100 mg/day)  | Headaches/month   | Silberstein (2004) | -1.4 (-2.3 to -0.39) |                                 |                 |
| 20 (100 mg/day)  | Headaches/month   | Pooled (HA/Month): | -0.93 (-1.4 to -0.44) | Q = 1.42, df = 2, I² = 0.0% |                 |
| 20 (200 mg/day)  | Headaches/month   | Brandes (2004)   | -1.5 (-2.0 to -0.95) |                                 |                 |
| 20 (200 mg/day)  | Headaches/month   | Silberstein (2004) | -1.4 (-2.3 to -0.36) |                                 |                 |
| 20 (200 mg/day)  | Headaches/month   | Silberstein (2006) | -0.50 (-1.9 to 0.95) |                                 |                 |
| 20 (200 mg/day)  | Headaches/month   | Pooled (HA/Month): | -1.4 (-1.8 to 0.92) | Q = 1.61, df = 2, I² = 0.0% |                 |
| 20 (all doses)   | Headaches/month   | Pooled (HA/Month): | -0.98 (-1.3 to -0.66) | Q = 8.52, df = 7, I² = 17.8% |                 |
| 24 (50 mg/day)   | Headaches/month   | Brandes (2004)   | -0.40 (-1.2 to 0.44) |                                 |                 |
| 24 (50 mg/day)   | Headaches/month   | Silberstein (2004) | -0.50 (-1.5 to 0.48) |                                 |                 |
| 24 (50 mg/day)   | Headaches/month   | Pooled (HA/Month): | -0.44 (-1.1 to 0.20) | Q = 0.02, df = 1, I² = 0.0% |                 |
| 24 (100 mg/day)  | Headaches/month   | Brandes (2004)   | -1.0 (-1.8 to -0.18) |                                 |                 |
| 24 (100 mg/day)  | Headaches/month   | Lipton (2011)    | -1.4 (-2.2 to -0.60) |                                 |                 |
| 24 (100 mg/day)  | Headaches/month   | Silberstein (2004) | -1.3 (-2.3 to -0.34) |                                 |                 |
| 24 (100 mg/day)  | Headaches/month   | Pooled (HA/Month): | -1.2 (-1.7 to -0.74) | Q = 0.49, df = 2, I² = 0.0% |                 |
| 24 (200 mg/day)  | Headaches/month   | Brandes (2004)   | -1.5 (-2.2 to -0.84) |                                 |                 |
| 24 (200 mg/day)  | Headaches/month   | Silberstein (2004) | -1.3 (-2.3 to -0.31) |                                 |                 |
| 24 (200 mg/day)  | Headaches/month   | Pooled (HA/Month): | -1.4 (-2.0 to -0.89) | Q = 0.11, df = 1, I² = 0.0% |                 |
| 24 (All doses)   | Headaches/month   | Pooled (HA/Month): | -1.1 (-1.4 to -0.77) | Q = 6.4, df = 6, I² = 6.4% |                 |
| Valproate       | Headaches/month   | Freitag (2002)   | -0.20 (-0.61 to 0.21) |                                 |                 |
| 4              | Headaches/month   | Klapper (1997)   | -1.8 (-2.6 to -0.95) |                                 |                 |
| 4              | Headaches/month   | Mathew (1995)    | -1.8 (-3.6 to -0.03) |                                 |                 |
| 4              | Headaches/month   | Pooled (HA/Month): | -1.4 (-2.2 to -0.56) | Q = 14.48, df = 2, I² = 51.6% |                 |
| 8              | Headaches/month   | Freitag (2002)   | -0.25 (-0.51 to 0.01) |                                 |                 |
| 8              | Headaches/month   | Hering (1992)    | -6.8 (-12.10 to -1.5) |                                 |                 |
| 8              | Headaches/month   | Klapper (1997)   | -1.6 (-2.3 to -0.95) |                                 |                 |
| 8              | Headaches/month   | Mathew (1995)    | -2.1 (-3.6 to -0.56) |                                 |                 |
| 8              | Headaches/month   | Pooled (HA/Month): | -1.5 (-2.2 to -0.76) | Q = 17.35, df = 3, I² = 42.6% |                 |
| 12             | Headaches/month   | Freitag (2002)   | -0.45 (-0.86 to -0.04) |                                 |                 |
| 12             | Headaches/month   | Jensen (1994)    | -2.6 (-5.5 to 0.26) |                                 |                 |
| 12             | Headaches/month   | Klapper (1997)   | -1.7 (-2.4 to -0.96) |                                 |                 |
| 12             | Headaches/month   | Mathew (1995)    | -2.8 (-4.8 to -0.74) |                                 |                 |
| 12             | Headaches/month   | Pooled (HA/Month): | -1.5 (-2.1 to -0.80) | Q = 24.7, I² = 63.6% |                 |

(Continued)
| Drug          | Time Point (weeks) | Metric          | Study (Year)          | Pooled Mean Difference (95% CI) | Heterogeneity |
|--------------|-------------------|-----------------|-----------------------|---------------------------------|---------------|
| **Vigabatrin** |                   |                 |                       |                                 |               |
|              | 4                 | Headaches/month | Ghose (2002)          | -0.54 (-1.9 to 0.77)            |               |
|              | 8                 | Headaches/month | Ghose (2002)          | -0.27 (-2.3 to 1.7)             |               |
|              | 12                | Headaches/month | Ghose (2002)          | -0.42 (-2.3 to 1.6)             |               |
| **Beta-Blockers** |                 |                 |                       |                                 |               |
| Acebutolol   | 4                 | Headaches/month | Nanda (1977)          | 0.10 (-0.75 to 0.95)            |               |
|              | 8                 | Headaches/month | Nanda (1977)          | -0.50 (-1.35 to 0.35)           |               |
|              | 12                | Headaches/month | Nanda (1977)          | -0.68 (-1.68 to 0.32)           |               |
| Alprenolol   | 8                 | Headaches/month | Ekbom (1975)         | 0.20 (-0.91 to 1.3)             |               |
| Atenolol     | 8                 | Headaches/month | Stensrud (1980)      | -1.5 (-3.0 to -0.04)            |               |
|              | 12                | Headaches/month | Forsman (1983)       | -5.4 (-12.6 to 1.8)             |               |
|              | 12                | Headaches/month | Johansson (1987)     | -2.05 (-3.76 to 0.48)           |               |
| Bisoprolol   | 4                 | Headaches/month | Van de Ven (1997)    | -0.40 (-0.67 to 0.07)           | Q = 0.80, df = 1, I² = 0.0% |
|              | 8                 | Headaches/month | Van de Ven (1997)    | -0.61 (-1.11 to -0.16)          |               |
| Metoprolol   | 4                 | Headaches/month | Langor (1985)        | -0.63 (-1.5 to 0.25)            |               |
|              | 8                 | Headaches/month | Andersson (1983)     | -1.5 (-2.4 to -0.60)            |               |
|              | 8                 | Headaches/month | Kangasniemi (1987)   | -0.70 (-1.4 to -0.03)           |               |
|              | 8                 | Headaches/month | Steiner (1987)       | -0.80 (-1.7 to 0.13)            |               |
|              | 12                | Pooled SMD      | -2.2 (-3.7 to -0.67) | Q = 1.02, I² = 0.0%             |               |
| Oxprenolol   | 8                 | Headaches/month | Ekbom (1977)         | -0.80 (-3.9 to 2.3)             |               |
| Pindolol     | 4                 | Headaches/month | Ekbom (1972)         | 2.9 (-1.0 to 6.8)               | Q = 0.49, I² = 0.0% |
|              | 4                 | Headaches/month | Sjaastad (1972)      | 1.5 (-5.5 to 2.6)               |               |
|              | 4                 | Pooled HA/Month | 1.2 (-2.5 to 4.9)    | Q = 3.44, df = 3, I² = 0.00%   |               |
| Propranolol  | 4                 | Headaches/month | Dahlof (1987)        | -1.1 (-2.2 to 0.05)             |               |
|              | 4                 | Headaches/month | Diener (2004)        | -1.1 (-1.9 to -0.28)            |               |
|              | 4                 | Headaches/month | Pradalier (1989)     | -1.5 (-2.1 to -0.87)            |               |
|              | 4                 | Headaches/month | Stensrud (1976)      | -1.1 (-3.5 to 1.3)              |               |
|              | 4                 | Pooled HA/Month | -1.1 (-1.5 to -0.74) | Q = 11.08, df = 4, I² = 54.9%  |               |
|              | 8                 | Headache Index  | Zeigler (1987)       | -0.68 (-1.4 to 0.06)            |               |
|              | 8                 | Headaches/month | Ahuja (1985)         | -5.9 (-11.4 to -0.37)           |               |
|              | 8                 | Headaches/month | Al-Qassab (1993)     | 0.6 (-2.84 to 4.0)              |               |
|              | 8                 | Headaches/month | Diener (2004)        | -0.8 (-1.6 to -0.005)           |               |
|              | 8                 | Headaches/month | Holroyd (2010)       | -0.6 (-1.3 to 0.12)             |               |
|              | 8                 | Headaches/month | Pita (1977)          | -5.3 (-8.7 to -1.8)             |               |
|              | 8                 | Pooled HA/Month | -1.0 (-2.1 to -0.39) | Q = 11.08, df = 4, I² = 54.9%  |               |
|              | 12                | Headache index  | Nadelmann (1986)     | -0.54 (-1.11 to 0.04)           |               |
|              | 12                | Headaches/month | Borgesen (1974)      | -0.30 (-1.1 to -0.48)           |               |
|              | 12                | Headaches/month | Diener (2004)        | -0.80 (-1.6 to -0.02)           |               |
|              | 12                | Headaches/month | Forssman (1976)      | -1.8 (-3.9 to 0.4)              |               |
|              | 12                | Headaches/month | Holroyd (2010)       | -0.8 (-1.5 to -0.08)            |               |
|              | 12                | Headaches/month | Johnson (1986)       | -6.3 (-16.6 to 3.9)             |               |
|              | 12                | Headaches/month | Mikkelsen (1986)     | -2.4 (-7.9 to 3.1)              |               |
|              | 12                | Headaches/month | Pradalier (1989)     | -3.3 (-3.9 to -2.6)             |               |
|              | 12                | Headaches/month | Stovner (2013)       | -0.62 (-1.4 to 0.16)            |               |

(Continued)
| Drug | Time Point (weeks) | Metric                        | Study (Year)             | Pooled Mean Difference (95% CI) | Heterogeneity |
|------|-------------------|-------------------------------|--------------------------|--------------------------------|---------------|
|      |                   |                               |                          |                                |               |
|      |                   |                               |                          | -1.2 (-2.8 to 0.45)            |               |
|      |                   |                               |                          | -1.3 (-1.8 to -0.78)           |               |
|      |                   |                               |                          | -1.3 (-2.0 to -0.62)           | Q = 46.35, df = 10, \( I^2 = 78.4\% \) |
|      |                   |                               |                          | -12.9 (-31.8 to 5.9)           |               |
|      |                   |                               |                          | -1.1 (-2.2 to -0.01)           |               |
|      |                   |                               |                          | -0.90 (-2.6 to -0.19)          |               |
|      |                   |                               |                          | 0.5 (-0.22 to 1.2)             |               |
|      |                   |                               |                          | -1.3 (-2.0 to -0.62)           | Q = 46.35, df = 10, \( I^2 = 78.4\% \) |
|      |                   |                               |                          | -1.5 (-2.9 to -0.03)           |               |
|      |                   |                               |                          | -0.9 (-1.6 to -0.18)           |               |
|      |                   |                               |                          | -1.0 (-1.7 to -0.37)           | Q = 0.52, df = 1, \( I^2 = 0.0\% \) |
|      |                   |                               |                          | -2.3 (-5.2 to 0.63)            |               |
|      |                   |                               |                          | -0.70 (-1.5 to 0.07)           |               |
|      |                   |                               |                          | -0.85 (-1.8 to 0.07)           | Q = 1.01, df = 1, \( I^2 = 6.8\% \) |
|      |                   |                               |                          | -1.9 (-3.2 to -0.54)           |               |
|      |                   |                               |                          | -1.5 (-3.0 to 0.05)            |               |
|      |                   |                               |                          | -1.7 (-2.7 to -0.70)           | Q = 0.12, df = 1, \( I^2 = 0.0\% \) |
|      |                   |                               |                          | 15.0 hours (-5.3 to 35.3)      |               |
|      |                   |                               |                          | -1.6 (-3.3 to 0.15)            |               |
|      |                   |                               |                          | -0.20 (-0.72 to 0.32)          |               |
|      |                   |                               |                          | -3.8 (-4.8 to -2.8)            |               |
|      |                   |                               |                          | -2.0 (-5.5 to 1.6)             | Q = 2.92, df = 1, \( I^2 = 65.8\% \) |
|      |                   |                               |                          | -0.20 (-0.72 to 0.32)          |               |
|      |                   |                               |                          | -0.40 (-1.4 to 0.66)           |               |
|      |                   |                               |                          | -0.13 (-0.64 to 0.38)          |               |
|      |                   |                               |                          | 0.48 (-0.47 to 0.46)           |               |
|      |                   |                               |                          | 0.10 (-0.21 to 0.41)           |               |
|      |                   |                               |                          | -0.31 (-3.3 to 2.7)            |               |
|      |                   |                               |                          | -0.07 (-0.28 to 0.13)          | Q = 1.51, df = 3, \( I^2 = 0.0\% \) |
|      |                   |                               |                          | -0.36 (-0.88 to 0.16)          |               |
|      |                   |                               |                          | -1.5 (-2.4 to -0.73)           |               |
|      |                   |                               |                          | -2.2 (-4.2 to -0.24)           |               |
|      |                   |                               |                          | 0.17 (-0.54 to 0.88)           |               |
|      |                   |                               |                          | 0.94 (-0.45 to 2.32)           |               |
|      |                   |                               |                          | -3.4 (-5.7 to -1.1)            |               |
|      |                   |                               |                          | -0.09 (-2.3 to 0.30)           | Q = 22.35, df = 4, \( I^2 = 82.1\% \) |
|      |                   |                               |                          | -0.48 (-1.01 to 0.05)          |               |
|      |                   |                               |                          | -1.3 (-1.9 to -0.69)           |               |
|      |                   |                               |                          | 0.74 (0.03 to 1.5)             |               |
|      |                   |                               |                          | -0.01 (-1.4 to 1.4)            |               |
|      |                   |                               |                          | -2.8 (-5.2 to -0.48)           |               |
|      |                   |                               |                          | -0.65 (-2.0 to 0.74)           | Q = 22.41, df = 4, \( I^2 = 86.6\% \) |
|      |                   |                               |                          | 0.16 (-0.36 to 0.68)           |               |
| Drug        | Time Point (weeks) | Metric            | Study (Year)          | Pooled Mean Difference (95% CI) | Heterogeneity |
|-------------|-------------------|-------------------|-----------------------|-------------------------------|---------------|
| Verapamil   | 4                 | Headaches/month   | Solomon (1983)        | -2.9 (-7.8 to 1.9)            |               |
|             | 8                 | Headaches/month   | Markley (1984)        | -0.60 (-1.4 to 0.19)          |               |
| Flunarizine | 4                 | Headaches/month   | Diamond (1993)        | 0.60 (-0.35 to 0.47)          |               |
|             | 4                 | Headaches/month   | Frenken (1984)        | -1.3 (-2.4 to -0.24)          |               |
|             | 4                 | Pooled Ha/Month   |                       | -0.53 (-1.8 to 0.79)          | Q = 5.51, df = 1, I² = 81.9% |
|             | 4                 | Headache Index    | Mendenopoulos (1985)  | -0.63 (1.5 to 0.27)           |               |
|             | 4                 | Headache Index    | Pini (1986)           | 0.19 (-0.73 to 1.1)           |               |
|             | 4                 | Headache Index    | Pooled SMD            | -0.23 (-1.0 to 0.58)          | Q = 1.56, df = 1, I² = 35.8% |
|             | 4                 | Overall Pooled SMD|                       | -0.27 (-0.76 to 0.23)         | Q = 6.15, df = 3, I² = 51.2% |
|             | 8                 | Headaches/month   | Diamond (1993)        | -0.44 (-1.7 to 0.78)          |               |
|             | 8                 | Headaches/month   | Frenken (1984)        | -1.9 (-3.5 to -0.31)          |               |
|             | 8                 | Pooled Ha/Month   |                       | -1.1 (-2.5 to 0.34)           | Q = 2.04, df = 1, I² = 51.1% |
|             | 8                 | Headache Index    | Mendenopoulos (1985)  | -1.2 (-2.1 to -0.2)           |               |
|             | 8                 | Overall Pooled SMD|                       | -0.60 (-1.2 to 0.005)         | Q = 4.92, df = 2, I² = 59.3% |
|             | 12                | Headaches/month   | Diamond (1993)        | -0.61 (-1.8 to 0.65)          |               |
|             | 12                | Headaches/month   | Frenken (1984)        | -1.8 (-3.3 to -0.38)          |               |
|             | 12                | Headaches/month   | Louis (1981)          | -1.1 (-1.7 to -0.6)           |               |
|             | 12                | Pooled Ha/Month   |                       | -1.1 (-1.6 to -0.67)          | Q = 1.39, df = 2, I² = 0.0% |
|             | 12                | Headache Index    | Mendenopoulos (1985)  | -1.6 (-2.6 to -0.6)           |               |
|             | 12                | Headache Index    | Thomas (1989)         | -0.87 (2.0 to 0.24)           |               |
|             | 12                | Headache Index    | Pooled SMD            | -1.3 (-2.0 to -0.52)          | Q = 0.94, df = 1, I² = 0.0% |
|             | 12                | Overall Pooled SMD|                       | -0.84 (-1.3 to -0.34)         | Q = 10.33, df = 4, I² = 61.3% |
|             | 16                | Headaches/month   | Diamond (1993)        | -1.2 (-2.1 to -0.24)          |               |
|             | 16                | Headaches/month   | Sorensen (1986)       | -1.2 (-2.7 to 0.37)           |               |
|             | 16                | Pooled Ha/Month   |                       | -1.2 (-2.0 to -0.38)          |               |
|             | 20                | Headaches/month   | Diamond (1993)        | -0.36 (-2.4 to 1.69)          |               |
| Selective Serotonin Reuptake Inhibitors | | | | | |
| Feneritine  | 4                 | Headaches/month   | Orholm (1986)         | -0.20 (-1.3 to 0.93)          |               |
|             | 4                 | Headaches/month   | Zeeberg (1981)        | 0.00 (-1.8 to 1.8)            |               |
|             | 4                 | Pooled Ha/Month   |                       | -0.14 (-1.1 to 0.81)          | Q = 0.03, df = 1, I² = 0.0% |
|             | 8                 | Headaches/month   | Orholm (1986)         | -0.10 (-1.2 to 1.0)           |               |
|             | 8                 | Headaches/month   | Zeeberg (1981)        | -1.8 (-3.6 to -0.04)          |               |
|             | 8                 | Pooled Ha/Month   |                       | -0.81 (-2.5 to 0.83)          | Q = 2.53, df = 1, I² = 60.4% |
|             | 12                | Headaches/month   | Orholm (1986)         | 0.50 (-0.63 to 1.6)           |               |
|             | 12                | Headaches/month   | Zeeberg (1981)        | -1.4 (-3.2 to 0.36)           |               |
|             | 12                | Pooled Ha/Month   |                       | -0.33 (-2.2 to 1.5)           | Q = 3.16, df = 1, I² = 68.3% |
|             | 16                | Headaches/month   | Orholm (1986)         | 0.30 (-0.83 to 1.4)           |               |

(Continued)
### Table 5. (Continued)

| Drug              | Time Point (weeks) | Metric            | Study (Year)         | Pooled Mean Difference (95% CI) | Heterogeneity |
|-------------------|-------------------|-------------------|----------------------|---------------------------------|---------------|
| **Fluoxetine**    |                   |                   |                      |                                 |               |
| -                 | 4                 | Headache index    | Adly (1993)          | -0.34 (-1.27 to 0.59)           |               |
| -                 | 4                 | Headache index    | d’Amato (1999)       | -0.08 (-0.63 to 0.48)           |               |
| -                 | 4                 | Headaches/month   | Steiner (1998)       | -0.71 (-1.36 to -0.06)          |               |
| -                 | 8                 | Headache index    | Adly (1993)          | -0.74 (-1.70 to 0.22)           |               |
| -                 | 8                 | Headache index    | d’Amato (1999)       | -0.01 (-0.56 to 0.55)           |               |
| -                 | 8                 | Headaches/month   | Steiner (1998)       | -0.32 (-0.98 to 0.35)           |               |
| -                 | 8                 | Pooled SMD        |                      | -0.35 (-0.75 to 0.05)           | Q = 2.11, df = 3, $I^2 = 5.2\%$ |
| -                 | 12                | Headache index    | Adly (1993)          | -1.02 (-2.01 to -0.03)          |               |
| -                 | 12                | Headache index    | d’Amato (1999)       | -0.32 (-0.88 to 0.24)           |               |
| -                 | 12                | Headaches/month   | Steiner (1998)       | -0.74 (-1.44 to -0.03)          |               |
| -                 | 12                | Pooled SMD        |                      | -0.57 (-0.97 to -0.17)          | Q = 1.77, df = 2, $I^2 = 0.0\%$ |
| -                 | 16                | Headache index    | d’Amato (1999)       | -0.64 (-1.22 to -0.07)          |               |
| -                 | 20                | Headache index    | d’Amato (1999)       | -0.32 (-0.88 to 0.24)           |               |
| -                 | 8                 | Pooled SMD        |                      | -0.23 (-0.63 to 0.16)           | Q = 1.76, $I^2 = 0.0\%$ |
| -                 |                   |                   |                      |                                 |               |
| **Sertraline**    |                   |                   |                      |                                 |               |
| -                 | 4                 | Headache index    | Landy (1999)         | 0.44 (-0.59 to 1.5)             |               |
| -                 | 8                 | Headache index    | Landy (1988)         | 0.08 (-0.94 to 1.09)            |               |
| -                 |                   | Pooled SMD (12 weeks) |                  | -0.35 (-0.75 to 0.05)          | Q = 7.49, df = 4, $I^2 = 46.6\%$ |
| **Serotonin Norepinephrine Reuptake Inhibitors** | | | | | |
| Venlafaxine       | 8                 | Headaches/month   | Ozyalcin (2004)      | -2.0 (-4.0 to -0.06)            |               |
| **Serotonin Antagonist** | | | | | |
| Pizotifen         |                   |                   |                      |                                 |               |
| -                 | 4                 | Headaches/month   | Arthur (1971)        | -0.51 (-1.07 to 0.05)           |               |
| -                 | 4                 | Headaches/month   | Ryan (1968)          | -0.36 (-0.86 to 0.15)           |               |
| -                 | 4                 | Pooled HA/month   |                      | -0.42 (-0.80 to -0.05)          | Q = 0.16, df = 1, $I^2 = 0.0\%$ |
| -                 | 4                 | Headache index    | Carroll (1975)       | 0.18 (-0.87 to 1.23)            |               |
| -                 | 4                 | Headache index    | Lawrence (1977)      | -0.04 (-0.78 to 0.70)           |               |
| -                 | 4                 | Pooled SMD        |                      | -0.15 (-0.47 to 0.17)           | Q = 6.40, df = 1, $I^2 = 0.0\%$ |
| -                 | 4                 | Overall Pooled SMD|                      | -0.30 (-0.62 to 0.02)           | Q = 6.40, df = 7, $I^2 = 0.0\%$ |
| -                 | 8                 | Headaches/month   | Kangasniemi (1979)   | -0.57 (-1.26 to 0.12)           |               |
| -                 | 8                 | Headaches/month   | Osterman (1977)      | -0.63 (-1.4 to 0.1)             |               |
| -                 | 8                 | Pooled HA/month   |                      | -0.60 (-1.1 to -0.08)           | Q = 0.01, df = 1, $I^2 = 0.0\%$ |
| -                 | 8                 | Headache index    | Lawrence (1977)      | -0.56 (-1.32 to 0.20)           |               |
| -                 | 8                 | Overall Pooled SMD|                      | -0.48 (-0.85 to -0.12)          | Q = 1.37, df = 4, $I^2 = 0.0\%$ |
| -                 | 12                | Headaches/month   | Bellavance (1990)    | -0.49 (-0.86 to -0.12)          |               |
| -                 | 12                | Headaches/month   | Cleland (1997)       | -0.41 (-0.83 to 0.14)           |               |
| -                 | 12                | Headaches/month   | Hughes (1971)        | -0.26 (-1.03 to 0.52)           |               |
| -                 | 12                | Pooled HA/month   |                      | -0.43 (-0.66 to -0.21)          | Q = 0.30, df = 2, $I^2 = 0.0\%$ |
| -                 | 12                | Headache index    | Lawrence (1977)      | -0.56 (-1.32 to 0.20)           |               |
| -                 | 12                | Overall Pooled SMD|                      | -0.44 (-0.69 to -0.20)          | Q = 0.48, df = 5, $I^2 = 0.0\%$ |
| **Tricyclic Antidepressants** | | | | | |
| Amitriptyline     | 4                 | Headache index    | Couch (2011)         | -0.34 (-0.62 to -0.05)          |               |
| -                 | 4                 | Headache index    | Zeigler (1987)       | -0.52 (-1.25 to 0.21)           |               |
| -                 | 4                 | Pooled SMD        |                      | -0.57 (-0.92 to -0.23)          | Q = 0.08, df = 1, $I^2 = 0.0\%$ |
| -                 | 24                | Headaches/month   | Gomersall (1973)     | -1.29 (-1.79 to -0.46)          |               |
| -                 | 24                | Headache index    | Mathew (1981)        | -1.31 (-1.85 to -0.77)          |               |
| -                 | 24                | Pooled SMD        |                      | -1.2 (-1.7 to -0.82)            | Q = 0.35, df = 2, $I^2 = 0.0\%$ |

(Continued)
blockers tested including acebutolol (n = 1), alprenolol (n = 1), atenolol (n = 3), bisoprolol (n = 1), metoprolol (n = 4), oxprenolol (n = 1), pindolol (n = 2), propranolol (n = 19) and timolol (n = 4).

Beta blockers no more effective than placebo included acebutolol, alprenolol, bisoprolol, oxprenolol and pindolol (Table 5). Beta-blockers superior to placebo for episodic migraine headaches (Table 5) included atenolol, metoprolol, propranolol (Fig 7) and timolol. Seven studies found that propranolol reduced headache by 50% (Table 7). Neither atenolol (1 study) nor propranolol (2 studies) were effective for chronic migraine (Table 6).

**Calcium Channel Blockers.** Calcium blockers headache trials tested cyclandelate (n = 1), nicardipine (n = 1), nifedipine (n = 2), nimodipine (n = 5) and verapamil (n = 2). All studies focused on episodic migraines (Table 2). Overall there were a total of 878 participants who

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Table 5. (Continued)

| Drug       | Time Point (weeks) | Metric               | Study (Year)       | Pooled Mean Difference (95% CI)       | Heterogeneity |
|------------|--------------------|----------------------|--------------------|---------------------------------------|---------------|
| Clomipramine | 4                  | Headaches/month      | Langohr (1985)     | 0.10 (-1.2 to 1.01)                   |               |
|            | 4                  | Headaches/month      | Loldrup (1989)     | -0.51 (-0.81 to -0.20)                |               |
|            | 4                  | Headaches/month      | Noone (1980)       | -0.3 (-1.19 to 0.58)                  |               |
|            |                    |                      |                    | **Pooled SMD** -0.46 (-0.74 to -0.18) |               |
| Doxepin    | 4                  | Headache index       | Morand (1979)      | -0.77 (-1.54 to 0.00)                 |               |
| Opiptramol | 4                  | Headaches/month      | Jacobs (1972)      | -1.2 (-2.1 to -0.3)                   |               |
|            | 12                 |                      | Jacobs (1972)      | -1.3 (-2.5 to -0.12)                  |               |

SMD: Standardized Mean Difference

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Fig 2. Alpha blockers compared to placebo for episodic migraine headaches.

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Fig 2. Alpha blockers compared to placebo for episodic migraine headaches.
averaged 35 years in age (range 15–65) with 78% women. The average rate of withdrawals was 18%. Study duration averaged 11 weeks (range 4–20) with a mean of 52 participants (range 12–192). No calcium channel blocker was more effective than placebo, including cyclendelate, nicardipine, nifedipine, nimodipine and verapamil (Table 5). When the dihydropyridines (nicardipine, nifedipine, nimodipine) were pooled, they were no better than placebo at reducing headaches.

**Flunarizine.** While classified as a calcium channel blocker, flunarizine has no influence on blood pressure and its side effect profile suggests that its site of action is on cellular receptors other than the calcium channel [231,232]. Flunarizine is not available in the United States. There were 7 studies of episodic migraines, totaling 332 participants (Table 2). Studies averaged 47 participants, 36.4 years in age, 77% women, 12.5 weeks in duration and 9% dropouts. Four studies reported headache frequency and three reported headache outcomes based on a headache index. Flunarizine was superior to placebo at 8 and 12 weeks (Table 5, Fig 8), though not at 4 weeks. Only a single trial reported the likelihood of a 50% reduction in headache with flunarizine with insignificant results (Table 7).

**Selective Serotonin Reuptake Inhibitors (SSRI)/ Selective Norepinephrine Reuptake inhibitors (SNRI).** There were six SSRI and one SNRI placebo controlled trials, five focusing on migraines and 1 on chronic daily headaches. There were a total of 335 participants who averaged 35 years in age (range 15–65) with 78% women. The average rate of withdrawals was 18%. Study duration averaged 11 weeks (range 4–20) with a mean of 52 participants (range 12–192). No calcium channel blocker was more effective than placebo, including cyclendelate, nicardipine, nifedipine, nimodipine and verapamil (Table 5). When the dihydropyridines (nicardipine, nifedipine, nimodipine) were pooled, they were no better than placebo at reducing headaches.

### Table 6. Placebo controlled comparisons of continuous outcomes among patients with chronic migraine headache (≥ 15 headaches/month).

| Chronic Daily Headache | 12 Headaches/month | Saper (1994) | -0.40 (-1.1 to 0.35) |
|------------------------|--------------------|-------------|----------------------|
| Flupoxetine            | 12 Headaches/month | Saper (1994) | -0.40 (-1.1 to 0.35) |
| Gabapentin             | 8 Headaches/month  | Spira (2003) | -2.7 (-5.2 to 0.28)  |
| Levetiracetam          | 82 Headaches/month | Beran (2010) | -3.6 (-7.7 to 0.56)  |

| Chronic Migraines (15 or more headaches/month) | 6 Headaches/month | Stensrud (1980) | 0.32 (-0.73 to 1.38) |
|-----------------------------------------------|------------------|-----------------|----------------------|
| Atenolol                                     | 6 Headaches/month | Saper (2002) | -1.1 (-2.4 to 0.16)  |
| Propranolol                                   | 8 Headaches/month | Saper (2002) | -1.0 (-2.3 to 0.30)  |
| Tizanidine                                    | 12 Headaches/month | Saper (2002) | -0.50 (-1.6 to 0.62) |
| Topiramate                                    | 4 Headaches/month | Diener (2007) | -4.9 (-7.7 to -2.1)  |
| Topiramate                                    | 4 Headaches/month | Mei (2006) | -9.2 (-15.7 to -2.7) |
| Topiramate                                    | 4 Headaches/month | Silvestrini (2003) | -5.0 (-9.2 to -0.81) |
| Topiramate                                    | 8 Headaches/month | Diener (2007) | -3.1 (-5.9 to -0.29) |
| Topiramate                                    | 8 Headaches/month | Mei (2006) | -12.7 (-10.2 to -6.2) |
| Topiramate                                    | 8 Headaches/month | Silvestrini (2003) | -12.5 (-17.1 to -7.9) |
| Topiramate                                    | 12 Headaches/month | Diener (2007) | -6.0 (-8.8 to -3.2)  |
| Topiramate                                    | 12 Headaches/month | Mei (2006) | -12.2 (-18.7 to -5.7) |
| Topiramate                                    | 16 Headaches/month | Diener (2007) | -7.6 (-10.4 to -4.8) |
| Valproate                                     | 4 Headaches/month | Yurekli (2008) | -12.6 (-17.9 to -7.3) |
| Valproate                                     | 12 Headaches/month | Sarchelli (2014) | -4.3 (-7.1 to -1.5)  |
| Valproate                                     | 12 Headaches/month | Yurekli (2008) | -14.3 (-19.5 to -9.1) |
| Valproate                                     | 12 Headaches/month | Yurekli (2008) | -10.9 (-18.5 to -3.4) |

Pooled SMD: -0.34 (-1.23 to 0.56) Q = 0.13, df = 2, I^2 = 56.1%  
Pooled (HA/Month): -9.1 (-16.3 to -1.9) Q = 9.33, df = 2, I^2 = 78.6%  
Pooled (HA/Month): -8.4 (-14.3 to -2.5) Q = 0.81, df = 1, I^2 = 0.0%  
Pooled (HA/Month): -10.9 (-18.5 to -3.4) Q = 26.2, df = 1, I^2 = 92.4%

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averaged 36.9 years in age (range 18–65) with 81% women (Table 2). The average rate of withdrawals was 25% (range 0–41%). Study duration averaged 12 weeks (range 8–20) with a mean of 56 participants (range 27–111). Specific drugs tested include three SSRIs (femoxitine, n = 1, fluoxetine, n = 4 and sertraline, n = 1), and one SNRI (venlafaxine, n = 1). Four of the SSRI trials reported a headache index. One SSRI trial and the SNRI trial reported frequency of headaches per month.

For migraine headaches, two SSRI’s, femoxitine and sertraline, were no more effective than placebo while fluoxetine was effective at 12 weeks (Fig 9). A single trial of venlafaxine found benefit at 8 weeks (Table 5). For chronic daily headache a single trial of fluoxetine found no benefit (Table 6). Only a single trial (fluoxetine) investigated the likelihood of reducing headaches by at least 50% and found no benefit over placebo (Table 7).

Serotonin Antagonists. Pizotifen is a serotonin antagonist, commonly used for migraine treatment in the 1970’s and 80’s. There were 9 placebo controlled trials with a total of 600 participants and all focused on episodic migraine headaches (Table 2). The average rate of withdrawals was 20% (range 0–48). Study duration averaged 8 weeks (range 4–12) with a mean of 67 participants (range 26–176). Two studies reported a headache index, the other 7 headache frequency. Pizotifen was superior to placebo at all time points (Fig 10, Table 5). No trials reported on the likelihood of achieving at least 50% improvement in headaches.

Tricyclic Antidepressants (TCA)

There were 8 trials comparing a TCA to placebo, one focusing on chronic daily headaches, the remainder on episodic migraine headaches. There were a total of 1570 participants. The average rate of withdrawals was 37% (range 20–52%). Study duration averaged 10 weeks (range 4–24) with a mean of 143 participants (range 10–554). Tricyclic’s studied included
Table 7. Placebo controlled comparisons of >50% improvement in episodic migraine headaches (<15 migraines/month).

| Drug                        | Time Point (weeks) | Study (Year)       | RR (95% CI)       | Heterogeneity |
|-----------------------------|--------------------|--------------------|-------------------|---------------|
| **Angiotensin Converting Enzyme Inhibitors** |                    |                    |                   |               |
| Captopril                   | 8                  | Sonbolestan (2013) | 5.6 (1.4–21.9)    |               |
| Lisinopril                  | 12                 | Schrader (2012)    | 0.82 (0.46–1.5)   |               |
| **Angiotensin Receptor Blockers** |                    |                    |                   |               |
| Candesartan                | 12                 | Tronvik (2003)     | 18.0 (2.5–130.4)  |               |
| Telmisartan                | 12                 | Diemer (2009)      | 1.6 (0.85–3.0)    |               |
|                            | 12                 | **Pooled RR**      | **4.4 (0.43–46.2)** | Q = 5.2, df = 1 I² = 80.8% |
| **Anticonvulsants**         |                    |                    |                   |               |
| Acetazolamide               | 12                 | Vahedi (2002)      | 0.92 (0.42–2.0)   |               |
| Carisbamate                 | 12                 | Cady (2009)        | 0.75 (0.58–0.98)  |               |
| Lamotrigine                 | 4                  | Gupta (2006)       | 1.4 (0.86–2.2)    |               |
|                            | 12                 | Steiner (1997)     | 0.20 (-0.36 to 0.76) |          |
| Levetiracetam               | 12                 | Verma (2003)       | 1.4 (0.86–2.4)    |               |
| Oxcarbazepine               | 15                 | Silberstein (2008) | 0.90 (0.59–1.4)   |               |
| Topiramate                  | 4                  | Edwards (2003)     | 4.2 (1.3–13.7)    |               |
|                            | 4                  | Gupta (2006)       | 2.1 (1.3–3.2)     |               |
|                            | 12                 | **Pooled RR:**     | **2.4 (1.3–4.2)** | Q = 11.27, df = 1 I² = 21.0% |
| Valproate                   | 12                 | Jensen (1994)      | 2.8 (1.3–6.3)     |               |
|                            | 12                 | Klapper (1997)     | 2.3 (1.6–3.3)     |               |
|                            | 12                 | Mathew (1995)      | 3.6 (1.5–8.4)     |               |
|                            | 12                 | **Pooled RR:**     | **2.1 (1.5–3.0)** | Q = 9.1, df = 3 I² = 45.1% |
| **Beta-blockers**           |                    |                    |                   |               |
| Propranolol                 | 4                  | Stensrud (1976)    | 1.25 (0.55–2.8)   |               |
|                            | 8                  | Pita (1977)        | 17.0 (1.0–281.9)  |               |
|                            | 8                  | Zeigler (1993)     | 2.5 (0.65–9.7)    |               |
|                            | 8                  | **Pooled RR:**     | **4.3 (0.79–23.6)** | Q = 1.45, df = 1 I² = 31.1% |
| Metoprolol                  | 4                  | Langohr (1985)     | 1.2 (0.86–1.5)    |               |
| Timolol                     | 8                  | Stellar (1984)     | 1.6 (1.1–2.4)     |               |
|                            | 12                 | Tfelt-Hansen (1984)| 1.9 (1.4–2.5)     |               |
| **Calcium Channel Blockers**|                    |                    |                   |               |
| Cinnarizine                 | 4                  | Togha (2007)       | 0.98 (0.74–1.3)   |               |
| Cyclendalate                | 24                 | Diener (1996)      | 1.3 (0.8–2.1)     |               |

(Continued)
**Table 7.** (Continued)

| Drug               | Time Point (weeks) | Study (Year) | RR (95% CI) | Heterogeneity |
|--------------------|--------------------|--------------|-------------|---------------|
| Flunarizine        | 12                 | Thomas (1991) | 2.5 (0.6–10.9) |               |
|                    | 16                 | Bunoso (1998) | 0.99 (0.72–1.4) |               |
|                    | 16                 | Diener (2002) | 1.0 (0.88–1.2) |               |
|                    | 16                 | **Pooled RR:** | **1.02 (0.99–1.1)** | Q = 1.6, df = 1, $I^2 = 82.4\%$ |
| Nifedipine         | 24                 | Albers (1989) | 0.45 (0.21–0.95) |               |
| Fluoxetine         | 4                  | Singh (2002) | 4.5 (1.1–18.8) |               |
|                    | 12                 | Saper (1994) | 1.0 (0.57–1.8) |               |
| **Tricyclic Antidepressants** |        |              |             |               |
| Amitriptyline      | 4                  | Couch (1976) | 2.2 (1.0–4.8) |               |
|                    |                    | Couch (1979) | 1.60 (1.0–2.5) |               |
|                    | 4                  | **Pooled RR:** | **1.7 (1.2–2.6)** | Q = 0.54, df = 1, $I^2 = 0.0\%$ |
|                    | 8                  | Nelson (1998) | 2.22 (1.3–3.9) |               |
|                    | 8                  | Zeigler (1993) | 0.83 (0.43–1.6) |               |
|                    | 8                  | **Pooled RR:** | **1.1 (0.6–2.0)** | Q = 0.64, df = 1, $I^2 = 3.0\%$ |
|                    | 12                 | Canepari (1985) | 1.60 (0.31–3.1) |               |
|                    | 26                 | Dodick (2009) | 0.82 (0.61–1.1) |               |
|                    | 8                  | Nelson (1998) | 2.22 (1.3–3.9) |               |
|                    | 8                  | Zeigler (1993) | 0.83 (0.43–1.6) |               |
|                    | 8                  | **Pooled RR:** | **1.1 (0.6–2.0)** | Q = 0.64, df = 1, $I^2 = 3.0\%$ |
| Clomipramine       | 4                  | Langohr (1985) | 0.94 (0.53–1.7) |               |
| **Tetracyclic**    |                    |              |             |               |
| Maprotiline        | 12                 | Amelin (2000) | 0.76 (0.32–1.8) |               |

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![Fig 4. Topiramate compared to placebo for episodic migraine headaches.](doi:10.1371/journal.pone.0130733.g004)
Fig 5. Valproate compared to placebo for episodic migraine headaches.

doi:10.1371/journal.pone.0130733.g005

Fig 6. Dose response relationship of headache to topiramate dose.

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Fig 7. Propranolol compared to placebo for episodic migraine headaches.
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Fig 8. Flunarizine compared to placebo for episodic migraine headaches.
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Fig 9. SSRI/SNRIs compared to placebo for episodic migraine headaches.

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Fig 10. Pizotifen compared to placebo for episodic migraine headaches.

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Fig 11. TCAs compared to placebo for episodic migraine headaches.

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Fig 12. Amitriptyline compared to placebo for migraine headaches.

doi:10.1371/journal.pone.0130733.g012
Table 8. Characteristics of comparative effectiveness trials.

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Comparison Drugs | Headache Measure | Study design (washout, weeks) | Duration, weeks | Sample size | Dropping Age | Female |
|-----------------------|---------------|-----------------------------|------------------|-----------------|-------------------------------|----------------|-------------|---------------|---------|
| Afshari [180], 2012, Iran | Episodic | 7.6 | Topiramate (50) v. Valproate (400) | Frequency | Parallel | 12 | 76 | 26% | 30.7 | 79% |
| Albers [181], 1989, USA | Episodic | 4.3 | Propranolol (180) v. Nifedipine (90) | Frequency | Parallel | 24 | 40 | 50% | 35.2 | 85% |
| Amelin [182], 2000, Russia | Episodic | 4.3 | Amitriptyline (25) v. Fluoxetine (20) | Frequency | Parallel | 12 | 46 | 23% | 36 | 95% |
| Andersson [183], 1973, Denmark | Episodic | 2.3 | Pizotifen (2) v. Methysergide (4) | Frequency | Crossover (0) | 12 | 73 | 33% | ns | 84% |
| Andersson [242], 1981, Denmark | Episodic | 5.7 | Propranolol (160) v. Femoxetine (400) | Frequency | Crossover (0) | 8 | 49 | 24% | 38 | 69% |
| Ashtari [185], 2008, Iran | Episodic | 5.95 | Propranolol (80) v. Topiramate (50) | Frequency | Parallel | 8 | 62 | 3% | 30.8 | 82% |
| Bank [186], 1994, Hungary | Episodic | ns | Amitriptyline (25) v. Fluvoxamine (50) | Frequency | Parallel | 12 | 44 | 23% | 34 | 80% |
| Bellavance [163], 1990, Canada | Episodic | 6.7 | Pizotifen (1.5) v. Naproxen (1100) | Frequency | Parallel | 12 | 176 | 14% | 32.5 | 79% |
| Bordini [190], 1997, Brazil | Episodic | 3.9 | Propranolol (60) v. Flunarizine (10) | Headache Index | Parallel | 24 | 52 | 13% | ns | 91% |
| Bostani [191], 2013, Iran | Episodic | 6.1 | Valproate (400) v. Cinnarizine (50) | Frequency | Parallel | 12 | 132 | 21% | 32.2 | 68% |
| Bulut [192], 2004, Turkey | Episodic | 3.5 | Amitriptyline (75) v. Venlafaxine (150) | Frequency | Crossover (4) | 12 | 52 | 32% | 31.9 | 85% |
| Cady [193], 2011, USA | Episodic | 5.9 | Topiramate (100) v. FrovaTriptan (5-w) | Frequency | Parallel | 8 | 55 | 20% | 37.5 | 78% |
| Cerbo [194], 1986, Italy | Episodic | ns | Flunarizine (15) v. Pizotifen (1.5) | Frequency | Crossover (2) | 8 | 27 | 33% | ns | ns |
| Diener [106], 1996, Germany | Episodic | 4 | Propranolol(120) v. Cephalexin (1200) v. Placebo | Duration (hours) | Parallel | 12 | 214 | 17% | 39 | 78% |
| Diener [195], 2002, EU | Episodic | 3 | Propranolol (160) v. Flunarizine (5) v. Flunarizine (10) | Frequency | Parallel | 16 | 783 | 18% | 37 | 81% |
| Diener [73], 2004, EU | Episodic | 3.9 | Propranolol (160) v. Topiramate (100) v. Placebo | Frequency | Parallel | 26 | 568 | 37% | 40.8 | 80% |
| Dodick [196], 2009, USA | Episodic | 6.9 | Amitriptyline (100) v. Topiramate (100) | Frequency | Parallel | 26 | 331 | 43% | 38.8 | 85% |
| Formisano [198], 1991, Italy | Episodic | 4 | Propranolol (120) v. Nimodipine (120) | Frequency | Parallel | 12 | 22 | 14% | 39.2 | 55% |
| Forssman [199], 1972, Sweden | Episodic | 6.8 | Pizotifen (3) v. Methysergide (3) | Frequency | Crossover (0) | 10 | 22 | 23% | 40.3 | 53% |
| Gawel [200], 1992, Canada | Episodic | 4.7 | Propranolol (160) v. Flunarizine (10) | Frequency | Parallel | 16 | 94 | 19% | 35.7 | 90% |
| Gerber [201], 1991, Germany | Episodic | 3.5 | Propranolol (120) v. Metoprolol (200) v. Nifedipine (20) | Frequency | Parallel | 12 | 58 | 28% | 42.4 | 81% |

(Continued)
| Author, year, Country | Migraine Type | Baseline Headache Frequency | Comparison Drugs | Headache Measure | Study design (washout, weeks) | Duration, weeks | Sample size | Dropouts | Age Female |
|------------------------|--------------|-----------------------------|------------------|-----------------|-----------------------------|----------------|-------------|----------|------------|
| Gupta [202], 2007, India | Episodic | 6.9 | Topiramate (50) v. Lamotrigine (50) | Frequency | Crossover (1) | 4 | 57 | 7% | 29.4 78% |
| Havanka-Kannianen [141], 1987, Finland | Episodic | 5.2 | Nimodipine (120mg) v. Pizotifen (1.5) v. Placebo | Frequency | Crossover (4) | 12 | 43 | 14% | 37.6 79% |
| Hübbe [35], 1973, Denmark | Episodic | ns | Pizotifen (1.5) v. Prochlorperazine (15) v. Placebo | Frequency | Crossover (0) | 8 | 50 | 32% | 35 71% |
| Kalita [204], 2013, India | Episodic | 10.8 | Amitriptyline (50) v. Valproate (1000) | Frequency | Parallel | 24 | 300 | 0% | 32 80 |
| Kangasniemi [167], 1979, Finland | Episodic | 6.2 | Pizotifen (1.5) v. Divascan (5) v. Placebo | Frequency | Crossover (4) | 7 | 50 | 13% | 37 71% |
| Kangasniemi [205], 1983, Finland | Episodic | 7.2 | Propranolol (160) v. Femoxitine (400) | Frequency | Crossover (1) | 16 | 29 | 17% | 37 86% |
| Kangasniemi [116], 1984, Finland | Episodic | 5.3 | Propranolol (240) v. Metoprolol (200) | Frequency | Crossover (3) | 8 | 36 | 8% | 33.8 89% |
| Kaniecki [206], 1997, USA | Episodic | 4.4 | Divalproex (1500) v. Propranolol (240) v. Placebo | Headache Index | Parallel | 12 | 37 | 14% | ns 81% |
| Kass [178], 1980, Norway | Episodic | ns | Propranolol (40) v. Clonidine (0.05) | Frequency | Crossover (0) | 16 | 23 | 9% | 39.7 70% |
| Keskinbora [207], 2008, Turkey | Episodic | 6.1 | Amitriptyline (150) v Topiramate (200) | Frequency | Parallel | 12 | 63 | 16% | 37 67% |
| Krymchantowski [209], 2012, Brazil | Episodic | 7 | Topiramate (100) v. Nortriptyline (30) v. combination | Frequency | Parallel | 10 | 38 | 13% | 36 85% |
| Langohr [175], 1985, Germany | Episodic | ns | Clomipramine (100) v. Metoprolol (100) v. Placebo | Frequency | Crossover (4) | 4 | 36 | 43% | 44 67% |
| Louis [210], 1982, Belgium/Netherlands | Episodic | 2.2 | Flunarizine (10) v. Pizotifen (3) | Frequency | Crossover (0) | 16 | 75 | ns | 37 57% |
| Louis [179], 1985, Belgium | Episodic | ns | Metoprolol (100) v. Clonidine (0.1) | Frequency | Crossover (2) | 8 | 33 | 6% | 33.5 81% |
| Lucking [211], 1988, Germany | Episodic | 6 | Propranolol (120) v Flunarizine (10) | Frequency | Parallel | 16 | 434 | 23% | 42 82% |
| Ludin [212], 1989, Switzerland | Episodic | 6.3 | Propranolol (120) v. Flunarizine (10) | Frequency | Parallel | 16 | 87 | 17% | 42 74% |
| Luo [213], 2012, China | Episodic | 4.5 | Topiramate () v. Flunarizine (5) v. combination | Frequency | Parallel | 48 | 150 | 16% | 43 71% |
| Mathew [118], 1981, USA | Unclear | ns | Amitriptyline (75) v. Propranolol (160) v. Placebo | Frequency | Parallel | 24 | 554 | 22% | 38 95% |
| Mitsikostas [214], 1997, Greece | Episodic | 4.6 | Valproate (1000) v. Flunarizine (10) | Frequency | Parallel | 8 | 44 | ns | 35.4 73% |

(Continued)
Table 8. (Continued)

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Comparison Drugs | Headache Measure | Study design (washout, weeks) | Duration, weeks | Sample size | Drop-outs | Age | Female |
|-----------------------|---------------|-----------------------------|------------------|-----------------|-------------------------------|----------------|-------------|-----------|-----|--------|
| Mohammadianinejad [215], 2011, Iran | Episodic | 7.4 | Topiramate (100) v. Zonisamide (200) | Frequency | Parallel | 12 | 80 | 6% | 34.3 | 69% |
| Olerud [216], 1986, Sweden | Episodic | 4.6 | Propranolol (80) v. Nadolol (80) | Frequency | Parallel | 12 | 28 | ns | ns | ns |
| Olsson [217], 1984, Sweden | Episodic | 5.4 | Propranolol (80) v. Metoprolol (100) | Frequency | Crossover (4) | 8 | 56 | 5% | 39 | 73% |
| Osterman [169], 1977, Sweden | Episodic | | Pizotifen (0.5) v. Divascan v. Placebo | Frequency | Crossover (2) | 8 | 30 | 10% | 37 | 70% |
| Presthus [218], 1971, Norway | Episodic | | Pizotifen (1.5) v. Methysergide (3) | Frequency | Crossover (1) | 21 | 21 | 10% | 42.7 | 67% |
| Rampello [219], 2004, Italy | Episodic | | Amitriptyline (50) v. Citalopram (20) | Frequency | Parallel | 16 | 88 | 0% | 39 | 63% |
| Rascol [220], 1986, France | Episodic | 4.3 | Flunarizine (10) v. Pizotifen (2) | Frequency | Parallel | 16 | 35 | 9% | 38 | 71% |
| Ryan [170], 1968, USA | Episodic | 8.5 | Pizotifen (4) v. Methysergide (4) v. Placebo | Frequency | Crossover (0) | 4 | 62 | ns | ns | ns |
| Ryan [221], 1984, USA | Episodic | 6.5 | Propranolol (160) v. Nadolol (80) v. Nadolol (160) | Frequency | Parallel | 12 | 48 | 6% | ns | 73% |
| Scholz (188), 1987, Germany | Episodic | | Propranolol (80) v. Metoprolol (100) v. Nifedipine (40) v. Flunarizine (10) | Frequency | Parallel | 12 | 109 | 24% | 40.4 | 83% |
| Shaygannejad [223], 2006, Iran | Episodic | 5.4 | Topiramate (50) v. Valproate (500) | Crossover (8) | Parallel | 8 | 64 | 0% | 34.1 | 60% |
| Shimell [224], 1990, S Africa | Episodic | 4.7 | Propranolol (240) v. Flunarizine (10) | Frequency | Parallel | 16 | 57 | 2% | 34 | 70% |
| Sorensen [225], 1991, Denmark | Episodic | 4.3 | Metoprolol (200) v. Flunarizine (10) | Frequency | Parallel | 20 | 149 | 15% | 42 | 79% |
| Stovner, 2013, Norway | Episodic | | Candesartan (16), Propranolol (160) | Frequency | Crossover | 12 | 61 | 15% | 37 | 82% |
| Sudilovsky [226], 1987, USA | Episodic | 5.3 | Nadolol (80) v. Nadolol (160) | Frequency | Parallel | 8 | 168 | 20% | ns | ns |
| Stensrud (107), 1980, Norway | Episodic | 5.6 | Propranolol (160) v. Atenolol (100) v. Placebo | Crossover (1) Crossover (1) | Parallel | 6 | 7 | 20% | 25 | 69% |
| Tarasova [227], 2008, Russia | Episodic | | Amitriptyline () v. Fluvoxamine () | Frequency | Parallel | | | | | |
| Togha [228], 2008, Iran | Episodic | 7.2 | Valproate (600) v. Cinnarizine (75) | Frequency | Parallel | 12 | 125 | 37% | 34.1 | 80% |
| Vilming [229], 1985, Sweden/Norway | Episodic | 6 | Metoprolol (100) v. Pizotifen (1.5) | Frequency | Crossover (0) | 4 | 35 | ns | 37.6 | 83% |
| Zain [230], 2013, Pakistan | Episodic | 11.32 | Topiramate (200) v. Gabapentin (1200) | Frequency | Parallel | 12 | 80 | 0% | 32 | 80% |
| Ziegler [136], 1987, USA | Episodic | Ns | Amitriptyline (150) v. Propranolol (240) v. Placebo | Frequency | Crossover (4) | 4 | 30 | 44% | 38 | 73% |

(Continued)
amitriptyline (n = 5), clomipramine (n = 2) doxepin (n = 1) and opipramol (n = 1). Four trials reported headache frequency and 4 used a headache index as their outcome measure.

For episodic migraines, amitriptyline, clomipramine and doxepin were better than placebo (Table 5, Fig 11), while opipramol (Table 5) was ineffective. Amitriptyline was the best studied TCA (Fig 12), though two of the studies were only 4 weeks in duration. Amitriptyline was more likely than placebo to produce a 50% reduction in episodic migraine headaches (Table 7). A single trial found amitriptyline ineffective for chronic daily headaches (Table 6).

Comparative Effective Trials

There were a total of 60 trials with comparisons between different prophylactic drugs for headaches, 55 including subjects with episodic headaches, five with chronic migraine headaches. Not all prophylactic drugs were directly compared with each other (Table 8). Quality ratings for these trials are given in Table 9. Drugs that were frequently compared to other active drugs include amitriptyline, metoprolol, pizotifen, propranolol, topiramate and valproate. There were few differences in effectiveness between the different drugs. Amitriptyline was no more effective than SSRIs, venlafaxine, topiramate or propranolol. Among beta-blockers, metoprolol was superior to clonidine, flunarizine and nifedipine and propranolol was better than femoxetine. Propranolol was equivalent to metoprolol, atenolol, nadolol as well as to flunarizine and topiramate (Table 10). Among the anticonvulsants, topiramate was equivalent to flunarizine, lamotrigine and to valproate and valproate was equivalent to flunarizine. For chronic migraines, propranolol was better than nortriptyline.

Network Meta-analysis

Candidate drugs for the network meta-analysis were those drugs found effective for treatment of episodic migraine headaches with at least 3 randomized clinical trials. These included eleven different drugs used in prophylaxis of episodic migraine headaches (Fig 13). Indirect comparisons of these eleven individual drugs using meta-regression suggested that amitriptyline was more effective than several of the other drugs including candesartan (p = 0.04), fluoxetine

| Author, year, Country | Migraine Type | Baseline Headache Frequency | Comparison Drugs | Headache Measure | Study design (washout, weeks) | Duration, weeks | Sample size | Drop-outs | Age | Female |
|-----------------------|--------------|-----------------------------|------------------|-----------------|-----------------------------|----------------|-------------|-----------|-----|--------|
| Bartolini [187], 2005, Italy | Chronic Migraine | 26.6 | Topiramate (75) v. Valproate (750) | Frequency | Parallel | 8 | 49 | 14% | 41.8 | 70% |
| Behan [188], 1986, UK | Chronic Migraine | 15 | Pizotifen (1.5) v. Naproxen (1100) | Frequency | Parallel | 12 | 74 | 45% | ns | 82% |
| Domingues [197], 2009, Brazil | Chronic Migraine | 16.7 | Nortriptyline (40) v. Propranolol (80) | Frequency | Parallel | 6 | 76 | 42% | ns | ns |
| Krymchantowski [208], 2002, Brazil | Chronic (transformed) migraine | 25.7 | Amitriptyline (40) v. Amitriptyline (40)+Fluoxetine (40) | Frequency | Parallel | 9 | 39 | 44% | 36.4 | 67% |
| Stensrud (107), 1980, Norway | Chronic | 22 | Propranolol (160) v. Atenolol (100) v. Placebo | Crossover (1) | Crossover (1) | Parallel | 6 | 28 | 20% | 25 | 69% |

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Table 9. Quality Assessment among comparative effectiveness trials.

| Study                          | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|--------------------------------|-------------------|--------------------|-------------------------------|-------------------------------|-------------------|----------------------------------|-------------------------------------|---------------------|-------------------|
| **EPISODIC MIGRAINES**         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Afshari [180], 2012,           | 4                 | No                 | Unclear                       | Unclear                       | Unclear           | No                               | Unclear               | Yes                 | No                |
| Topiramate/valproate           |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Albers [181], 1989,            | 5                 | No                 | Yes                           | Yes                           | No                | No                               | No                    | No                  | Yes               |
| Propranolol/Nifedipine         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Amelin [182], 2000,            | 4                 | No                 | No                            | Unclear                       | No                | No                               | Unclear               | Yes                 | No                |
| Amitriptyline/Fluoxetine      |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Andersson [183], 1973,         | 4                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Yes               |
| Pizotifen/Methysergide         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Andersson [242], 1981,         | 4                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | No                |
| Propranolol/Fenofibrate        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Ashari [185], 2008,            | 5                 | No                 | Yes                           | Yes                           | Unclear           | No                               | Yes                   | Unclear             | Yes               |
| Propranolol/Topiramate         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Bank [186], 1994,              | 4                 | No                 | Unclear                       | Unclear                       | No                | Unclear                          | Yes                   | Unclear             | Yes               |
| Amitriptyline/Fluvoxamine     |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Bartolini [187], 2005,         | 3                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Yes               |
| Topiramate/Valproate           |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Behan [188], 1986,             | 2                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Yes               |
| Pizotifen/Naproxen             |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Bellavance [183], 1990,        | 3                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Yes               |
| Pizotifen/Naproxen             |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Bordini [190], 1997,           | 4                 | No                 | Unclear                       | Yes                           | No                | No                               | No                    | No                  | Unclear           |
| Propranolol/Flunarazine        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Bulut [192], 2004,             | 6                 | No                 | Unclear                       | Yes                           | No                | Unclear                          | Yes                   | Yes                 | Yes               |
| Amitriptyline/Venlafaxine      |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Cady [193], 2011,              | 3                 | Unclear            | Unclear                       | No                            | Unclear           | Unclear                          | Yes                   | Unclear             | Yes               |
| Topiramate/Froyatriptan        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Cerbo [194], 1986,             | 6                 | Yes                | Unlcern                        | Yes                           | Yes               | Unclear                          | Unclear               | Unclear             | Unclear           |
| Flunarizine/Pizotifen          |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Diener [106], 1996,            | 4                 | Yes                | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Unclear           |
| Propranolol/Cyclendalate/Placebo|                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Diener [195], 2002,            | 8                 | No                 | Yes                           | Yes                           | No                | Unclear                          | Unclear               | Unclear             | Yes               |
| Propranolol/Flunarizine        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Diener [73], 2004,             | 8                 | Yes                | Unclear                       | Unclear                       | Yes               | Yes                             | Unclear               | Yes                 | Yes               |
| Propranolol/Topiramate/Placebo |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Dodick [196], 2009,            | 8                 | No                 | Yes                           | Yes                           | Yes               | Yes                             | Yes                   | Yes                 | Yes               |
| Amitriptyline/Topiramate       |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Domingues [197], 2009,         | 4                 | No                 | Unclear                       | Unclear                       | Unclear           | Unclear                          | Unclear               | Unclear             | Unclear           |
| Norfripinyl/Propranolol        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Formisano [198], 1991,         | 4                 | No                 | Unclear                       | No                             | No                | No                               | No                    | No                  | Unclear           |
| Propranolol/Nimodipine         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Forssman [199], 1972,          | 5                 | No                 | Unclear                       | No                             | Yes               | Unclear                          | Unclear               | Unclear             | Unclear           |
| Pizotifen/Methysergide         |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |
| Gawel [200], 1992,             | 4                 | No                 | Unclear                       | Unclear                       | No                | No                               | Unclear               | Yes                 | Yes               |
| Propranolol/Flunarizine        |                   |                    |                               |                               |                   |                                  |                                      |                     |                   |

(Continued)
| Study                        | Jadad Score (0–8) | Intention to Treat | Adequate sequence generation | Adequate concealed allocation | Adequate Blinding | Incomplete outcome data addressed | Free of selective outcome reporting | Free of “other” bias | Industry sponsored |
|-----------------------------|-------------------|--------------------|-------------------------------|-----------------------------|-------------------|----------------------------------|-----------------------------------|---------------------|--------------------|
| Gerber [201], 1991, Propranolol/Metoprolol/Nifedipine | 3                 | No                 | Unclear                       | Unclear                     | Unclear           | No                               | Yes                  | Unclear             | Unclear            |
| Gupta, 2007, Lamotrigin/Topiramate/Placebo            | 8                 | Yes                | Yes                           | Yes                         | Yes               | Unclear                          | Unclear              | Unclear             | Yes                |
| Havanka-Kannianen [141], 1987, Nimodipine/Pizotifen/Placebo | 3                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Hübbe [35], 1973, Pizotifen/Prochlorperazine/Placebo | 3                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Yes                  | No                  | Yes                |
| Kangasniemi [167], 1979, Pizotifen/Divascan/Placebo   | 6                 | No                 | 50 (32%)                      | 37 (71%)                    | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Kangasniemi [205], 1983, Propranolol/Femoxicline     | 2                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Kangasniemi [116], 1984, Propranolol/Femoxicline/Placebo | 2                 | No                 | 29 (17%)                      | 37 (86%)                    | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Kaniecki [206], 1997, Divalproex/Propranolol/Placebo  | 4                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Kaas, 1980, Norway, Propranolol/Clonidine             | 4                 | Unclear            | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | No                 |
| Keskinbora [207], 2008, Amitriptyline/Topiramate     | 6                 | No                 | Unclear                       | Yes                         | Yes               | No                               | Yes                  | Yes                 | Unclear            |
| Krymchantowski [208], 2002, Amitriptyline/Amtriptyline+Fluoxetine | 5                 | No                 | Unclear                       | Unclear                     | Yes               | Unclear                          | Unclear              | Unclear             | No                 |
| Krymchantowski [209], 2012, Topiramate/ Norltypine/Combination | 8                 | No                 | Yes                           | Yes                         | Yes               | Unclear                          | Unclear              | Unclear             | Unclear            |
| Langohr [175], 1985, Clomipramine/Metoprolol/Placebo  | 4                 | No                 | Unclear                       | Unclear                     | Unclear           | No                               | Yes                  | Yes                 | Yes                |
| Louis [210], 1982, Flunarizine/Pizotifen              | 4                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Louis, 1985, Metoprolol/Clonidine                     | 4                 | Unclear            | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | No                 |
| Lucking [211], 1988, Propranolol/Flunarizine          | 4                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Yes                |
| Ludin [212], 1989, Propranolol/Flunarizine            | 3                 | Yes                | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Luo [213], 2012, Topiramate/Flunarizine/Combination   | 2                 | No                 | Unclear                       | Unclear                     | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
| Mathew [118], 1981, Amitriptyline/Propranolol/Placebo | 2                 | No                 | Unclear                       | No                          | No                | No                               | Yes                  | Unclear             | Unclear            |
| Mitsikostas [214], 1997, Valproate/Flunarizine        | 4                 | No                 | Unclear                       | No                          | Unclear           | Unclear                          | Unclear              | Unclear             | Unclear            |
propranolol (p = 0.009), topiramate (p = 0.005) and valproate (p = 0.009, Fig 12), and no different than atenolol (p = 0.20), flunarizine (p = 0.06), clomipramine (p = 0.15) or metoprolol (p = 0.15). The network meta-analysis found no differences between the other drugs in the relative effectiveness in the prophylaxis against migraine headaches. (p = 0.21).
| Drug 1    | Drug 2       | Study (year) | Standardized Mean Difference (95% CI)δ | Heterogeneity     |
|----------|--------------|--------------|---------------------------------------|-------------------|
| **Episodic Migraines (<14 headaches/month)** |              |              |                                       |                   |
| Amitriptyline | Fluoxetine   | Amelin (2000) | -0.14 (-0.85 to 0.58)                |                   |
| Amitriptyline | Fluvoxamine  | Bank (1994)  | 0.37 (-0.20 to 0.93)                 |                   |
| Amitriptyline | SSRI         | Pooled SMD   | 0.17 (-0.32 to 0.65)                 | Q = 1.15, df = 1, I^2 = 12.9% |
| Amitriptyline | Topiramate   | Dodick (2009)| -0.08 (-0.30 to 0.13)                |                   |
| Amitriptyline | Topiramate   | Keskinbora (2008)| 0.31 (-0.30 to 0.92) |                   |
| Amitriptyline | Topiramate   | Pooled SMD   | 0.01 (-0.32 to 0.33)                 | Q = 1.41, df = 1, I^2 = 29.2% |
| Amitriptyline | Venlafaxine  | Bulut (2004) | -0.12 (-0.51 to 0.26)                |                   |
| Amitriptyline | Propranolol  | Ziegler (1987)| 0.17 (-0.55 to 0.88)                  |                   |
| Flunarizine  | Flunarizine + Topiramate | Luo (2012)| 0.21 (-0.23 to 0.64)                |                   |
| Metoprolol  | Flunarizine  | Scholz (1981)| -0.83 (-1.65 to -0.01)               |                   |
| Metoprolol  | Flunarizine  | Sorensen (1991)| -0.35 (-0.69 to -0.02) |                   |
| Metoprolol  | Flunarizine  | Pooled SMD   | -0.43 (-0.77 to -0.10)               | Q = 1.06, df = 1, I^2 = 5.8% |
| Metoprolol  | Nifedipine   | Gerber (1991)| -0.66 (-1.31 to -0.01)               |                   |
| Metoprolol  | Nifedipine   | Scholz (1987)| -0.92 (-1.78 to -0.06)               |                   |
| Metoprolol  | Nifedipine   | Pooled SMD   | -0.75 (-1.27 to -0.24)               | Q = 0.24, df = 1, I^2 = 0.0% |
| Metoprolol  | Clomipramine | Langohr (1985)| -1.4 (-2.8 to 0.03)                  |                   |
| Metoprolol  | Clonidine    | Louis (1985) | -0.54 (-1.07 to -0.01)               |                   |
| Metoprolol  | Pizotifen    | Vliming (1985)| -0.43 (-1.15 to 0.30)               |                   |
| Pizotifen   | Flunarizine  | Cerbo (1986) | 0.19 (-0.74 to 1.12)                 |                   |
| Pizotifen   | Flunarizine  | Louis (1982) | 0.14 (-0.34 to 0.63)                 |                   |
| Pizotifen   | Flunarizine  | Rascol (1986)| 0.40 (-0.29 to 1.08)                 |                   |
| Pizotifen   | Flunarizine  | Pooled SMD   | 0.22 (-0.14 to 0.59)                 | Q = 0.36, df = 2, I^2 = 0.0% |
| Pizotifen   | Divascan     | Osterman (1977)| -0.38 (-1.14 to 0.39)               |                   |
| Pizotifen   | Methysergide | Andersson (1973)| -0.17 (-0.74 to 0.40)               |                   |
| Pizotifen   | Methysergide | Forsmann (1972)| 0.10 (-0.66 to 0.85)               |                   |
| Pizotifen   | Methysergide | Presthus (1971)| 0.24 (-0.64 to 1.12)               |                   |
| Pizotifen   | Methysergide | Ryan (1968)  | -0.13 (-0.63 to 0.37)                |                   |
| Pizotifen   | Methysergide | Pooled SMD   | -0.06 (-0.37 to 0.26)               | Q = 0.83, df = 3, I^2 = 0.0% |
| Pizotifen   | Nimodipine   | Havanka (1987)| 0.11 (-0.59 to 0.71)                 |                   |
| Pizotifen   | Naproxen     | Bellavance (1990)| 0.10 (-0.27 to 0.46)               |                   |
| Pizotifen   | Prochloperazine | Hübbe (1973)| -0.33 (-0.96 to 0.29)                |                   |
| Propranolol | Atenolol     | Stensrud (1980)| 0.02 (-0.84 to 0.88)               |                   |
| Propranolol | Clonidine    | Kaas (1980)  | 0.03 (-0.58 to 0.63)                 |                   |
| Propranolol | Cyclandelate | Diemer (1996)| -0.07 (-0.38 to 0.24)               |                   |
| Propranolol | Feneoxetine  | Andersson (1981)| -0.40 (-1.05 to 0.25)               |                   |
| Propranolol | Feneoxetine  | Kangasniemi (1983)| -2.03 (-2.66 to -1.39) |                   |
| Propranolol | Feneoxetine  | Pooled SMD   | -1.21 (-2.8 to -0.37)               | Q = 17.35, df = 1, I^2 = 88.5% |
| Propranolol | Flunarizine  | Bordini (1997)| -0.32 (-0.40 to 1.05)               |                   |
| Propranolol | Flunarizine  | Diener (2002)| -0.38 (-0.52 to -0.24)               |                   |
| Propranolol | Flunarizine  | Gawel (1992) | 0.58 (0.12 to 1.04)                 |                   |
| Propranolol | Flunarizine  | Lucking (1988)| -0.20 (-0.67 to 0.27)               |                   |
| Propranolol | Flunarizine  | Ludin (1989) | -0.21 (-0.73 to 0.30)                |                   |
| Propranolol | Flunarizine  | Scholz (1987)| -0.37 (-1.16 to 0.43)               |                   |
| Propranolol | Flunarizine  | Shimell (1990)| -0.02 (-0.55 to 0.50)               |                   |
| Propranolol | Flunarizine  | Pooled SMD   | -0.04 (-0.34 to 0.26)               | Q = 20.62, df = 6, I^2 = 70.9% (Continued) |
### Placebo effect

There were 78 studies that provided baseline headache frequency that included 4579 episodic migraine sufferers who were randomized to placebo. On average, patients randomized to the placebo group experienced 5.3 (95% CI: 4.9–5.8) headaches/month at baseline. Patients receiving placebos experienced a significant decline in headache frequency by 4 weeks, an effect that persisted through 12 weeks. By weeks 16, 20 and 24, the number of headaches experienced by patients given placebo increased back to values that were not different than baseline (Fig 14).

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**Table 10. (Continued)**

| Drug 1     | Drug 2          | Study (year)         | Standardized Mean Difference (95% CI)δ | Heterogeneity |
|------------|-----------------|----------------------|---------------------------------------|---------------|
| Propranolol| Metoprolol      | Olsson (1984)        | 0.00 (-0.46 to 0.46)                  |               |
| Propranolol| Metoprolol      | Scholz (1987)        | 0.03 (-0.58 to 0.65)                  |               |
| **Propranolol** | **Metoprolol** | **Pooled SMD** | **0.15 (-0.27 to 0.57)** | **Q = 1.14, df = 1, I² = 12.6** |
| Propranolol| Nadolol         | Olerud (1986)        | 0.37 (-0.39 to 1.13)                  |               |
| Propranolol| Nadolol         | Ryan (1984)          | -0.42 (-1.15 to 0.27)                 |               |
| Propranolol| Nadolol         | Sudilovsky (1987)    | 0.28 (-0.08 to 0.64)                  |               |
| **Propranolol** | **Nadolol**     | **Pooled SMD**       | **0.19 (-0.18 to 0.56)**              | **Q = 2.81, df = 2, I² = 28.9%** |
| Propranolol| Nifedipine      | Albers (1989)        | 0.84 (-0.12 to 1.79)                  |               |
| Propranolol| Nifedipine      | Gerber (1991)        | -0.63 (-1.30 to 0.05)                 |               |
| Propranolol| Nifedipine      | Scholz (1987)        | -0.46 (-1.29 to 0.37)                 |               |
| **Propranolol** | **Nifedipine** | **Pooled SMD**       | **-0.14 (-0.98 to 0.71)**             | **Q = 10.41, df = 2, I² = 61.6%** |
| Propranolol| Nimodipine      | Formisano (1991)     | -0.19 (-1.10 to 0.73)                 |               |
| Propranolol| Topiramate      | Ashtari (2008)       | -0.24 (-0.27 to 0.75)                 |               |
| Propranolol| Topiramate      | Diener (2004)        | 0.12 (-0.08 to 0.32)                  |               |
| Propranolol| Topiramate      | **Pooled SMD**       | **-0.02 (-0.30 to 0.33)**             | **Q = 1.65, df = 2, I² = 39.5%** |
| Topiramate | Flunarizine     | Luo (2012)           | 0.23 (-0.07 to 0.53)                  |               |
| Topiramate | Frovatriptan (abortive) | Cady (2011)          | -0.49 (-1.09 to 0.11)                 |               |
| Topiramate | Topiramate+Flunarizine | Luo (2012)          | 0.35 (-0.07 to 0.78)                  |               |
| Topiramate | Lamotrigine     | Gupta (2007)         | -0.30 (-0.83 to 0.22)                 |               |
| Topiramate | Topiramate + Nortriptyline | Krymchantowski (2012) | 0.53 (0.04 to 1.02)                  |               |
|           |                 | Afshari (2012)       | -0.32 (-0.85 to 0.20)                 |               |
|           |                 | Shayanannejad (2006) | -0.19 (-0.68 to 0.30)                 |               |
| Topiramate | Valproate       | **Pooled SMD**       | **-0.28 (-0.70 to 0.15)**             | **Q = 0.09, df = 1, I² = 0.0%** |
| Topiramate | Zonisamide      | Mohammadianinejad (2011) | -0.26 (-0.72 to 0.19)             |               |
| Valproate  | Cinnarizine     | Togha (2008)         | -0.07 (-0.42 to 0.28)                 |               |
| Valproate  | Flunarizine     | Mitsikostas (1997)   | -0.06 (-0.67 to 0.56)                 |               |
| **Chronic Migraine (>15 headaches/month)**
| Amitriptyline | Amitriptyline+Fluoxetine | Krymchantowski (2002) | -0.44 (-1.20 to 0.33)             |               |
| Pizotifen  | Naproxen        | Behan (1986)         | 0.08 (-0.56 to 0.73)                  |               |
| Propranolol| Atenolol        | Stensrud (1980)      | 0.08 (-1.40 to 1.56)                  |               |
| Propranolol| Nortriptyline   | Domingues (2009)     | -0.83 (-0.06 to -1.61)                |               |
| Topiramate | Valproate       | Bartolini (2005)     | -0.13 (-0.72 to 0.46)                 |               |

δ negative number favors drug 1, positive number favors drug 2 in these comparisons.

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Fig 13. Network meta-analysis

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Fig 14. Placebo effect of treatment of episodic migraine headaches.

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Patients receiving prophylactic treatment were more likely than those receiving placebo to experience side effects (RR: 1.27, 95% CI: 1.19 to 1.37) and to withdraw from treatment (RR: 1.18, 95% CI: 1.08–1.29). The specific side effects varied by study medication (Table 11). Drowsiness was the most common side effect, increased among patients taking gabapentin, pizotifen, topiramate, TCA and valproate. Tricyclic antidepressants also caused dry mouth and weight gain. Beta-blockers were associated with feeling depressed, dizzy and insomnia. Topiramate increased rates of nausea and paresthesia. Pizotifen had marked increased rates of weight gain with participants averaging 4.3 kg (95% CI: 3.0–5.6).

Network meta-analysis and direct comparisons found no difference in likelihood of experiencing “any” side effect or in the rate of withdrawing from studies.

Sensitivity Analysis
There was evidence of publication bias for beta-blockers (Egger p = 0.02), and for each of topiramate (p = 0.001) and valproate (p = 0.04). There was no evidence of publication bias for the remaining drugs or classes. The metatrim test reduced the effect estimate four these four drugs, though only for valproate did the adjusted effect become insignificant (beta-blocker SMD: -0.24, 95% CI: -0.45 to -0.04; topiramate: SMD: -0.35, 95% CI: -0.57 to -0.12; valproate: SMD: -0.40, 95% CI: -0.90 to 0.10).

There were a number of quality problems (Tables 4 and 9). However, total Jadad score (p = 0.51), intention to treat (p = 0.84), sequence generation (p = 0.47), concealed allocation (p = 0.18), blinding (p = 0.84) or industry sponsorship (p = 0.17) had no relationship or impact on pooled outcomes.

The amount of heterogeneity varied considerably among the various drugs and drug classes. Longer duration of treatment was associated with greater effects for tricyclic antidepressants.

**Table 11. Side Effects Compared with Placebo.**

|                      | Alpha Blockers | Anti-convulsants | Beta Blockers | Calcium Channel Blockers | Flunarizine | SSRI | TCA |
|----------------------|----------------|------------------|---------------|--------------------------|-------------|------|-----|
| **“Any” side effect** | 1.25 (0.91–1.71) | 1.20 (1.14–1.27) | 1.65 (1.41–1.93) | 1.25 (1.03–1.53) | 1.26 (0.67–2.37) | 1.0 (0.51–1.97) | 1.54 (1.37–1.74) |
| Withdrawal           | 1.07 (0.65–1.78) | 1.23 (1.13–1.34) | 1.29 (1.03–1.61) | 1.14 (0.84–1.57) | 1.0 (0.3–3.2) | 1.13 (0.79–1.61) | 1.53 (1.27–1.85) |
| Depression           | 3.0 (0.13–70.6) | ns               | 4.1 (1.1–15.2) | 0.2 (0.01–4.0) | 0.7 (0.1–3.4) | ns   | ns  |
| Dizziness            | 1.80 (0.36–9.08) | 1.61 (1.16–2.21) | 1.75 (1.04–2.95) | 1.19 (0.45–3.18) | ns         | 1.28 (0.23–7.14) | 1.20 (0.77–1.86) |
| Fatigue              | 2.65 (0.94–7.51) | 2.22 (1.67–2.96) | 1.19 (0.90–1.56) | 3.07 (1.26–7.48) | 1.3 (0.7–2.1) | ns   | 1.84 (1.25–2.71) |
| Dry Mouth            | 7.09 (2.31–21.7) | 2.33 (0.43–12.8) | ns             | 0.21 (0.01–4.27) | 0.26 (0.03–2.3) | ns   | 2.32 (1.63–3.28) |
| Nausea/vomiting      | 1.50 (0.27–8.3)  | 1.44 (1.01–2.03) | 1.8 (1.05–3.02) | 0.68 (0.37–1.24) | 0.12 (0.01–2.0) (1 study) | 2.15 (0.80–5.8) | 1.18 (0.42–3.3) |
| Parasthesias         | 6.2 (1.5–26.3)   | 4.2 (2.7–6.6)    | 1.4 (0.49–4.2) | 5.0 (0.25–101.9) | ns         | ns   | 1.5 (0.26–9.0) (1 study) |
| Sleep disturbance    | ns              | 0.84 (0.53–1.33) | 1.64 (1.08–2.5) | ns           | ns         | 1.27 (0.66–2.5) | 0.63 (0.36–1.1) |
| Weight gain          | ns              | 1.02 (0.12–8.5)  | 6.1 (0.73–51.3) | 3.08 (0.60–15.9) | 0.79 (0.36–1.71) (4 studies) | ns   | 1.65 (1.02–3.04) |

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Side Effects

Patients receiving prophylactic treatment were more likely than those receiving placebo to experience side effects (RR: 1.27, 95% CI: 1.19 to 1.37) and to withdraw from treatment (RR: 1.18, 95% CI: 1.08–1.29). The specific side effects varied by study medication (Table 11). Drowsiness was the most common side effect, increased among patients taking gabapentin, pizotifen, topiramate, TCA and valproate. Tricyclic antidepressants also caused dry mouth and weight gain. Beta-blockers were associated with feeling depressed, dizzy and insomnia. Topiramate increased rates of nausea and paresthesia. Pizotifen had marked increased rates of weight gain with participants averaging 4.3 kg (95% CI: 3.0–5.6).

Network meta-analysis and direct comparisons found no difference in likelihood of experiencing “any” side effect or in the rate of withdrawing from studies.
(β = -0.06, 95% CI: -0.09 to -0.03) as well as for valproate (β = -0.02, 95% CI -0.04 to -0.01) and flunarizine (β = -0.03, 95% CI -0.07 to -0.001). The other treatment options did not appear to be time-sensitive. There was no relationship between type of measurement (frequency vs. headache index) and outcomes (p = 0.72). Age, percent women, sample size, dropout rate, percent of maximum dose attained, study design and whether or not depressed patients were allowed to participate had no relationship with outcomes.

Discussion

There has long been consensus that some drugs are useful in prophylaxis against migraine headaches. Our review confirms that there is good evidence for amitriptyline, atenolol, flunarizine, fluoxetine, metoprolol, pizotifen, propranolol, timolol, topiramate and valproate in reducing episodic migraine headache. At baseline, episodic migraine sufferers averaged slightly over six headaches per month and most drugs reduced the number of headaches by 1 or 2 per month. Amitriptyline had the greatest benefit and while the network meta-analysis suggested that it was the most effective drug for preventing migraine headaches, this was not confirmed in clinical trials in which amitriptyline was directly compared with other drugs (including SSRIs, topiramate and propranolol), though all candidate drugs have not been included. Beta-blockers (atenolol, propranolol, timolol), anticonvulsants (topiramate, valproate), flunarizine and pizotifen had moderate benefit in reducing headache burden while the serotonin reuptake inhibitors had a small effect.

On average, across the effective prophylactic medications, migraine sufferers had about twice the chance of experiencing at least a 50% reduction in headaches as those receiving placebo. Our pooled risk reduction (ARR: 0.15, 95% CI: 0.09–0.21) suggests that 7 people would need to be treated to produce 50% reduction in headache burden in one subject. Side effects were common, but were predictable based on the drug mechanisms of action and are well-known.

There was a significant placebo effect that was seen within 4 weeks of placebo initiation with a gradual increase in the benefit of placebo on headaches through 12 weeks. By week 16, patients randomized to placebo had a gradual increase in the number of headaches experienced with no difference from baseline through 24 weeks of treatment. This is similar to the placebo effect we saw in our meta-analysis of pediatric migraine trials [233]. Uncontrolled trials of drugs for treatment of migraine headaches are still published, our data reinforces the importance of placebo controls.

Our study is the first to pool all the data from the numerous randomized controlled clinical trials to explore potential differences for both continuous and dichotomous outcomes and for both episodic and chronic migraine headaches. We also avoid a common error found in previous meta-analyses in which researchers pooled the outcome at the end of the study, regardless of the time point. This inappropriately pooled studies of different treatment durations.

There have been no previous systematic reviews of ACE/ARB, flunarizine or beta-blockers other than propranolol for migraine headaches. A recent Neurology Academy review was limited by several factors: 1) it included only studies since 2009, 2) it provided only qualitative statements about the level of evidence with no formal pooling of data and 3) it had no comparative effectiveness data [27]. While our findings are similar to previous reviews of anticonvulsants [234], the beta-blocker propranolol [235], anticonvulsants [236] and tricyclic antidepressants [237], we found some important differences. Anticonvulsants were less effective than a 2004 Cochrane review [234], though our review includes nearly twice as many studies. A 2004 Cochrane beta-blocker review included exclusively propranolol, while we include all beta-blockers. Our 2010 TCA review [237] inappropriately pooled both migraine and tension headaches together. Our 1996 review [238] also combined migraine and tension
headaches, likely inappropriate given potentially important pathophysiologic differences. A 2005 Cochrane review of SSRIs found no benefit[239], but that trial was largely based on tension headaches and it also combined both migraine and tension headaches in their pooled analysis. In contrast, our larger review focuses on migraine headaches and suggests a modest effect from fluoxetine. To date, there have been no quantitative systematic reviews comparing the different classes of treatment, though one recent qualitative systematic review concluded that the choice should be tailored to patients based on side effects and comorbidities [240].

A recent systematic review examined the efficacy of prophylactic treatment for episodic migraine headaches[28] in reducing headaches by 50%, a dichotomous outcome. Our study includes both continuous and dichotomous outcomes and examines the effects for both episodic and migraine headaches. That study was limited to English language only and includes a smaller number of studies than this analysis. Our results are similar and in agreement with their conclusion that there is no difference in efficacy between the different drugs; however we found that the benefit for most drugs was less than they reported.

Our study has a number of important limitations. First the pooled differences between the various drugs and classes suggested important clinical differences. Some drugs had a large effect in headache reduction, others only small or modest ones. Our network meta-analysis suggested superiority for amitriptyline, a finding not confirmed in head-head trials. While there have been 51 trials directly comparing different drugs, these comparisons have been somewhat haphazard and many important potential comparisons have not been made.

Conclusions
Our data suggests that the current practice of tailoring prophylactic medication according to patient characteristics and expected side effects is a good approach. Patients with migraine headaches and hypertension should consider trials with a beta blocker. Patients with depression may benefit from either SSRI or TCA. Patients with restless leg syndrome or another indication for an anticonvulsant may benefit from topiramate or valproate. Our analysis suggests that amitriptyline is more effective than the other medications, this has not been confirmed in the limited number of direct comparative effectiveness trials that have been conducted. The placebo effect, that lasts through at least 12 weeks in our study, suggests that non-placebo controlled trials should not be performed. Nearly all studies of headache treatment were 24 weeks or less in duration, this is an important limitation since migraine is a chronic condition. Whether treatment benefit persists, increases or wanes is unknown and deserving of further studies. The paucity of head-to-head comparative effectiveness trials between some classes of medication also indicates a direction for future headache research.

Supporting Information
S1 File. PRISMA Checklist.
(DOC)

Author Contributions
Conceived and designed the experiments: JLJ EC RSD WC AG NS JK. Performed the experiments: JLJ EC RSD CE WC AG NS JK. Analyzed the data: JLJ EC RSD. Contributed reagents/materials/analysis tools: JLJ EC RSD CE WC AG NS JK. Wrote the paper: JLJ EC RSD CE WC AG NS JK.
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