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Steroids for preventing recurrence of acute severe migraine headaches: a meta-analysis

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Background and purpose: Recurrence of migraine headaches after treatment is common. The evidence regarding steroids for preventing migraine headache recurrence is controversial. This meta-analysis examined the effectiveness of steroids for prevention of recurrent headaches.

Methods: Databases (PubMed, Embase and the Cochrane Library) and conference proceedings were searched for randomized controlled trials comparing steroids and placebo in the treatment of migraine headaches. Two independent reviewers assessed studies and extracted data. Relative risks (RRs) of headache recurrence and adverse events were calculated and reported with 95% confidence intervals (95% CIs).

Results: Eight studies with 905 patients were included. Pooled analysis showed that when steroids were added to standard abortive therapy they reduced the rate of moderate or severe headache recurrence after 24–72 h of follow-up evaluation (RR = 0.71; 95% CI = 0.59–0.86). There was no significant benefit of steroids compared with placebo in the proportion of totally resolved migraines (RR = 1.11; 95% CI = 0.94–1.32). The side effects of steroids are mild and not significant except for dizziness. Subgroup meta-analysis showed that parenteral dexamethasone tends to be more effective in reducing moderate or severe recurrent headaches (RR = 0.68; 95% CI = 0.55–0.84). However, no significant differences were found between oral administration and parenteral administration of steroids ($P = 0.37$).

Conclusion: When steroids are added to standard abortive therapy for migraine headaches, they are effective and safe for preventing moderate or severe headache recurrence.

Introduction

Migraine headaches are common diagnoses of patients presenting to the emergency department (ED) [1]. The 1-year prevalence for migraines is 11.7% (17.1% in women and 5.6% in men) in the USA [2]. Numerous agents, including sumatriptan, dihydroergotamine, ergotamine, chlorpromazine, prochlorperazine and others, have proven beneficial for acute migraines [3–7]. However, the recurrence of migraine headaches within 24–72 h after treatment is common. Recurrent headaches have been reported to occur in 23%–87% of subjects within 24 h and 45% of patients with a headache reported headache-related functional impairment [8]. Neurogenic inflammation has been proposed as an important pathophysiological mechanism in migraine generation and relapse [9]. Intravenous dexamethasone has been shown to be effective in decreasing the incidence of severe recurrent headache after treatment [10]. However, other randomized controlled trials (RCTs) have failed to document the same results [8,11–14]. A meta-analysis by Colman *et al.* [15] was performed to evaluate the role of parenteral dexamethasone in preventing migraine recurrence. However, this previous study mainly focused on intravenous dexamethasone. Recently, some studies on oral steroids for prevention of recurrent migraine have been reported [16,17].

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This study aimed to assess the evidence from RCTs on the effectiveness and tolerability of steroids for acute migraine headaches in adults and the prevention of recurrence of these headaches.

Methods

Search strategy and selection criteria

Electronic databases (PubMed, Embase and Cochrane Library) were searched for RCTs that compared steroids and placebo in the treatment of migraine headaches using the terms 'headache' or 'migraine' and several terms to identify steroids as follows: 'steroids', 'corticosteroids', 'dexamethasone', 'prednisone', 'prednisolone', 'methylprednisolone' or 'hydrocortisone' (from 1950 to December 2012). Terms were explored whenever possible within each database. The word 'random' was required to appear in the title or abstract in Embase search. Conference proceedings on neurology, headache and emergency medicine and the reference lists of potentially relevant studies were also searched manually. Language of publication and publication form were not limitations.

Studies were included in our analysis if they met the following criteria: (i) the design was a prospective RCT; (ii) patients were diagnosed with acute migraines; (iii) studies reported the efficacy of steroids as adjuvant therapy for acute migraines, compared with placebo.

Data extraction and quality assessment

Two of the authors (Y.H. and X.C.) performed an independent search using the above strategy to identify potentially relevant papers. Full manuscripts of potentially relevant studies were obtained and reviewed using pre-defined eligibility criteria. Information on study characteristics, patient characteristics, intervention strategies, follow-up duration, outcomes and adverse events was abstracted from the original reports and transferred to specially designed, pre-tested paper forms by two independent reviewers (Y.H. and X.C.). Disagreements were resolved by consensus.

Quality assessments were evaluated with the Jadad Quality Scale [18], which evaluates the reported randomization, blinding and withdrawals in a clinical trial and assigns a score from 0 to 5, with higher scores indicating higher quality in the conduct or reporting of the trial [15].

Data synthesis and analysis

The primary outcome considered was a moderate or severe headache (defined as relapse) within 24–72 h of treatment. Secondary outcomes considered were the proportion of patients with a migraine that was totally resolved (pain-free) and adverse events associated with the treatment.

χ^2 and I^2 statistics were used to test for heterogeneity (25%, 50% and 75% representing low, moderate and high heterogeneity, respectively) [19]. Fixed-effects models were used when I^2 was <50%; otherwise, random-effects models were used for analysis. For dichotomous variables, pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated. The number needed to treat (NNT) was calculated on the basis of the pooled RR. Publication bias was explored with the use of funnel plots. Subgroup analyses comparing parenteral dexamethasone with placebo and oral steroid treatment with placebo and a subgroup analysis in primary outcome according to the dosage of dexamethasone were carried out. To assess the effect of individual studies on the pooled RR, an influence analysis was performed in which the pooled RR was recalculated omitting one study at a time. P values are two-tailed and statistical significance was set at 0.05. All analyses were performed with RevMan software (version 5.1 for Windows; Cochrane Collaboration, Copenhagen, Denmark).

Results

Selected studies and characteristics

The selection of studies for inclusion in the meta-analysis is shown in Fig. 1. Two investigators worked

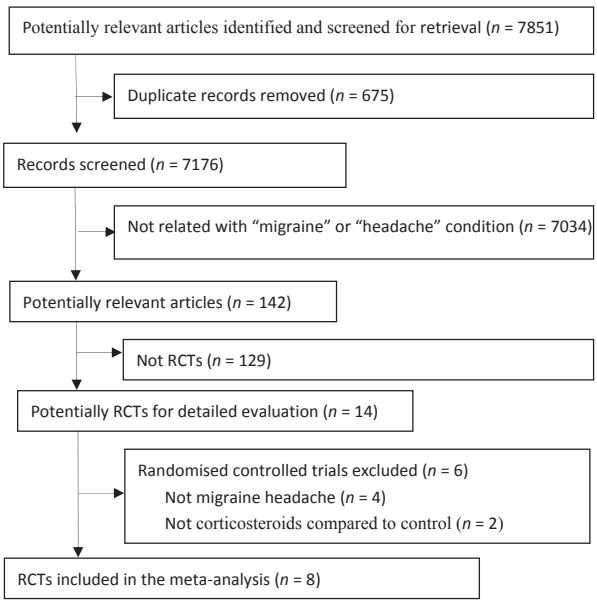

Figure 1 Flow of papers through review. RCT, randomized controlled trial.

Table 1 Characteristics of studies included in the meta-analysis

Study	Patients (*n*)	Treatment/Comparison	Concomitant therapy	Follow-up (h)	Jadad score
Friedman 2007 [8]	205	DXM 10 mg iv/placebo	Metoclopramide and diphenhydramine iv	24	5
Innes 1999 [10]	98	DXM 24 mg iv/placebo	Standard abortive therapy	48–72	5
Jones 2003 [11]	70	DXM 20 mg iv or im/placebo	Standard abortive therapy	48	5
Fiesseler 2006 [12]	85	DXM 10 mg iv/placebo	Standard abortive therapy	24–48	4
Rowe 2008 [13]	112	DXM 15 mg iv/placebo	Standard abortive therapy	48–72	5
Donaldson 2008 [14]	99	DXM 24 mg iv/placebo	Standard abortive therapy	72	5
Kelly 2008 [16]	61	DXM 10 mg oral/placebo	Chlorpromazine or prochlorperazine iv	24	5
Fiesseler 2011 [17]	173	DXM 10 mg iv once or prednisone 40 mg oral for 2 days/corresponding placebo	Standard abortive therapy	24 –72	5

DXM, dexamethasone; iv, intravenously; im, intramuscularly.

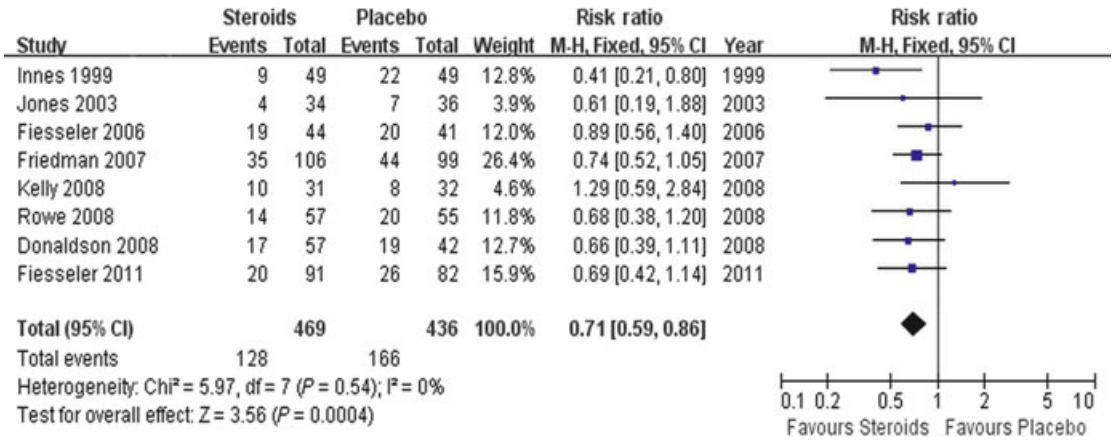

Figure 2 Forest plot of the effectiveness of steroids plus standard abortive therapy for moderate or severe recurrent migraine headache compared with placebo plus standard abortive therapy.

independently (Y.H. and X.C.) to identify potentially relevant papers using the search strategy defined earlier. Of the initial 7851 records, 14 required a review of the full manuscript. Finally, eight RCTs with a total of 905 patients satisfying the inclusion criteria were identified and analyzed [8,10–14,16,17]. All enrolled patients were aged >17 years. No disagreements on inclusion of trials occurred between reviewers. Six of the eight primary papers were published [8,10,13,14,16,17]; two were in abstract form [11,12] and the data were acquired through correspondence with the main author or prior meta-analyses. Table 1 summarizes the key features of the included trials. Seven of the included trials [8,10,11,13,14,16,17] had a score of 5 and one trial [12] had score of 4 by the Jadad Quality Scale, indicating the high quality of these studies according to randomization, blinding and description of withdrawals and dropouts.

There were different headache severity scales for treatment outcome in the included literature. However, most of these scales defined the severity of headache based on requiring another visit to the physician, interference in daily activities and requiring self-medication. The primary outcome was defined as moderate or severe headache relapse, including headaches that interfered in daily activities or required a visit to a physician.

Primary outcome

Pooled data included the results of 905 patients from eight high-quality clinical trials. There was no significant heterogeneity when tested using the I^2 statistic ($I^2 = 0\%$). Therefore fixed-effects models were used for the analyses. The combined result of all trials suggested a significant benefit of steroids compared with placebo in addition to standard abortive therapy for acute migraine headache (RR = 0.71; 95% CI = 0.59–0.86; Fig. 2). On the basis of the pooled RR, the estimated NNT to prevent one moderate or severe recurrent headache was 10 (95% CI = 6–22). There was no evidence of publication bias identified by visual inspection of the funnel plot (Fig. S1).

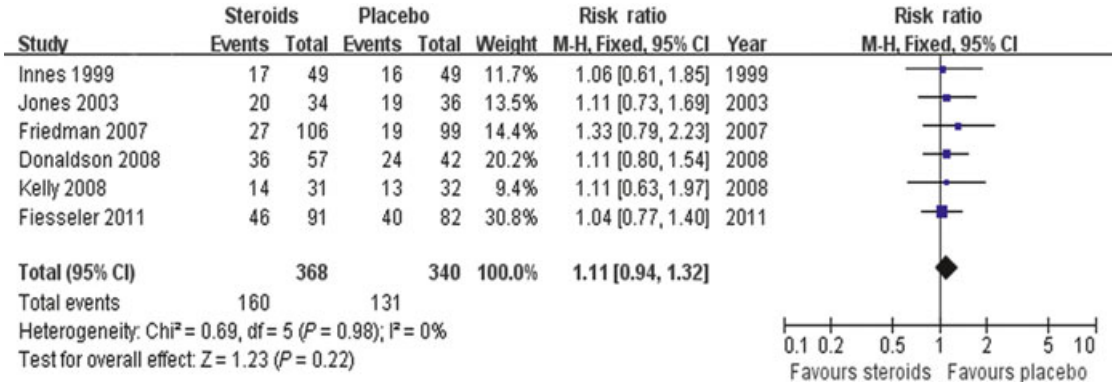

Figure 3 Forest plot. The effectiveness of steroids for rate of totally resolved migraine headache compared with placebo.

Secondary outcome

Six studies (n = 708) reported the proportion of patients with a migraine that totally resolved or who were persistently pain-free [8,10,11,14,16,17]. Data were pooled from these studies and calculated using the fixed-effects model, which suggested no significant benefit of steroids compared with placebo for the proportion of totally resolved migraines (RR = 1.11; 95% CI = 0.94–1.32; Fig. 3).

Adverse events

Six of the included studies (n = 648) reported specific adverse events [8,10,11,13,14,16]. Patients treated with steroids were more likely to have dizziness (RR = 2.78; 95% CI = 1.02–7.61; Fig. 4). No significant differences were found between steroids and placebo groups for restlessness, drowsiness, nausea or vomiting, tingling, numbness, swelling and any other adverse events (Fig. 4).

Subgroup analyses

Six of the studies (n = 669) compared parenteral dexamethasone with placebo [8,10–14], one study compared oral dexamethasone with placebo (n = 63) [16] and one study compared intravenous dexamethasone or oral prednisone with placebo (n = 173) [17]. Subgroup meta-analysis of the studies comparing parenteral dexamethasone with placebo showed that parenteral dexamethasone significantly decreased the primary outcome (RR = 0.68; 95% CI = 0.55–0.84; Fig. 5). The estimated NNT to prevent one severe recurrent headache was 8 (95% CI = 5–18).

Two of the studies included patients who received oral steroid treatment (n = 78), allowing for a subgroup comparison with those who received parenteral treatment. For the primary outcome of moderate or severe migraine headaches, no significant difference was found between oral administration and parenteral administration of steroids (RR = 0.82; 95% CI = 0.53–1.27; P = 0.37).

A subgroup analysis was also performed on primary outcome according to the dosage of dexamethasone. Studies that used 15 mg or more of dexamethasone (n = 4) showed a stronger treatment effect (RR = 0.58; 95% CI = 0.42–0.80) than those that used <15 mg (RR = 0.80; 95% CI = 0.63–1.01). However, the difference between the two subgroups was not significant (χ^2 = 2.52; P = 0.11).

Sensitivity analyses

Multiple methods were performed to test sensitivity, and the primary results were not influenced by the use of fixed-effects models compared with random-effects models, odds ratios compared with RRs, and recalculation by omitting one study at a time.

Discussion

Headaches comprise approximately 5% of ED visits, and more than half of patients with migraine headaches will have recurrence of symptoms within 48 h of initial abortive therapy [20]. The concept of using an inexpensive and safe medication to prevent recurrent headaches is compelling not only for controlling pain but also because it may reduce the number of repeat ED visits for patients seeking migraine treatment [20]. Steroids have been extensively studied for preventing migraine recurrence; however, the results of RCTs are still controversial [8,11–14].

This systematic review and meta-analysis summarizes the current RCTs for comparing steroids and placebo for treatment of migraine headaches. Our

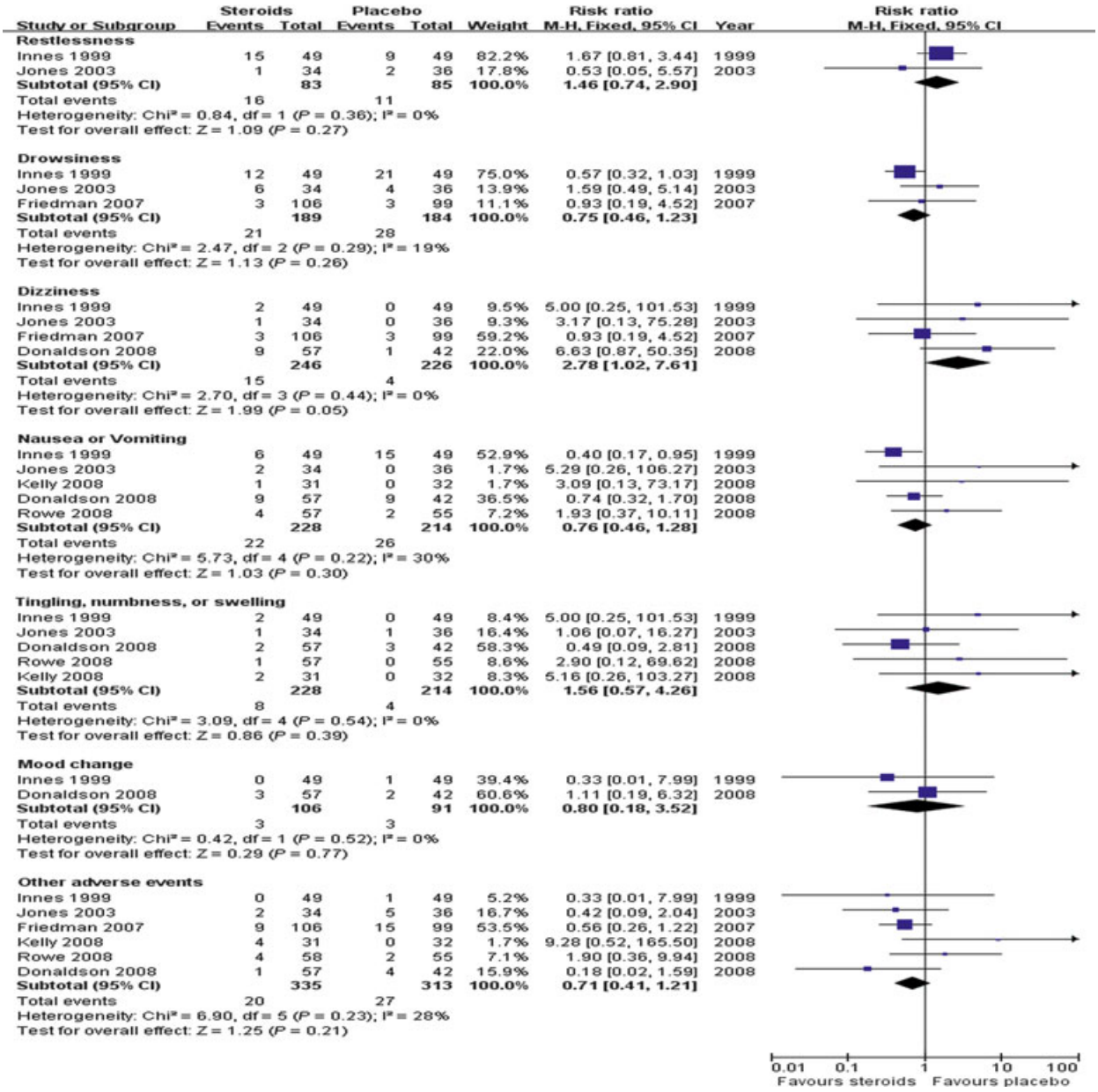

Figure 4 Forest plot of side effects between steroids and placebo groups.

results suggest that, on the basis of standard abortive therapy, steroids reduce moderate or severe recurrence of headaches by approximately 29% within 24–72 h. However, our results suggest no significant benefit of steroids compared with placebo for the proportion of totally resolved migraines. The side effects of steroids are mild and not significant, except for dizziness.

Two prior meta-analyses on dexamethasone treatment for migraine headaches have been published [15,21]. A meta-analysis by Colman *et al.* [15] concluded that, when a single dose of parenteral dexamethasone is added to standard abortive therapy for a migraine headache, it is associated with a 26% relative reduction in headache recurrence (NNT = 9) within 72 h. This previous study did not include studies using oral steroids. However, intravenous access was not obtained in all patients with migraine headaches. Another meta-analysis by Singh *et al.* [21] included an RCT using oral dexamethasone and obtained similar results to Colman *et al.*'s study but they did not perform subgroup analyses. Recently, another study that compared intravenous dexamethasone or oral prednisone with placebo failed to show a benefit of steroid treatment for recurrent migraine headaches [17].

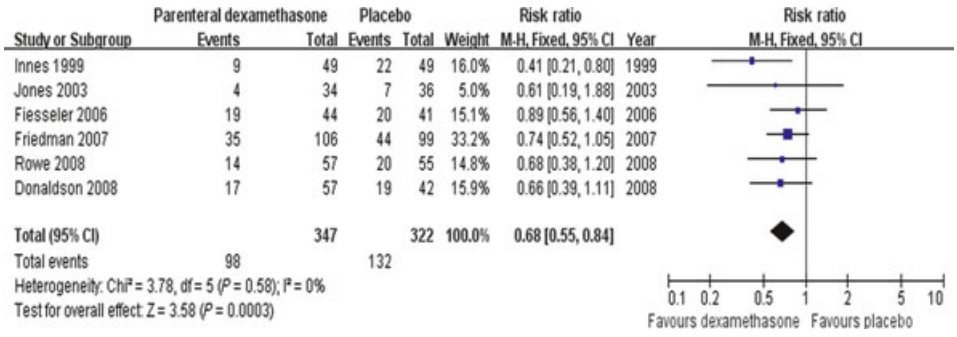

Figure 5 Forest plot of the effectiveness of parenteral dexamethasone plus standard abortive therapy for moderate or severe recurrent migraine headache compared with placebo plus standard abortive therapy.

In contrast to Colman *et al.*'s study [15], the study by Baden and Hunter [22] was not included in our analysis. Baden and Hunter [22] administered dexamethasone to prevent the recurrence of 'benign headache', and the inclusion criteria may have allowed a large proportion of patients with no migraines to be included. Our study included two studies with patients who received oral steroid treatment, allowing for a subgroup comparison with those who received parenteral treatment. Subgroup meta-analysis of the studies showed that parenteral dexamethasone significantly decreased the primary outcome (RR = 0.68; 95% CI = 0.55–0.84). The estimated NNT to prevent one severe recurrent headache was 8 (95% CI = 5–18). However, no significant differences were found between oral administration and parenteral administration of steroids. This result suggests that oral administration of steroids is as effective as parenteral administration.

Similar to Colman *et al.*'s study [15], in our work a retrospective subgroup analysis was also performed on the primary outcome according to the dosage of dexamethasone. Studies that used 15 mg or more of dexamethasone showed a stronger treatment effect than those that used <15 mg. This result showed a trend for a dose-dependent effect for the use of dexamethasone. However, the difference between the two subgroups was not significant. Future studies comparing different doses on prevention of moderate and severe migraine headaches are urgently required.

Limitations

This meta-analysis has some limitations. First, to meet the definition of a recurrent migraine, the original migraine must have largely resolved. However, not all trials tackled this specifically. Therefore, the primary outcome of moderate or severe headache relapse, including those that interfered in daily activities or required a physician's visit after 24–72 h, was defined. Second, the confounding interventions between different abortive agents, steroids and the relapse of headaches could not be clarified. Although opioids are not recommended as a first-line treatment by the American Academy of Neurology, prior studies have demonstrated that the majority of ED patients receive opioids for headaches, which may be associated with higher relapse rates than other agents as abortive agents [17,23,24]. Third, for some of the subgroup analyses, such as oral administration of steroids, only very few studies were available for pooling data. Further studies are needed to access the effect of oral administration of steroids for migraine. Finally, the characteristics of patients most likely to benefit from steroid treatment could not be identified because of the relatively small number of patients available for subgroup analysis.

Conclusion

The results of our analysis suggest that, when steroids are added to abortive migraine therapy, they reduce the occurrence of moderate and severe recurrent headaches within 24–72 h by 29%. The adverse effects of steroids are mild and not significant, except for dizziness. Further studies are required to determine the most appropriate dosage of steroids for migraine headaches and to investigate the characteristics of patients most likely to benefit from steroid treatment.

Disclosure of conflict of interest

The authors declare no financial or other conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plot of primary outcome comparison: steroids versus placebo for moderate or severe recurrent migraine headache.

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