Impact of the botulinum-A toxin on prevention of adult migraine disorders

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A systematic review of the impact of botulinum-A toxin as a therapeutic regimen for the management of adult migraine disorders is shown to that Botulinum-A toxin provides a more significant reduction in the number of headache episodes per month relative to placebo (MD: -0.61, 95% CI: -1.02 to -0.19). In subgroup analysis, botulinum-A toxin significantly reduced headache episodes per month relative to placebo for chronic migraine (MD: -1.68, 95% CI: -3.31 to -0.06), migraine (MD: -2.43, 95% CI: -4.08 to -0.77), and follow-up time in 16 weeks (MD: -2.19, 95% CI: -3.84 to -0.53). Statistical differences were not found in subgroup analyses of data relating to chronic migraine, episodic migraine, and other treatment course durations. An analysis of chronic and episodic migraine, botulinum-A toxin did not significantly differ from placebo in the proportion of patients achieving a fifty percent reduction in the number of headaches per month. In terms of patients’ subjective reporting of headaches, botulinum toxin A conferred significant improvements when assessment questionnaires of migraine disability and migraine impact were analyzed. However, differences were not substantial with data from the 6-item headache impact test. This meta-analysis demonstrated that botulinum-A toxin as a therapeutic regimen improved the impact of chronic migraines after 16 weeks of therapy, although this was not the case for episodic migraine.

Keywords
Migraine; botulinum-A toxin; headache episodes; treatment-related adverse events; meta-analysis

1. Introduction
Migraine is a common headache disease, affecting approximately 15% of the population and occurring more commonly in females (Vos et al., 2016). Without effective treatments, migraines can reduce living quality, increase the economic burden, and weaken production capacity (Linde et al., 2012; Vos et al., 2016). Moreover, migraine attacks remain an issue for patients despite the availability of acute and prophylactic treatments (Linde et al., 2013a,b). Meanwhile, relevant studies (Ekkert et al., 2019) confirmed that the visual cortex excitability might be linked to higher disability.

Botulinum-A toxin or botulinum toxin type A (BTX-A) had been demonstrated to relieve pain associated with a variety of conditions, including migraine headaches (Ranoux et al., 2008). It is speculated that this is achieved through blockage of sensory pain signals to the central nervous system, thereby promoting a reduction in central sensitization (Gazerani et al., 2006). It is well established that inflammatory mediators sensitize peripheral pain receptors through a cascade reaction, which in turn leads to the sensitization of central receptors and persistent pain (Gazerani et al., 2006). BTX-A is known to interfere with these inflammatory pathways. In the peripheral nerves, pain stimulation leads to calcitonin gene-related peptide and substance P release, which in turn induces the release of histamine and cytokines, thereby directly sensitizing or activating pain sensation. In addition to acting on peripheral pain-related vasoactive substances and receptors, some experiments have confirmed that BTX-A may directly inhibit central pain transmission, and its mechanism may be similar to endogenous opioids (Mazzocchio and Calio, 2015). However, Gazerani et al. (2006) found that the BTX-A inhibits peripheral sensitization of nociceptive fibers and indirectly reduces central sensitization. The exact mechanism of BTX-A is still controversial, but existing research has demonstrated that BTX-A had a particular effect on the prevention of chronic migraine attacks, but the mechanism of analgesia is still unclear, and there are still differences between the experimental studies. During the migraine cycle (a period when health and pain alternate), the brain’s abnormal functions fluctuate according to specific moments in the cycle itself. During the onset period, migraine brains are characterized by low levels of preactivation of all sensory and associative cortices. The response of the affected cortex to external repeated stimuli was initially low, and then the nerve activity gradually increased as the stimulus continued (de Tommaso et al., 2014).

Based on a six-month study of 162 patients, Binder (1998) filed a patent for the use of BTX-A in the treatment of migraine at the onset of headache symptoms. Subsequently, several clinical stud-
ies have confirmed the feasibility and efficacy of this approach (Elkind et al., 2006; Evers et al., 2004; Relja et al., 2007; Silberstein et al., 2000). In 2010, the US Food and Drug Administration approved BTX-A for the treatment of chronic migraine, based on the findings of the PREEMPT studies (Aurora et al., 2010; Diener et al., 2010). To date, the intramuscular formulation of BTX-A is the only treatment approved for the prevention of chronic migraine in the European Union (Frampton and Silberstein, 2018). Uncertainty remains, however, regarding the place of BTX-A among oral pharmacological prophylactics, its role in different migraine subtypes, its dosage, and optimal treatment duration. Questions also persist around which patient-related factors might predict response to different treatment protocols (Clare et al., 2019; Jackson et al., 2012; Teunis, 2019). As a further source of uncertainty, national guidance differs in their recommendations, while guidance from (for example) the European Federation of Neurological Societies has not been updated since 2009 and thus does not mention BTX-A at all (Negro et al., 2015; Pedraza et al., 2015). Rational use of therapies is important, not only from the healthcare economics perspective but in terms of reducing disability and improving patients’ quality of life. To encapsulate the body of data generated so far on this topic, we performed a systematic review and meta-analysis to investigate the impact of BTX-A as a therapeutic regimen for the management of adult migraine disorders.

2. Materials and methods
2.1 Search strategy

Three electronic databases, PubMed, EMBASE, and the Cochrane Library, were searched from their inception to July 6, 2019. Studies were identified that investigated the impact of BTX-A for the management of migraine. Search terms included: "Migraine Disorders," "Migraine Headache," "Hemicrania Migraine," "Migraine Variant," "Migraine," "Sick Headaches," "Botulinum Toxins," "Botulimum," "Onabotulinum Toxin" and "Clostridium botulinum Toxins."

2.2 Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were: (1) studies, participants of which were over 18 years of age; (2) comparisons of BTX-A with placebo; (3) studies conducted under a randomized controlled trial (RCT) design; and (4) studies reported in the English language.

The exclusion criteria for this meta-analysis are: (1) studies that included participants with migraine caused by known disorders, such as cephalic allodynia, cervical dystonia, and postlumbar puncture headaches; (2) studies whose interventions included topiramate, dysport, or a combination of treatments; (3) repeatability studies; or (4) studies where full texts were not available.

2.3 Risk of bias

The risk of bias of all studies was assessed according to the Cochrane Handbook (Version 5.1.0) (Higgins and Green, 2011). Hence, all included studies were assigned as "high risk," "unclear," or "low risk."

2.4 Data collection

We extracted relevant information from the included studies, as follows. (1) Basic characteristics: author, published year, region, sample, gender, age, migraine type, the severity of migraine, duration, and follow-up. (2) Interventions: the different dosages and usage of BTX-A and placebo; (3) Outcomes: primary outcomes were defined as the efficacy, including changes in headache episodes per month, fifty percent reduction in the number of headaches per month, headache impact using the 6-item headache impact test (HIT-6), migraine impact questionnaire (MIQ), and migraine disability assessment (MDAS) questionnaire. The secondary outcome was defined as adverse events (AEs), including treatment-related, severe AEs, injection-site pain, musculoskeletal stiffness, myalgia, nausea, neck pain, neck weakness, paresthesias, tiredness, muscle weakness, palpebral fissure, and blepharoptosis.

2.5 Statistical analysis

The effect size of relative risk (RR) (Deeks, 2002) with 95% confidence interval (CI) was employed for dichotomous outcomes and weighted mean difference (MD) (Higgins and Green, 2011) with 95% CI for continuous outcomes. The statistic value of I2 using the chi-square test was used to evaluate and measure the size of heterogeneity. An I2 value of greater than 40% with a significance level of P < 0.1 signified heterogeneity (Higgins and Green, 2011; Higgins and Thompson, 2002). Migraine type, different follow-up times, and different measurement scales were predetermined as the primary source of heterogeneity for primary outcomes, and subgroup analysis was used to address this heterogeneity. Funnel plots were used to qualitatively detect publication bias (Copas and Shi, 2000). All statistical analyses were carried out using R software (Versions 3.2.0).

3. Results

3.1 Basic characteristics and risk of bias of included studies

Of the initial 809 studies identified from PubMed, EMBASE, and the Cochrane Library, 73 were excluded due to duplication. A further 678 studies were excluded based on our inclusion and exclusion criteria after titles and abstracts had been read. The remaining 58 studies were read in full. As a result, 18 RCTs (Anand et al., 2006; Aurora et al., 2010, 2007; Barrientos and Chana, 2003; Cady et al., 2014; Diener et al., 2010; Elkind et al., 2006; Evers et al., 2004; Freitag et al., 2008; Hou et al., 2015; Laurretii et al., 2014; Lipton et al., 2016; Matharu et al., 2017; Relja et al., 2007; Sandrini et al., 2011; Saper et al., 2007; Silberstein et al., 2000; Vo et al., 2007) met our inclusion and exclusion criteria (Fig. 1). The basic characteristics of these studies are shown in Table 1. Table S1 shows the assessment of the risk of bias of included studies.

3.2 Changes in headache episodes per month

The Twenty-nine RCTs, including 4,031 patients, compared BTX-A and placebo and evaluated the outcome of change in headache episodes per month. Fig. 2 illustrates a significant difference between BTX-A and placebo in terms of the reduction in headache episodes per month (MD: -0.61, 95% CI: -1.02 to -0.19) in a random-effects model.

Based on a subgroup analysis of migraine-type we found that, relative to placebo, BTX-A significantly reduces the number of headache episodes per month for chronic migraine (MD: -1.68, 95% CI: -3.31 to -0.06) and migraine (MD: -2.43, 95% CI: -4.08 to -0.77), but no statistical difference was found for episodic migraine (MD: -0.01, 95% CI: -0.19 to 0.18) (Fig. 2). In a subgroup analysis
of different treatment durations, BTX-A significantly decreased the number of migraine episodes per month at 16 weeks relative to controls (MD: -2.19, 95% CI: -3.84 to -0.53), but there was no statistical difference at 12 weeks (MD: -0.23, 95% CI: -0.52 to 0.07) or 24 weeks (MD: -0.01, 95% CI: -0.46 to 0.45) (Fig. S1).

3.3 Fifty percent reduction in the number of headaches per month

Ten RCTs, including 2,576 patients, compared BTX-A and placebo and evaluated the outcome of a fifty percent reduction in the number of headaches per month. As shown in Fig. 3, BTX-A did not lead to a significant change in the fifty percent reduction in the number of headaches per month compared to placebo (RR: 1.16, 95% CI: 0.93 to 1.44) in a random-effects model.

Based on the subgroup analysis of migraine type, we found that BTX-A and placebo did not significantly differ concerning the outcome of fifty percent reduction in headache episodes per month for chronic migraine (RR: -1.42, 95% CI: -0.61 to 3.31) or episodic migraine (RR: 1.09, 95% CI: 0.94 to 1.26) in Fig. 3.

3.4 Headache impact

For the headache impact, which was based on different scoring systems, we found that BTX-A significantly improved the MIDAS questionnaire (MD: -15.80, 95% CI: -25.47 to -6.13), and MIQ (MD: -3.13, 95% CI: -4.82 to -1.43) compared to placebo in a random-effects model. However, BTX-A did not significantly improve headache impact as assessed by the HIT-6 (MD: -4.03, 95% CI: -8.32 to 0.26) (Fig. 4).

3.5 Adverse events

Sixteen RCTs, including 3,715 patients, compared BTX-A and placebo and evaluated the outcome of treatment-related AEs. Compared with placebo, BTX-A significantly increases treatment-related AEs (RR: 1.54, 95% CI: 1.25 to 1.93) in a random-effects model (Table 2).

In an analysis of specific AEs in BTX-A relative to placebo, we found statistically significant difference in incidences of headache (RR: 2.11, 95% CI: 1.35 to 3.30), injection-site pain (RR: 4.93, 95% CI: 2.25 to 10.8), musculoskeletal stiffness (RR: 30.1, 95% CI: 1.80 to 502.6), myalgia (RR: 5.70, 95% CI: 2.52 to 12.9), neck pain (RR: 3.44, 95% CI: 1.37 to 8.64), paresthesias (RR: 4.99,
95% CI: 1.73 to 14.4), muscle weakness (RR: 17.4, 95% CI: 9.57 to 31.8), palpebral fissure (RR: 7.55, 95% CI: 4.05 to 14.1), and blepharoptosis (RR: 14.2, 95% CI: 4.57 to 44.0). No statistical difference was found in other AEs, including nausea (RR: 2.18, 95% CI: 0.57 to 8.39), neck weakness (RR: 9.00, 95% CI: 0.52 to 156.7), and tiredness (RR: 1.25, 95% CI: 0.54 to 2.87) (Table 2).

### 3.6 Adverse events

Funnel plots of primary outcomes were generated (Fig. S2). These plots did not indicate the existence of publication bias concerning the consequences of change in headache episodes per month (Fig. S2A), a fifty percent reduction in the number of headaches per month (Fig. S2B), or headache impact (Fig. S2C).

### 4. Discussion

This meta-analysis combined 18 studies to confirm that BTX-A can reduce patients' headache episodes per month. There were, however, some discrepancies in the efficacy of BTX-A that were revealed when we stratified our analysis by treatment duration, with the finding that a significant difference in the change in headache episodes per month between BTX-A and placebo occurred after 16 weeks, but not at 12 or 24 weeks. Despite this, our findings at 12 weeks are similar to those of the recent meta-analysis by (Bruloy et al., 2019), wherein a mean difference in the change of migraine frequency of -0.23 (95 percent CI, -0.47 to 0.02; \( P = 0.08 \)) was reported. Furthermore, our overall results are consistent with those of Herd et al. (Herd et al., 2019) regarding changes in headache episodes per month. Intramuscular BTX-A for chronic migraine prevention is based on a previous study of its effectiveness in transient muscle relaxation (Burstein et al., 2014; Gooriah and Ahmed, 2015; Simpson, 2004). While our meta-analysis found that patients with episodic migraine did not benefit from BTX-A, it was therapeutically effective in chronic migraine. However, in reviewing the results of original studies of chronic migraine, only one study (Frampton and Silberstein, 2018) showed that the changes in headache episodes per month were significant after treatment with BTX-A, and none of them (Cady et al., 2014; Evers et al., 2004; Lauretti et al., 2014; Sandrini et al., 2011; Vo et al., 2007) was effectively relieved. Of course, in addition to considering the impact of migraine headaches, effective individualized treatment requires the careful evaluation of the clinical features and overall medical history in each chronic migraine patient (Barbanti and Ferroni, 2017).
Figure 3. Forest plot of subgroup analysis based on migraine-type in changes in a fifty percent reduction in the number of headaches per month.

| Study           | Experimental Events Total | Control Events Total | Risk Ratio | RR 95%-CI | Weight (fixed) | Weight (random) |
|-----------------|---------------------------|----------------------|------------|------------|----------------|-----------------|
| **subgroup = Chronic migraine** |                           |                      |            |            |                |                 |
| Sandrini 2011   | 19                        | 9                    | 2.27       | [1.25; 4.11] | 1.5%           | 7.8%            |
| Freitag 2008    | 6                         | 3                    | 2.00       | [0.59; 6.79] | 0.5%           | 2.7%            |
| Matharu 2017    | 285                       | 688                  | 0.80       | [0.71; 0.90] | 62.5%          | 17.5%           |
| Fixed effect model | 733                      | 743                  | 0.85       | [0.76; 0.94] | 64.5%          | ---             |
| Random effects model |                     |                      | 1.42       | [0.61; 3.31] | 28.0%          | ---             |

| **Heterogeneity: I² = 85%, t² = 0.4381, p < 0.01** |

| **subgroup = Episodic migraine** |                           |                      |            |            |                |                 |
| Rejia 2007 (PNR225) | 29                        | 85                   | 1.36       | [0.83; 2.24] | 3.4%           | 9.4%            |
| Rejia 2007 (PR225)  | 15                        | 44                   | 0.87       | [0.50; 1.50] | 3.1%           | 8.6%            |
| Rejia 2007 (PNR150) | 30                        | 82                   | 1.46       | [0.90; 2.39] | 3.3%           | 9.5%            |
| Rejia 2007 (PR150)  | 20                        | 43                   | 1.19       | [0.73; 1.93] | 3.0%           | 9.7%            |
| Rejia 2007 (PNR75)  | 32                        | 83                   | 1.54       | [0.95; 2.50] | 3.4%           | 9.7%            |
| Rejia 2007 (PR75)   | 18                        | 40                   | 1.15       | [0.70; 1.89] | 2.9%           | 9.4%            |
| Aurora 2007        | 91                        | 203                  | 0.88       | [0.71; 1.08] | 16.3%          | 15.7%           |
| Fixed effect model | 580                      | 520                  | 1.09       | [0.94; 1.26] | 35.5%          | ---             |
| Random effects model |                     |                      | 1.13       | [0.92; 1.38] | 72.0%          | ---             |

| **Heterogeneity: I² = 34%, t² = 0.0235, p = 0.17** |

**Fixed effect model** 1313 1263

| **Random effects model** |                           |                      | 0.93       | [0.85; 1.02] | 100.0%         | ---             |

**Residual heterogeneity: I² = 64%, p < 0.01**

| 0.2 | 0.5 | 1 | 2 | 5 |

Figure 4. Forest plot of subgroup analysis based on different measurement scales in headaches impact.

Regarding safety, this meta-analysis found that treatment-related AEs were significantly increased with BTX-A relative to placebo. These differences remained significant when considering specific complications, including headache, injection-site pain, musculoskeletal stiffness, myalgia, neck pain, paresthesias, muscle weakness, palpebral fissure, and blepharoptosis. Related studies (Herd et al., 2019) have also reported that BTX-A increases treatment-related AEs, but event types were reportedly mild and short-lived.

At present, the consensus of most research institutes is to prevent the onset of a migraine, especially for chronic migraines. Measures to prevent chronic migraines mainly include orally administered drugs, behavioral management techniques, alternative physical therapies, and nutraceutical therapies (Agostoni and Barbanti, 2019). Orally administered medications, such as beta-blockers, anticonvulsants, serotonin antagonists, and calcium-channel blockers, are used in the management of chronic migraine (Sarchielli et al., 2012). If drug interventions are not found to be effective, other preventive approaches may be used (Agostoni and Barbanti, 2019). These include patient education, substance abuse management, lifestyle changes, and management of comorbidities.
| Author | Year | Region | Sample (Female) | Age | Migraine type | Severity of migraine | Botulinum Toxin A, Dose (U) | Control | Duration (days) | Follow-up (weeks) |
|--------|------|--------|----------------|-----|---------------|---------------------|---------------------------|---------|----------------|------------------|
| Silberstein et al. (2000) | 2000 | USA | 123 (105) | 22-63 | Migraine | Severe, Mild | Botulinum toxin A 25 U; Botulinum toxin A 75 U | Placebo | 90 | 12 |
| Barrientos and Chana (2003) | 2003 | USA | 30 (24) | 18-66 | Migraine | Severe | Botulinum toxin A 50 U | Placebo | 90 | 12 |
| Evers et al. (2004) | 2004 | London | 60 () | 18-65 | Chronic migraine | Severe | Botulinum toxin A 100 U; Botulinum toxin A 16 U | Placebo | 90 | 12 |
| Anand et al. (2006) | 2006 | India | 32 (24) | 18-50 | Migraine | Severe | Botulinum toxin A 50 U | Placebo | 90 | 12 |
| Elkind et al. (2006) | 2006 | USA | 418 | 44.6/43.6/44.3/43.8 | Episodic migraine | Severe, Mild | Botulinum toxin A 25 U; Botulinum toxin A 7.5 U | Placebo | 360 | 16 |
| Vo et al. (2007) | 2007 | USA | 32 (27) | 42.5 | Chronic migraine | Severe | Botulinum toxin A (brand not reported), weight-based dosing | Placebo | 84 | 12 |
| Saper et al. (2007) | 2007 | USA | 232 (199) | 43.6 | Episodic migraine | Severe | Botulinum toxin A 10 U; Botulinum toxin A 6 U; Botulinum toxin A 9 U; Botulinum toxin A 25 U | Placebo | 90 | 12 |
| Relja et al. (2007) | 2007 | London | 495 (322) | 43.2 | Episodic migraine | Severe | PNR: Botulinum toxin A 225 U; Botulinum toxin A 150 U; Botulinum toxin A 75 U; PR: Botulinum toxin A 225 U; Botulinum toxin A 150 U; Botulinum toxin A 75 U | PNR: Placebo; PR: Placebo | 300 | 12 |
| Aurora et al. (2007) | 2007 | USA | 809 (272) | 45 | Episodic migraine | Severe | PNR: Botulinum toxin A; PR: Botulinum toxin A | PNR: Placebo; PR: Placebo | 330 | 12 |
| Freitag et al. (2008) | 2008 | USA | NA | 42.2/42.5 | Chronic migraine | Severe, Mild | Botulinum toxin A 100 U | Placebo | 120 | 16 |
| Diener et al. (2010) | 2010 | Germany | 705 (602) | 41 | Chronic migraine | Moderate, Mild | Botulinum toxin A 155 U | Placebo | 392 | 24 |
| Aurora et al. (2010) | 2010 | USA | 679 (594) | 41.2 | Chronic migraine | Moderate, Mild | Botulinum toxin A 155 U | Placebo | 392 | 24 |
| Sandrinini et al. (2011) | 2011 | Italy | 68 (45) | 48.5 | Chronic migraine | Severe | Botulinum toxin A 100 U | Placebo | 84 | 12 |
| Cady et al. (2014) | 2014 | USA | 20 (15) | 48.5 | Chronic migraine | Severe | Botulinum toxin A 155 U | Placebo | 308 | 16 |
| Lauretti et al. (2014) | 2014 | Brazil | 37 (26) | 46 p<0.05/49 p<0.03/13 | Chronic migraine | Severe, Mild | Botulinum toxin A 25 U | 0.9% physiological saline | 84 | 12 |
| Hou et al. (2015) | 2015 | China | 102 (81) | 40.7 p<0.05 | Episodic or Chronic Migraine | Severe, Mild | Fixed (muscle)-sites injection of Botulinum toxin A 25 U; Acupoint-sites injection of Botulinum toxin A 25 U | Placebo | 120 | 16 |
| Lipton et al. (2016) | 2016 | North America, Europe | 1384 (603) | 41.1 p<0.05/10.4/41.5 p<0.05/10.7 | Chronic migraine | Severe, Mild | Botulinum toxin A 155 U | Placebo | 395 | 24 |
| Matharu et al. (2017) | 2017 | London | 1384 (603) | 41 | Chronic migraine | Severe, Moderate, Mild, or Headache-free | Botulinum toxin A 155 U | Placebo | 392 | 24 |

Note: PR, Placebo responders; PNR, Placebo non-responders; NA, Not reported.
5. Conclusions
This meta-analysis evaluated the efficacy and safety of BTX-A for the management of adult migraine disorders based on systematic review and meta-analysis of published studies on the topic. We demonstrated that BTX-A as a therapeutic regimen can improve the impact of chronic migraine after 16 weeks of therapy, but that this effect is not found in episodic migraine.

Author contributions
LW had full access to all of the data in the research and took responsibility for the integrity of the data and the accuracy of the data analysis. BS and LW designed the research. BS and LW acquired the data. LW conducted the analysis and interpreted the data. BS and LW drafted the manuscript.

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Conflict of Interest
The authors declare no conflict of interest.

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Table 2. Pooled outcomes of adverse events.

| Adverse events                        | Number | Sample | RR, 95%CI | I²  | P for I² |
|---------------------------------------|--------|--------|-----------|------|----------|
| Treatment-related adverse events      | 16     | 1864/1851 | 1.54 (1.25, 1.91) | 80%  | < 0.01   |
| Headache                              | 12     | 1670/1603 | 2.11 (1.35, 3.30) | 0%   | 0.54     |
| Injection-site pain                   | 6      | 1067/1021 | 4.93 (2.25, 10.8) | 0%   | 0.6      |
| Musculoskeletal stiffness             | 1      | 607/629   | 30.1 (1.80, 502.6) | NR   | NR       |
| Myalgia                               | 4      | 984/983   | 5.70 (2.52, 12.9) | 0%   | 0.84     |
| Nausea                                | 3      | 377/354   | 2.18 (0.57, 8.39) | 0%   | 0.75     |
| Neck pain                             | 8      | 1244/1244 | 3.44 (1.37, 8.64) | 69%  | < 0.01   |
| Neck weakness                         | 2      | 40/40     | 9.00 (0.52, 156.7) | NR   | NR       |
| Paresthesias                          | 6      | 604/576   | 4.99 (1.73, 14.4) | 0%   | 0.99     |
| Tiredness                             | 4      | 564/536   | 1.25 (0.54, 2.87) | 0%   | 0.46     |
| Muscle weakness                       | 11     | 1439/1431 | 17.4 (9.57, 31.8) | 0%   | 0.84     |
| Palpebral fissure                      | 11     | 1063/1034 | 7.55 (4.05, 14.1) | 25%  | 0.21     |
| Blepharoptosis                         | 7      | 811/793   | 14.2 (4.57, 44.0) | 0%   | 0.94     |

Note: NR, Not reported.
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### Table S1. Risk of bias assessment of individual study

| First Author           | Year | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other      |
|------------------------|------|----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|--------------------|------------|
| Silberstein et al. (2000) | 2000 | Low risk                   | Low risk               | Low risk                               | Unclear                       | Low risk               | Low risk           | Unclear    |
| Barrientos and Chana (2003) | 2003 | Unclear                    | Unclear                | Unclear                                | Low risk                       | Low risk               | Unclear           | High risk  |
| Evers et al. (2004)     | 2004 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk           | Low risk    |
| Anand et al. (2006)     | 2006 | Unclear                    | Unclear                | Unclear                                | Low risk                       | Low risk               | Unclear           | High risk  |
| Elkind et al. (2006)    | 2006 | Unclear                    | Low risk               | Low risk                               | Unclear                       | Low risk               | Low risk           | Unclear    |
| Aurora et al. (2007)    | 2007 | Low risk                   | Unclear                | Low risk                               | Low risk                       | High risk              | Low risk           | Unclear    |
| Relja et al. (2007)     | 2007 | Low risk                   | Unclear                | Low risk                               | Low risk                       | Unklear                | Low risk           | Unclear    |
| Saper et al. (2007)     | 2007 | Unclear                    | Low risk               | Low risk                               | Unclear                       | Low risk               | Low risk           | Unclear    |
| Vo et al. (2007)        | 2007 | Low risk                   | Unclear                | Low risk                               | Unclear                       | High risk              | Low risk           | Unclear    |
| Freitag et al. (2008)   | 2008 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Unclear                | Low risk           | Unclear    |
| Aurora et al. (2010)    | 2010 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk           | Unclear    |
| Diener et al. (2010)    | 2010 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk           | Unclear    |
| Sandrini et al. (2011)  | 2011 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Unclear                | Low risk           | Unclear    |
| Cady et al. (2014)      | 2014 | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk           | High risk  |
| Lauretti et al. (2014)  | 2014 | Low risk                   | Unclear                | Low risk                               | Low risk                       | Unclear                | Low risk           | High risk  |
| Hou et al. (2015)       | 2015 | Low risk                   | Unclear                | Low risk                               | Unclear                       | Low risk               | Low risk           | Unclear    |
| Lipton et al. (2016)    | 2016 | Low risk                   | Unclear                | Low risk                               | Unclear                       | Unclear                | Unclear           | Unclear    |
| Matharu et al. (2017)   | 2017 | Low risk                   | Low risk               | Low risk                               | Unclear                       | Unclear                | Unclear           | Unclear    |
Figure S1. Forest plot of subgroup analysis based on difference follow-up time in changes in headache episodes per month.
Figure S2. Funnel plots of primary outcomes.

Note: A was identified as the changes in headache episodes per month, B was identified as the changes in fifty percent reduction in number of headaches per month, and C was identified as the headaches impact.