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Systematic Review

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

Bin Shen[1] and Lan Wang[2,3,*]

[1]*Jiangsu Vocational College of Medicine, Yancheng, 224005, P. R. China*

[2]*Hubei University of Chinese Medicine, Wuhan, 430065, P. R. China*

[3]*Institute of Chinese Medicine Nephrology, Hubei Provincial Hospital of Traditional Chinese Medicine, Hubei Province Academy of Traditional Chinese Medicine, Wuhan, 430061, P. R. China*

*Correspondence: wanglanann11@163.com (Lan Wang)

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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 Caleo, 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," "Botulin," "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 (MIDAS) questionnaire. The secondary outcome was defined as adverse events (AEs), including treatment-related, severe AEs, headache, 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; Lauretti 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

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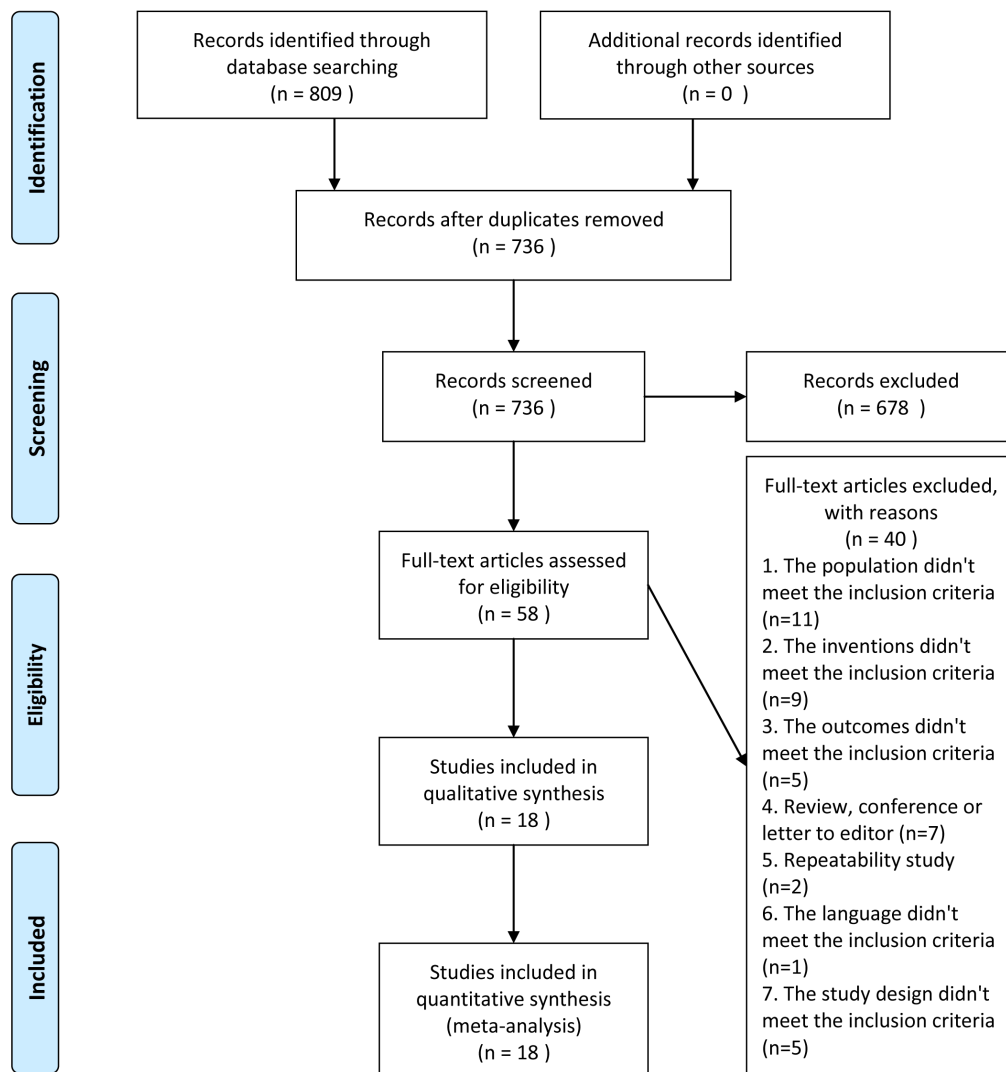
Figure 1. Flow diagram of the study selection process.

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,

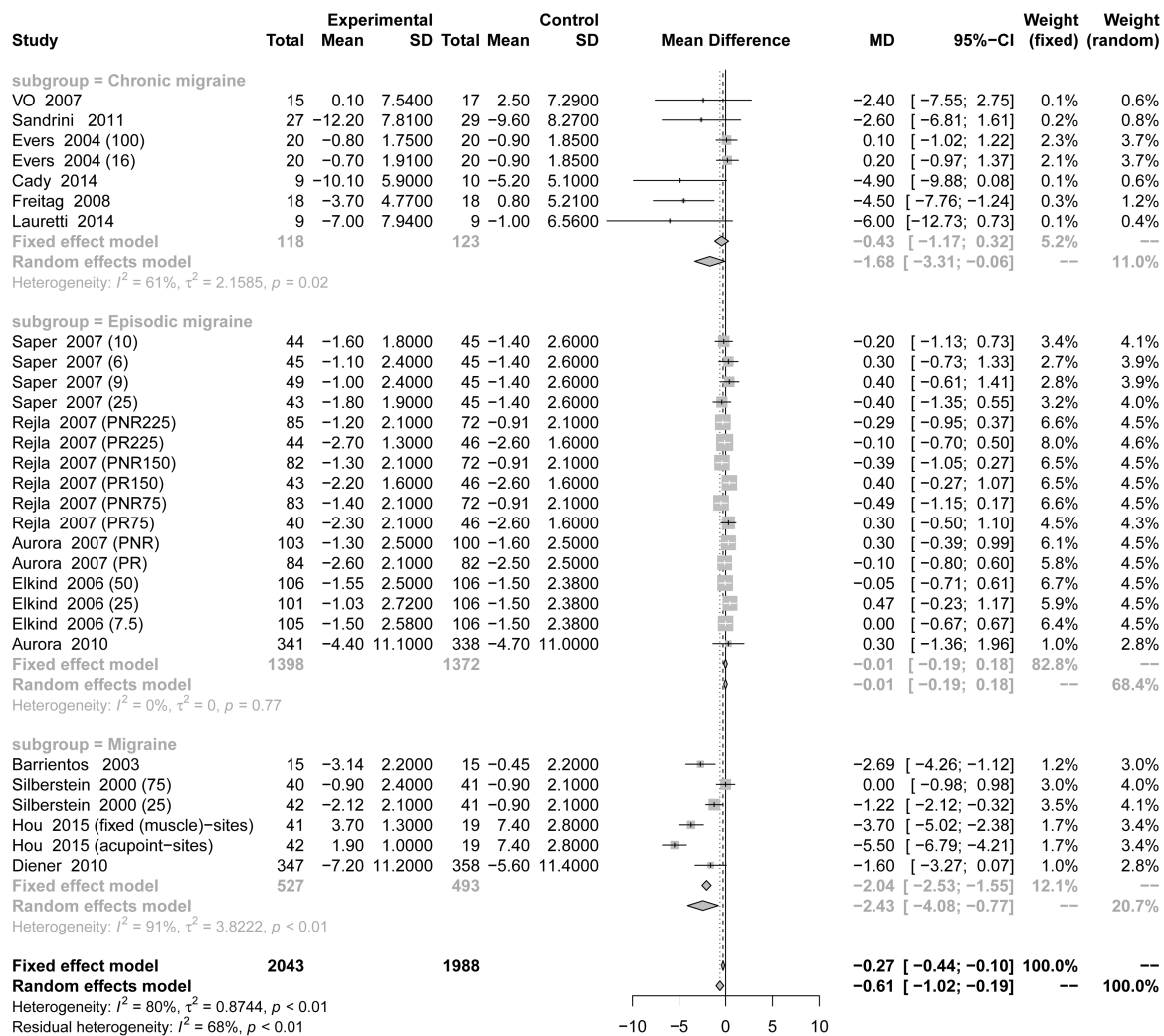| Study	Total	Experimental Mean	SD	Total	Control Mean	SD	Mean Difference	MD	95%−CI	Weight (fixed)	Weight (random)
subgroup = Chronic migraine											
VO 2007	15	0.10	7.5400	17	2.50	7.2900		−2.40	[−7.55; 2.75]	0.1%	0.6%
Sandrini 2011	27	−12.20	7.8100	29	−9.60	8.2700		−2.60	[−6.81; 1.61]	0.2%	0.8%
Evers 2004 (100)	20	−0.80	1.7500	20	−0.90	1.8500		0.10	[−1.02; 1.22]	2.3%	3.7%
Evers 2004 (16)	20	−0.70	1.9100	20	−0.90	1.8500		0.20	[−0.97; 1.37]	2.1%	3.7%
Cady 2014	9	−10.10	5.9000	10	−5.20	5.1000		−4.90	[−9.88; 0.08]	0.1%	0.6%
Freitag 2008	18	−3.70	4.7700	18	0.80	5.2100		−4.50	[−7.76; −1.24]	0.3%	1.2%
Lauretti 2014	9	−7.00	7.9400	9	−1.00	6.5600		−6.00	[−12.73; 0.73]	0.1%	0.4%
Fixed effect model	118			123				−0.43	[−1.17; 0.32]	5.2%	−−
Random effects model								−1.68	[−3.31; −0.06]	−−	11.0%
Heterogeneity: $I^2 = 61\%$, $\tau^2 = 2.1585$, $p = 0.02$											
subgroup = Episodic migraine											
Saper 2007 (10)	44	−1.60	1.8000	45	−1.40	2.6000		−0.20	[−1.13; 0.73]	3.4%	4.1%
Saper 2007 (6)	45	−1.10	2.4000	45	−1.40	2.6000		0.30	[−0.73; 1.33]	2.7%	3.9%
Saper 2007 (9)	49	−1.00	2.4000	45	−1.40	2.6000		0.40	[−0.61; 1.41]	2.8%	3.9%
Saper 2007 (25)	43	−1.80	1.9000	45	−1.40	2.6000		−0.40	[−1.35; 0.55]	3.2%	4.0%
Rejla 2007 (PNR225)	85	−1.20	2.1000	72	−0.91	2.1000		−0.29	[−0.95; 0.37]	6.6%	4.5%
Rejla 2007 (PR225)	44	−2.70	1.3000	46	−2.60	1.6000		−0.10	[−0.70; 0.50]	8.0%	4.6%
Rejla 2007 (PNR150)	82	−1.30	2.1000	72	−0.91	2.1000		−0.39	[−1.05; 0.27]	6.5%	4.5%
Rejla 2007 (PR150)	43	−2.20	1.6000	46	−2.60	1.6000		0.40	[−0.27; 1.07]	6.5%	4.5%
Rejla 2007 (PNR75)	83	−1.40	2.1000	72	−0.91	2.1000		−0.49	[−1.15; 0.17]	6.6%	4.5%
Rejla 2007 (PR75)	40	−2.30	2.1000	46	−2.60	1.6000		0.30	[−0.50; 1.10]	4.5%	4.3%
Aurora 2007 (PNR)	103	−1.30	2.5000	100	−1.60	2.5000		0.30	[−0.39; 0.99]	6.1%	4.5%
Aurora 2007 (PR)	84	−2.60	2.1000	82	−2.50	2.5000		−0.10	[−0.80; 0.60]	5.8%	4.5%
Elkind 2006 (50)	106	−1.55	2.5000	106	−1.50	2.3800		−0.05	[−0.71; 0.61]	6.7%	4.5%
Elkind 2006 (25)	101	−1.03	2.7200	106	−1.50	2.3800		0.47	[−0.23; 1.17]	5.9%	4.5%
Elkind 2006 (7.5)	105	−1.50	2.5800	106	−1.50	2.3800		0.00	[−0.67; 0.67]	6.4%	4.5%
Aurora 2010	341	−4.40	11.1000	338	−4.70	11.0000		0.30	[−1.36; 1.96]	1.0%	2.8%
Fixed effect model	1398			1372				−0.01	[−0.19; 0.18]	82.8%	−−
Random effects model								−0.01	[−0.19; 0.18]	−−	68.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.77$											
subgroup = Migraine											
Barrientos 2003	15	−3.14	2.2000	15	−0.45	2.2000		−2.69	[−4.26; −1.12]	1.2%	3.0%
Silberstein 2000 (75)	40	−0.90	2.4000	41	−0.90	2.1000		0.00	[−0.98; 0.98]	3.0%	4.0%
Silberstein 2000 (25)	42	−2.12	2.1000	41	−0.90	2.1000		−1.22	[−2.12; −0.32]	3.5%	4.1%
Hou 2015 (fixed (muscle)−sites)	41	3.70	1.3000	19	7.40	2.8000		−3.70	[−5.02; −2.38]	1.7%	3.4%
Hou 2015 (acupoint−sites)	42	1.90	1.0000	19	7.40	2.8000		−5.50	[−6.79; −4.21]	1.7%	3.4%
Diener 2010	347	−7.20	11.2000	358	−5.60	11.4000		−1.60	[−3.27; 0.07]	1.0%	2.8%
Fixed effect model	527			493				−2.04	[−2.53; −1.55]	12.1%	−−
Random effects model								−2.43	[−4.08; −0.77]	−−	20.7%
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 3.8222$, $p < 0.01$											
Fixed effect model	2043			1988				−0.27	[−0.44; −0.10]	100.0%	−−
Random effects model								−0.61	[−1.02; −0.19]	−−	100.0%
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.8744$, $p < 0.01$											
Residual heterogeneity: $I^2 = 68\%$, $p < 0.01$											

Figure 2. Forest plot of subgroup analysis based on migraine-type in changes in headache episodes per month.

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).
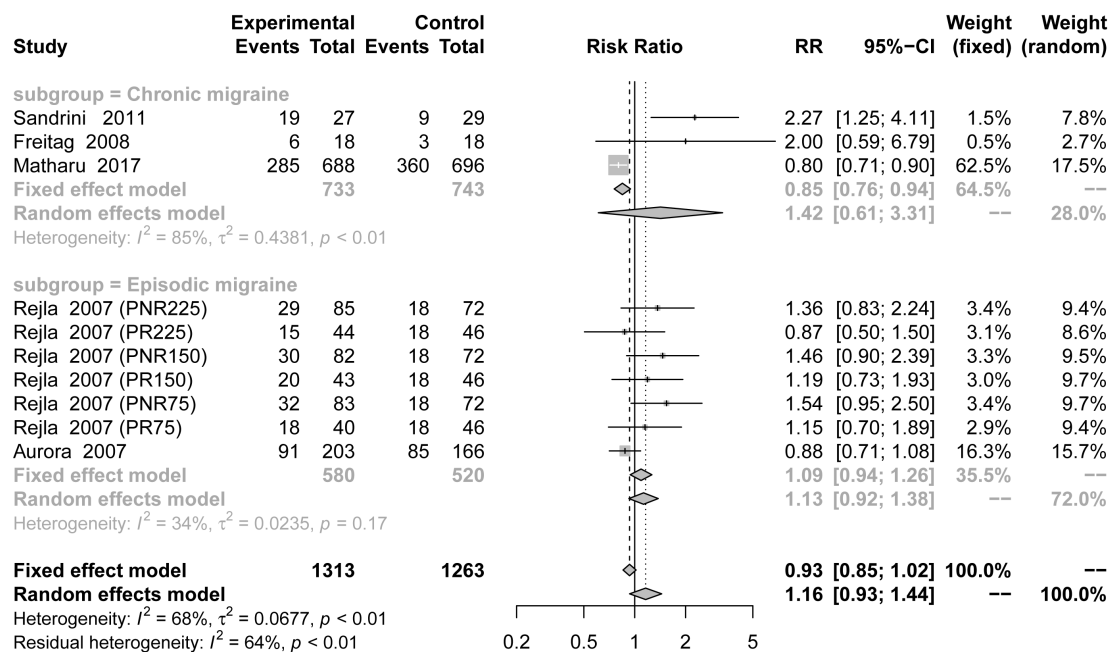
Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%–CI	Weight (fixed)	Weight (random)
subgroup = Chronic migraine									
Sandrini 2011	19	27	9	29		2.27	[1.25; 4.11]	1.5%	7.8%
Freitag 2008	6	18	3	18		2.00	[0.59; 6.79]	0.5%	2.7%
Matharu 2017	285	688	360	696		0.80	[0.71; 0.90]	62.5%	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: $I^2 = 85\%$, $\tau^2 = 0.4381$, $p < 0.01$									
subgroup = Episodic migraine									
Rejla 2007 (PNR225)	29	85	18	72		1.36	[0.83; 2.24]	3.4%	9.4%
Rejla 2007 (PR225)	15	44	18	46		0.87	[0.50; 1.50]	3.1%	8.6%
Rejla 2007 (PNR150)	30	82	18	72		1.46	[0.90; 2.39]	3.3%	9.5%
Rejla 2007 (PR150)	20	43	18	46		1.19	[0.73; 1.93]	3.0%	9.7%
Rejla 2007 (PNR75)	32	83	18	72		1.54	[0.95; 2.50]	3.4%	9.7%
Rejla 2007 (PR75)	18	40	18	46		1.15	[0.70; 1.89]	2.9%	9.4%
Aurora 2007	91	203	85	166		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: $I^2 = 34\%$, $\tau^2 = 0.0235$, $p = 0.17$									
Fixed effect model		1313		1263		0.93	[0.85; 1.02]	100.0%	––
Random effects model						1.16	[0.93; 1.44]	––	100.0%
Heterogeneity: $I^2 = 68\%$, $\tau^2 = 0.0677$, $p < 0.01$									
Residual heterogeneity: $I^2 = 64\%$, $p < 0.01$									

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.

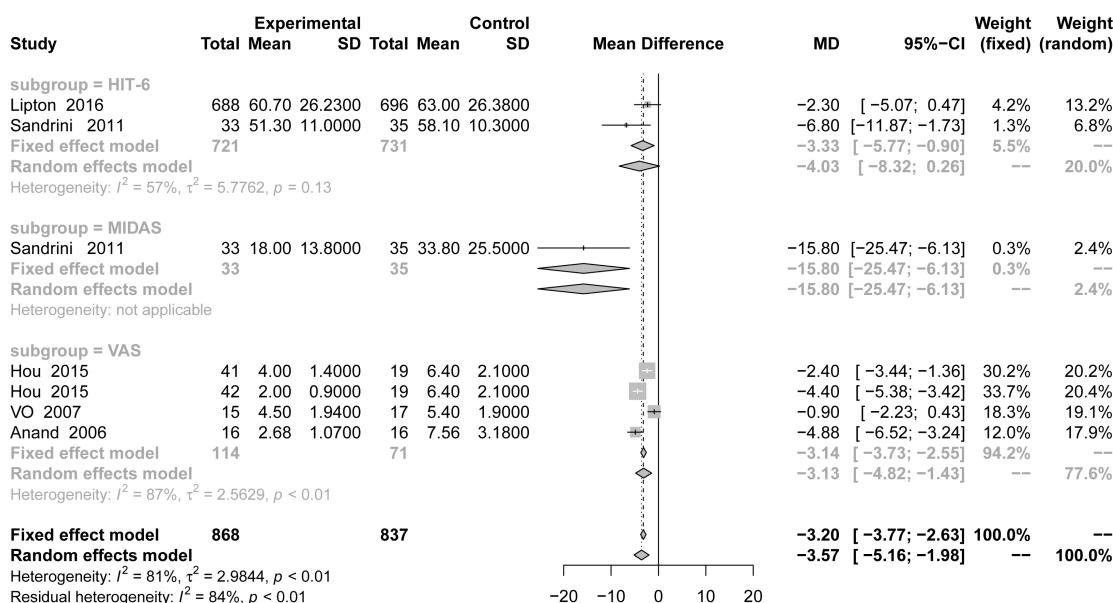| Study	Total	Experimental Mean	SD	Total	Control Mean	SD	Mean Difference	MD	95%–CI	Weight (fixed)	Weight (random)
subgroup = HIT-6											
Lipton 2016	688	60.70	26.2300	696	63.00	26.3800		−2.30	[−5.07; 0.47]	4.2%	13.2%
Sandrini 2011	33	51.30	11.0000	35	58.10	10.3000		−6.80	[−11.87; −1.73]	1.3%	6.8%
Fixed effect model	721			731				−3.33	[−5.77; −0.90]	5.5%	––
Random effects model								−4.03	[−8.32; 0.26]	––	20.0%
Heterogeneity: $I^2 = 57\%$, $\tau^2 = 5.7762$, $p = 0.13$											
subgroup = MIDAS											
Sandrini 2011	33	18.00	13.8000	35	33.80	25.5000		−15.80	[−25.47; −6.13]	0.3%	2.4%
Fixed effect model	33			35				−15.80	[−25.47; −6.13]	0.3%	––
Random effects model								−15.80	[−25.47; −6.13]	––	2.4%
Heterogeneity: not applicable											
subgroup = VAS											
Hou 2015	41	4.00	1.4000	19	6.40	2.1000		−2.40	[−3.44; −1.36]	30.2%	20.2%
Hou 2015	42	2.00	0.9000	19	6.40	2.1000		−4.40	[−5.38; −3.42]	33.7%	20.4%
VO 2007	15	4.50	1.9400	17	5.40	1.9000		−0.90	[−2.23; 0.43]	18.3%	19.1%
Anand 2006	16	2.68	1.0700	16	7.56	3.1800		−4.88	[−6.52; −3.24]	12.0%	17.9%
Fixed effect model	114			71				−3.14	[−3.73; −2.55]	94.2%	––
Random effects model								−3.13	[−4.82; −1.43]	––	77.6%
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 2.5629$, $p < 0.01$											
Fixed effect model	868			837				−3.20	[−3.77; −2.63]	100.0%	––
Random effects model								−3.57	[−5.16; −1.98]	––	100.0%
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 2.9844$, $p < 0.01$											
Residual heterogeneity: $I^2 = 84\%$, $p < 0.01$											

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.

Table 1. Characteristics of individual study

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	Lodon	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 50 U; 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	Lodon	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
Sandrini 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	Saline	308	16
Lauretti et al. (2014)	2014	Brazil	37 (26)	46 pm 13/49 pm 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 pm 9.0	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 pm 10.4/41.5 pm 10.7	Chronic migraine	Severe, Mild	Botulinum toxin A 155 U	Placebo	395	24
Matharu et al. (2017)	2017	Lodon	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.

Table 2. Pooled outcomes of adverse events.

Adverse events	Number	Sample	RR, 95%CI	I^2	P for I^2
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.

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 developed and tested the data collection form. BS and LW acquired the data. LW conducted the analysis and interpreted the data. BS and LW drafted the manuscript.

Acknowledgment

Conflict of Interest

The authors declare no conflict of interest.

References

Agostoni, E. C. and Barbanti, P. (2019) Current and emerging evidence-based treatment options in chronic migraine: a narrative review. *The Journal of Headache and Pain* **20**, 92.

Anand, K. S., Prasad, A., Singh, M. M., Sharma, S. and Bala, K. (2006) Botulinum toxin type A in prophylactic treatment of migraine. *American Journal of Therapeutics* **13**, 183-187.

Aurora, S. K., Dodick, D. W., Turkel, C. C., DeGryse, R. E., Silberstein, S. D., Lipton, R. B. and Diener, H. C. (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* **30**, 793-803.

Aurora, S. K., Gawel, M., Brandes, J. L., Pokta, S. and Vandenburgh, A.

M. (2007) Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache* **47**, 486-499.

Barbanti, P. and Ferroni, P. (2017) Onabotulinum toxin A in the treatment of chronic migraine: patient selection and special considerations. *Journal of Pain Research* **10**, 2319-2329.

Barrientos, N. and Chana, P. (2003) Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. *The Journal of Headache and Pain* **4**, 146-151.

Binder, W. (1998) A method for reduction of migraine headache pain. US Patent No. 5714468.

Bruloy, E., Sinna. R., Grolleau, J. L., Bout-Roumazeilles, A., Berard, E. and Chaput, B. (2019) Botulinum toxin versus placebo: a meta-analysis of prophylactic treatment for migraine. *Plastic and Reconstructive Surgery* **143**, 239-250.

Burstein, R., Zhang, X., Levy, D., Aoki, K. R. and Brin, M. F. (2014) Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: therapeutic implications for migraine and other pains. *Cephalalgia* **34**, 853-869.

Cady, R., Turner, I., Dexter, K., Beach, M. E., Cady, R. and Durham, P. (2014) An exploratory study of salivary calcitonin gene-related peptide levels relative to acute interventions and preventative treatment with onabotulinumtoxinA in chronic migraine. *Headache* **54**, 269-277.

Clare, P., Claire, L., Caroline, R., William, J., Julie, E., Natalie, J., Carl, E. and Sinclair, A. (2019) Cochrane systematic review and metaanalysis of botulinum toxin for the prevention of migraine. *BMJ Open* **9**, e027953.

Copas, J. and Shi J. Q. (2000) Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics* **1**, 247-262.

de Tommaso, M., Ambrosini, A., Brighina, F., Coppola, G., Perrotta, A., Pierelli, F., Sandrini, G., Valeriani, M., Marinazzo, D., Stramaglia, S. and Schoenen, J. (2014) Altered processing of sensory stimuli in patients with migraine. *Nature Reviews Neurology* **10**, 144-155.

Deeks, J. J. (2002) Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Statistics in Medicine* **21**, 1575-1600.

Diener, H. C, Dodick, D. W., Aurora, S. K., Turkel, C. C., DeGryse, R. E., Lipton, R. B., Silberstein, S. D. and Brin, M. F. (2010a) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* **30**, 804-814.

Ekkert, A., Noreikaite, K., Valiulis, V. and Ryliskiene, K. (2019) Migraine-linked characteristics of transcranial magnetic stimulation-induced phosphenes. *Journal of Integrative Neuroscience* **18**, 463-466.

Elkind, A. H., O'Carroll, P., Blumenfeld, A., DeGryse, R. and Dimitrova, R. (2006) A series of three sequential, randomized, controlled studies

of repeated treatments with botulinum toxin type A for migraine prophylaxis. *The Journal of Pain* **7**, 688-696.

Evers, S., Vollmer-Haase, J., Schwaag, S., Rahmann, A., Husstedt, I. W. and Frese, A. (2004) Botulinum toxin A in the prophylactic treatment of migraine--a randomized, double-blind, placebo-controlled study. *Cephalalgia* **24**, 838-843.

Frampton, J. E. and Silberstein, S. (2018) OnabotulinumtoxinA: a review in the prevention of chronic migraine. *Drugs* **78**, 589-600.

Freitag, F. G., Diamond, S., Diamond, M. and Urban, G. (2008) Botulinum toxin type A in the treatment of chronic migraine without medication overuse. *Headache* **48**, 201-209.

Gazerani, P., Staahl, C., Drewes, A. M. and Arendt-Nielsen, L. (2006) The effects of Botulinum toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization. *Pain* **122**, 315-325.

Gooriah, R. and Ahmed, F. (2015) OnabotulinumtoxinA for chronic migraine: a critical appraisal. *Therapeutics and Clinical Risk Management* **11**, 1003-1013.

Herd, C. P., Tomlinson, C. L., Rick, C., Scotton, W. J., Edwards, J., Ives, N. J., Clarke, C. E. and Sinclair, A. J. (2019) Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. *BMJ Open* **9**, e027953.

Higgins, J. P. T. and Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. London, CA: Cochrane.

Higgins, J. P. and Thompson, S. G. (2002) Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**, 1539-1558.

Hou, M., Xie, J. F., Kong, X. P., Zhang, Y., Shao, Y. F., Wang, C., Ren, W. T., Cui, G. F., Xin, L. and Hou, Y. P. (2015) Acupoint injection of onabotulinumtoxin A for migraines. *Toxins* **7**, 4442-4454.

Jackson, J. L., Kuriyama, A. and Hayashino, Y. (2012) Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. *The Journal of the American Medical Association* **307**, 1736-1745.

Lauretti, G., Rosa, C., Kitayama, A. and Lopes, B. (2014) Comparison of botox® or prosigne® and facial nerve blockade as adjuvant in chronic migraine. *Journal of Biomedical Science and Engineering* **7**, 446-452.

Linde, M., Gustavsson, A., Stovner, L. J., Steiner, T. J., Barre, J., Katsarava, Z., Lainez, J. M., Lampl, C., Lanteri-Minet, M., Rastenyte, D., Ruiz de la Torre, E., Tassorelliz, C. and Andree, C. (2012) The cost of headachedisorders in Europe: the Eurolight project. *European Journal of Neurology* **19**, 703-711.

Linde, M., Mulleners, W. M., Chronicle, E. P. and McCrory, D. C. (2013a) Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. *Cochrane Database of Systematic Reviews*, CD010608.

Linde, M., Mulleners, W. M., Chronicle, E. P. and McCrory, D. C. (2013b) Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. *Cochrane Database of Systematic Reviews*, CD010609.

Lipton, R. B., Rosen, N. L., Ailani, J., DeGryse, R. E., Gillard, P. J. and Varon, S. F. (2016) OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program. *Cephalalgia* **36**, 899-908.

Matharu, M., Halker, R., Pozo-Rosich, P., DeGryse, R., Manack, Adams.

A. and Aurora, S. K. (2017) The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. *The Journal of Headache and Pain* **18**, 78.

Mazzocchio, R. and Caleo, M. (2015) More than at the neuromuscular synapse: actions of botulinum neurotoxin A in the central nervous system. *Neuroscientist* **21**, 44-61.

Negro, A., Curto, M., Lionetto, L. and Martelletti, P. (2015) A two years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. *The Journal of Headache and Pain* **17**, 1.

Pedraza, M. I., de la Cruz, C., Ruiz, M., Lopez-Mesonero, L., Martinez, E., de Lera, M. and Guerrero, A. L. (2015) OnabotulinumtoxinA treatment for chronic migraine: experience in 52 patients treated with the PREEMPT paradigm. *Springerplus* **4**, 176.

Ranoux, D., Attal, N., Morain, F. and Bouhassira, D. (2008) Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Annals of Neurology* **64**, 274-283.

Relja, M., Poole, A. C., Schoenen, J., Pascual, J., Lei, X. and Thompson, C. (2007) A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia* **27**, 492-503.

Sandrini, G., Perrotta, A., Tassorelli, C., Torelli, P., Brighina, F., Sances, G. and Nappi, G. (2011) Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. *The Journal of Headache and Pain* **12**, 427-433.

Saper, J. R., Mathew, N. T., Loder, E. W., DeGryse, R. and VanDenburgh, A. M. (2007) A double-blind, randomized, placebo-controlled comparison of botulinum toxin type a injection sites and doses in the prevention of episodic migraine. *Pain Medicine* **8**, 478-485.

Sarchielli, P., Granella, F., Prudenzano, M. P., Pini, L. A., Guidetti, V., Bono, G., Pinessi, L., Alessandri, M., Antonaci, F., Fanciullacci, M., Ferrari, A., Guazzelli, M., Nappi, G., Sances, G., Sandrini, G., Savi, L., Tassorelli, C. and Zanchin, G. (2012) Italian guidelines for primary headaches: 2012 revised version. *The Journal of Headache and Pain* **13** Suppl 2, S31-S70.

Silberstein, S., Mathew, N., Saper, J. and Jenkins, S. (2000) Botulinum toxin type A as a migraine preventive treatment. *Headache* **40**, 445-450.

Simpson, L. L. (2004) Identification of the major steps in botulinum toxin action. *Annual Review of Pharmacology and Toxicology* **44**, 167-193.

Teunis, T. (2019) Botulinum toxin versus placebo: a meta- analysis of prophylactic treatment for migraine. *Plastic and Reconstructive Surgery* **143**, 239-250.

Vo, A. H., Satori, R., Jabbari, B., Green, J., Killgore, W. D., Labutta, R. and Campbell, W. W. (2007) Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. *Aerospace Medicine and Human Performance* **78**, B113-B118.

Vos, T., Allen, C., Arora, M., Barber, R. B., Bhutta, V., Brown, A., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coggeshall, M., Cornaby, L., *et al.* (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1545-1602.

Supplemental Materials

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	Unclear	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	Unclear	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	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Saper et al. (2007)	2007	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
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	Low risk
Diener et al. (2010)	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
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	Unclear	Low risk	Unclear	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	Low risk	Unclear	Unclear
Matharu et al. (2017)	2017	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear

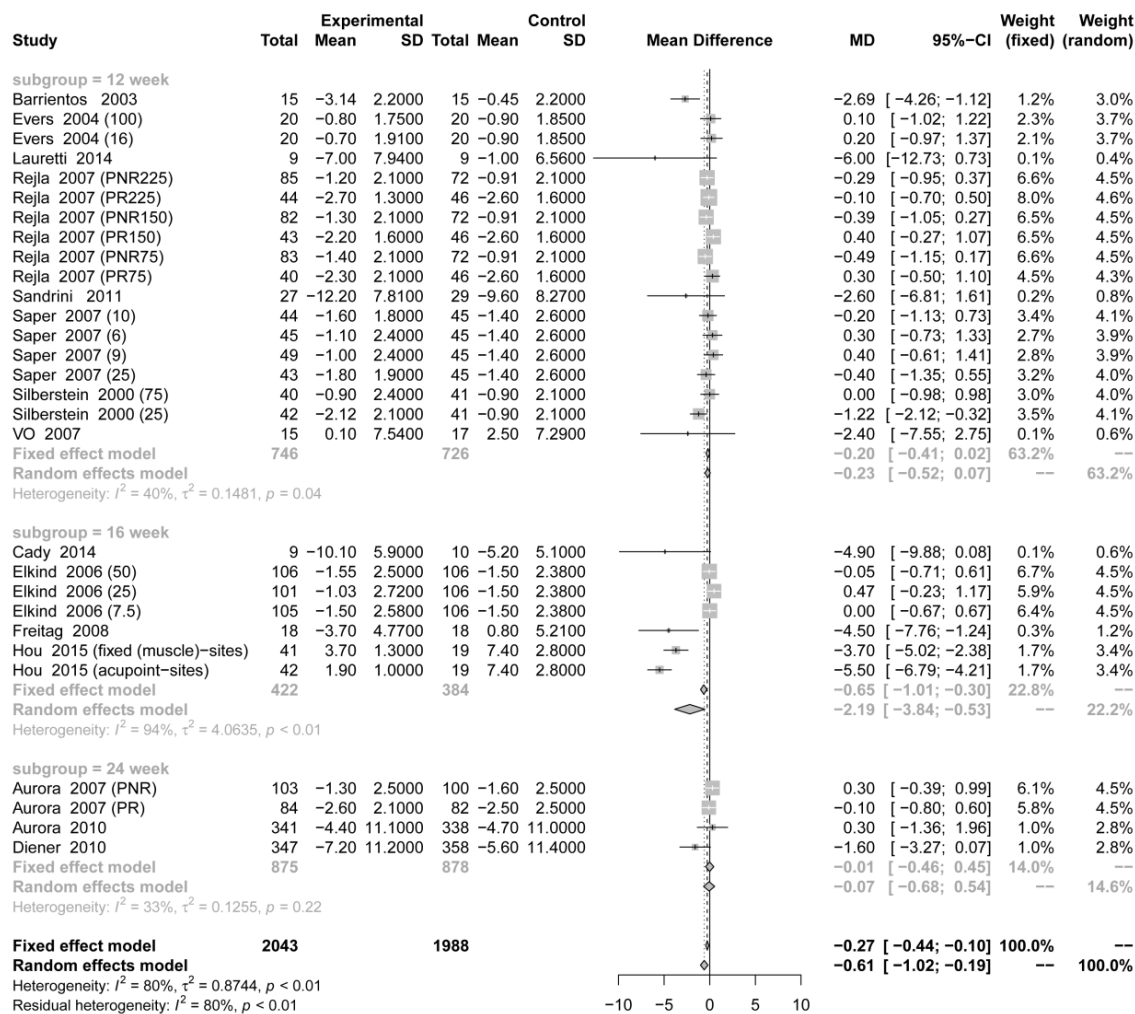|	Total	Experimental Mean	SD	Total	Control Mean	SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
Study											
subgroup = 12 week											
Barrientos 2003	15	−3.14	2.2000	15	−0.45	2.2000		−2.69	[−4.26; −1.12]	1.2%	3.0%
Evers 2004 (100)	20	−0.80	1.7500	20	−0.90	1.8500		0.10	[−1.02; 1.22]	2.3%	3.7%
Evers 2004 (16)	20	−0.70	1.9100	20	−0.90	1.8500		0.20	[−0.97; 1.37]	2.1%	3.7%
Lauretti 2014	9	−7.00	7.9400	9	−1.00	6.5600		−6.00	[−12.73; 0.73]	0.1%	0.4%
Rejla 2007 (PNR225)	85	−1.20	2.1000	72	−0.91	2.1000		−0.29	[−0.95; 0.37]	6.6%	4.5%
Rejla 2007 (PR225)	44	−2.70	1.3000	46	−2.60	1.6000		−0.10	[−0.70; 0.50]	8.0%	4.6%
Rejla 2007 (PNR150)	82	−1.30	2.1000	72	−0.91	2.1000		−0.39	[−1.05; 0.27]	6.5%	4.5%
Rejla 2007 (PR150)	43	−2.20	1.6000	46	−2.60	1.6000		0.40	[−0.27; 1.07]	6.5%	4.5%
Rejla 2007 (PNR75)	83	−1.40	2.1000	72	−0.91	2.1000		−0.49	[−1.15; 0.17]	6.6%	4.5%
Rejla 2007 (PR75)	40	−2.30	2.1000	46	−2.60	1.6000		0.30	[−0.50; 1.10]	4.5%	4.3%
Sandrini 2011	27	−12.20	7.8100	29	−9.60	8.2700		−2.60	[−6.81; 1.61]	0.2%	0.8%
Saper 2007 (10)	44	−1.60	1.8000	45	−1.40	2.6000		−0.20	[−1.13; 0.73]	3.4%	4.1%
Saper 2007 (6)	45	−1.10	2.4000	45	−1.40	2.6000		0.30	[−0.73; 1.33]	2.7%	3.9%
Saper 2007 (9)	49	−1.00	2.4000	45	−1.40	2.6000		0.40	[−0.61; 1.41]	2.8%	3.9%
Saper 2007 (25)	43	−1.80	1.9000	45	−1.40	2.6000		−0.40	[−1.35; 0.55]	3.2%	4.0%
Silberstein 2000 (75)	40	−0.90	2.4000	41	−0.90	2.1000		0.00	[−0.98; 0.98]	3.0%	4.0%
Silberstein 2000 (25)	42	−2.12	2.1000	41	−0.90	2.1000		−1.22	[−2.12; −0.32]	3.5%	4.1%
VO 2007	15	0.10	7.5400	17	2.50	7.2900		−2.40	[−7.55; 2.75]	0.1%	0.6%
Fixed effect model	746			726				−0.20	[−0.41; 0.02]	63.2%	−−
Random effects model								−0.23	[−0.52; 0.07]	−−	63.2%
Heterogeneity: I^2 = 40%, τ^2 = 0.1481, p = 0.04											
subgroup = 16 week											
Cady 2014	9	−10.10	5.9000	10	−5.20	5.1000		−4.90	[−9.88; 0.08]	0.1%	0.6%
Elkind 2006 (50)	106	−1.55	2.5000	106	−1.50	2.3800		−0.05	[−0.71; 0.61]	6.7%	4.5%
Elkind 2006 (25)	101	−1.03	2.7200	106	−1.50	2.3800		0.47	[−0.23; 1.17]	5.9%	4.5%
Elkind 2006 (7.5)	105	−1.50	2.5800	106	−1.50	2.3800		0.00	[−0.67; 0.67]	6.4%	4.5%
Freitag 2008	18	−3.70	4.7700	18	0.80	5.2100		−4.50	[−7.76; −1.24]	0.3%	1.2%
Hou 2015 (fixed (muscle)−sites)	41	3.70	1.3000	19	7.40	2.8000		−3.70	[−5.02; −2.38]	1.7%	3.4%
Hou 2015 (acupoint−sites)	42	1.90	1.0000	19	7.40	2.8000		−5.50	[−6.79; −4.21]	1.7%	3.4%
Fixed effect model	422			384				−0.65	[−1.01; −0.30]	22.8%	−−
Random effects model								−2.19	[−3.84; −0.53]	−−	22.2%
Heterogeneity: I^2 = 94%, τ^2 = 4.0635, p < 0.01											
subgroup = 24 week											
Aurora 2007 (PNR)	103	−1.30	2.5000	100	−1.60	2.5000		0.30	[−0.39; 0.99]	6.1%	4.5%
Aurora 2007 (PR)	84	−2.60	2.1000	82	−2.50	2.5000		−0.10	[−0.80; 0.60]	5.8%	4.5%
Aurora 2010	341	−4.40	11.1000	338	−4.70	11.0000		0.30	[−1.36; 1.96]	1.0%	2.8%
Diener 2010	347	−7.20	11.2000	358	−5.60	11.4000		−1.60	[−3.27; 0.07]	1.0%	2.8%
Fixed effect model	875			878				−0.01	[−0.46; 0.45]	14.0%	−−
Random effects model								−0.07	[−0.68; 0.54]	−−	14.6%
Heterogeneity: I^2 = 33%, τ^2 = 0.1255, p = 0.22											
Fixed effect model	**2043**			**1988**				**−0.27**	**[−0.44; −0.10]**	**100.0%**	**−−**
Random effects model								**−0.61**	**[−1.02; −0.19]**	**−−**	**100.0%**
Heterogeneity: I^2 = 80%, τ^2 = 0.8744, p < 0.01											
Residual heterogeneity: I^2 = 80%, p < 0.01											

Figure S1. Forest plot of subgroup analysis based on diffence follow-up time in changes in headache episodes per month.
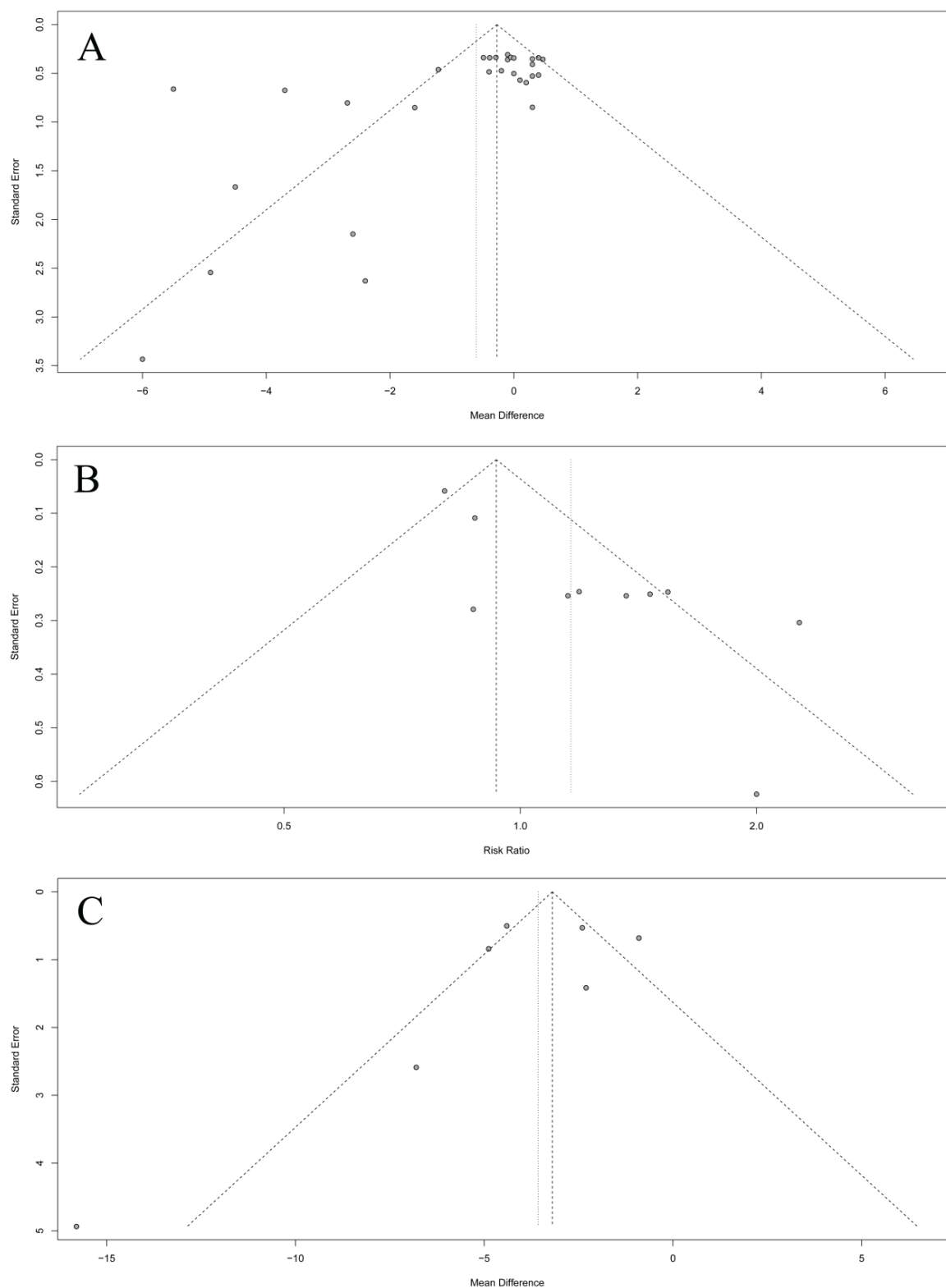
Figure S2. Funnel plots of primary outcomes.
Note: A was identified as the changes in headache episodes per month, B was identified as the changes in fifty percent reduction in number of headaches per month, and C was identified as the headaches impact.