The Efficacy of Botulinum Toxin in Cluster Headache: A Systematic Review

Aims: To conduct a systematic review of the literature on the use of botulinum toxin for the treatment of cluster headache. Methods: A systematic review and data quality analysis were performed using PRISMA and GRADE guidelines, respectively. Inclusion and exclusion criteria were outlined prior to the search and aimed to select prospective studies that examined the use of botulinum toxin for the treatment of cluster headache. Results: Three studies resulted from the search that each included 10 to 17 subjects. All three demonstrated significant improvement in the frequency of headaches that occurred as quickly as 1 week following treatment. There was low-quality evidence that botulinum toxin was effective in reducing headache frequency and severity by at least 50%. Injections into the sphenopalatine ganglion may have a higher incidence of adverse events. Conclusion: This review summarizes the only prospectively collected efficacy and safety data regarding the use of botulinum toxin in cluster headache. Off-label use should be considered in certain cases. Further study is warranted to better characterize injection paradigms and patient selection, given the encouraging but limited data available.
Table 1 Characteristics of the Studies Included

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Sample size</th>
<th>Botox treatment, frequency, dose</th>
<th>Location of injection</th>
<th>Headache history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bratbak et al, 2016</td>
<td>Prospective, open-label, uncontrolled</td>
<td>10 adults, aged 18 to 65 y</td>
<td>One treatment with onabotulinum toxin A; 25 IU or 50 IU</td>
<td>Transnasal SPG, under general anesthesia using preoperative CT and MRI</td>
<td>Intractable chronic cluster headaches (CCH) defined by failure (unsatisfactory effect, intolerable side effects, contraindications) with at least 2 drugs (verapamil, lithium, gabapentin, corticosteroids)</td>
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<td>Sostak et al, 2007</td>
<td>Prospective, open-label, uncontrolled</td>
<td>12 adults (9 chronic cluster headache, 3 episodic cluster headache)</td>
<td>One treatment with subsequent retreatment 3–10 mo after if condition recurred and patient responded to first treatment (onabotulinum toxin A, 50 IU)</td>
<td>Temporalis, frontalis, splenium capitis, trapezius; ipsilateral to headache site</td>
<td>Episodic or chronic cluster headache</td>
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<tr>
<td>Lampi et al, 2018</td>
<td>Prospective, open-label, uncontrolled</td>
<td>17 adults, aged 18 to 60 y</td>
<td>One treatment with onabotulinum toxin A, 155 IU</td>
<td>PREEMPT protocol</td>
<td>Refractory chronic cluster headache (based on the EHF definition), could continue prophylactic or abortive treatments pre-study; symptomatic CCH or occipital nerve stimulator placement were excluded</td>
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IU = IU; CT = computed tomography; MRI = magnetic resonance imaging; SPG = sphenopalatine ganglion; CCH = chronic cluster headaches; HIT-6 = Headache Impact Test-6; ITT = intention-to-treat; VAS = visual analog scale; PREEMPT = Phase III REsearch Evaluating Migraine Prophylaxis Therapy.

Materials and Methods

Search Strategy and Study Selection
This systematic review was performed with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was performed in June 2018, using Embase, the Cochrane library, and PubMed (which includes MEDLINE) databases. The search was repeated in September 2018 to update. Separate searches were performed in each database using the following terms (formatted for EMBASE): (‘botulinum toxin’/exp OR ‘botulinum toxin’ OR (botulinum AND (‘toxin’/exp OR toxin)) AND (‘cluster headache’/exp OR ‘cluster headache’), (‘botox’/exp OR botox) AND (‘cluster headache’/exp OR ‘cluster headache’ OR (‘cluster’/exp OR cluster) AND (‘headache’/exp OR headache))).

Eligibility criteria were defined prior to performing the literature search. To be included, studies could be prospective, nonrandomized or randomized, placebo controlled or comparative, with or without blinding, and needed to involve the use of botulinum toxin in cluster headaches. Studies were excluded if they were single case reports or retrospective case series, included pediatric patients, studied non–cluster headache syndromes, were published in any language other than English, included nonhuman subjects, lacked full-text availability for review, were duplicate publications of the same cohort data, or were abstracts presented at conferences without a published, comprehensive analysis reported. These criteria were agreed upon by two independent reviewers (B.F. and A.R.).

Using the above criteria, the titles of the search results were reviewed to look for duplicate studies. If the title described a study that would clearly be excluded based on the predefined criteria, it was removed. In all other studies, the abstracts were reviewed to determine what type of analysis was performed (case report, case series, abstract presentation, review, etc). The results were reviewed separately (B.F. and A.R.), and consensus was reached on which studies to include via discussion. The full texts of the remaining papers were then analyzed (B.F.).

Data Extraction and Assessment of Quality of Studies
Data were extracted from the articles identified relating to the presence of treatment and/or placebo arms; size of each group; type of botulinum toxin used; dose and frequency of treatment; time of treatment in cluster headache period; location of injections; study duration; and outcome measures, which were guided by International Headache Society (IHS) recommendations. A quality assessment was performed based on the GRADE criteria from Cochrane. Headache-specific outcome measures that were evaluated in more than two studies were chosen, and their quality was further analyzed with...
regard to being able to support conclusions on the effects of botulinum toxin. The data collected were not amenable to meta-analysis and forest plotting, so these were not performed.

**Results**

The search resulted in 727 studies. After removing duplicates, 484 articles remained. Using the pre-defined exclusion and inclusion criteria, the titles and abstracts were reviewed. Three studies were eligible for further examination (Fig 1) and were included in the review15–17 (Table 1). Other studies found that were abstracts/posters submitted for presentation did not have enough data to perform a thorough data quality analysis, but are mentioned in the Discussion.

**Study Characteristics**

All three studies were prospective, open-label, and uncontrolled. Studies ranged from 10 to 17 subjects. One study specifically targeted the SPG,17 while the other two performed injections in the head and neck muscles,15,16 one of which15 used the PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) protocol in migraine.16

All publications reported outcomes in patients with chronic cluster headache. Follow-up was 24 weeks in two studies.15,17 The other study followed up to see if patients needed retreatment, which was between 3 and 10 months following the first injection.16

Outcome measures were relatively similar. All studies used headache intensity and duration, as well as reduction in these qualities by at least 50%, as endpoints. Autonomic symptoms were used only in one study,17 and two used the Headache Impact Test 6 (HIT-6).15,17 Visual analog scale was used in one study.16 Two noted the use of abortive therapy.16,17 There was no specific mention regarding whether patients were having acute headaches at the time of treatment in any of the trials.

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Outcomes</th>
<th>Findings</th>
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<tr>
<td>24 wk with 2 wks run-in period</td>
<td>Headache Impact Test-6 (HIT-6), headache duration, intensity, autonomic symptoms, acute treatment, days of sick leave; responder = at least 50% reduction in headache frequency</td>
<td>ITT analysis (n = 9): Decrease in mean attack frequency per wk within 1 mo, from 14 to 5 (P = .038) that lasted to 6 mo (P = .042) maximum and a mean of 3 mo (P = .028); average attack reduction from baseline to 1–3 mo and 4–6 mo were 55% and 45%, respectively (both significant); decrease also noted in the severity of attacks (P = .028). Per protocol analysis (n = 7): Five patients showed at least 50% reduction in mean attack frequency; HIT-6 showed mean decrease of 13.2 points at 4 wks (P = .018), 8.2 at 8 wks (P = .064), and 11 at 24 wks (P = .075); mean attack intensity decreased significantly by 1 mo, which persisted at 6 mo (P = .043); mean duration of attacks did not show benefit; days without attack improved at 1 mo (P = .046) but this did not persist; headache severity index did not improve; use of abortive triptan did not improve</td>
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<td>90 d at most</td>
<td>Pain location and duration, intensity using VAS (0–10), concomitant symptoms, concomitant abortive or prophylactic use; primary endpoint was at least 50% reduction in headache intensity/ frequency</td>
<td>Three of nine chronic cluster headache patients met primary endpoint; two had no attacks after treatment, though one required an increase in verapamil dose before this occurred; only one patient was not on a prophylactic during trial; three received re-treatment at 3, 7, and 10 mo after first dose; none were able to discontinue prior prophylactic due to worsening of headache when weaning</td>
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<tr>
<td>24 wk with 4-wk run-in period</td>
<td>Headache frequency, duration, and intensity; HIT-6, HADS; primary endpoint was at least 50% change in headache days and min</td>
<td>Ten of 17 patients met primary endpoint; 3 had total cessation of attacks during period of study; no improvement was seen in 2; mean headache days decreased by 16 (P = .0001), and mean headache minutes decreased significantly (P = .0001); intensity decreased significantly; HIT-6 showed significant improvement (P = .021); no significant change in HADS; none had serious adverse events; 6 of 15 stopped preventive treatment; 4 decreased their verapamil dose</td>
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</table>
Table 2 Attack frequency decreased by at least 50%

<table>
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<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Responders to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bratbak et al, 2016</td>
<td>Sphenopalatine ganglion injection</td>
<td>5/7</td>
<td></td>
<td></td>
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<tr>
<td>Sostak et al, 2007</td>
<td>Facial injections</td>
<td>3/9</td>
<td></td>
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<tr>
<td>Lampl et al, 2018</td>
<td>PREEMPT protocol</td>
<td></td>
<td></td>
<td>10/17</td>
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Conclusion on quality:
- Remains low given the high risk of bias, as all are nonrandomized, nonplacebo controlled trials
- Remains low due to different injection paradigms with possible different efficacies
- Remains low, as lengths of follow-up differed in one study and were not well-established
- Downgrade by 1, as the studies were small, though there was consistent measurement of response in 50% of the study population

Quality of Evidence
The number of subjects with at least a 50% decrease in headache frequency was evaluated, as this was the only data point consistently reported in all three studies (Table 2). Though there were a number of patients who were labeled as responders, these data were deemed to be of low quality given differences among these studies and their small sizes. Also, these studies did not include a control group. Other outcome measures, such as headache intensity, were not consistently reported among these studies, making the quality of aggregate results very low per GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) criteria (Table 1).

Discussion
This is the first systematic review in the literature to study the use of botulinum toxin therapy to treat cluster headache. The data on the use of this modality for cluster headaches are limited, but encouraging. As noted in the American Headache Society guidelines in 2016, no recommendation was made regarding the use of botulinum toxin in cluster headaches due to lack of randomized controlled trials. In addition to the three studies covered in this review, other case series or prospective studies that reported on this topic included abstracts presented at meetings and a case report without data on injection protocol or outcome measures. In one abstract, response to botulinum toxin was seen as quickly as 6 days following treatment. Analogous to one of the studies in this review, one abstract reported that a protocol similar to that used in PREEMPT appeared to be beneficial.

The pathophysiology of cluster headache is unclear, but it is thought to involve the unilateral trigeminovascular system with involvement of the hypothalamus as well, ending with activation of the trigeminal nerve leading to release of CGRP with subsequent pain generation, though some have challenged this view. Autonomic symptoms appear to be derived from parasympathetic nerve fibers passing through the SPG to the periphery and from fibers from the superior salivatory nucleus passing through the carotid and otic ganglia. The hypothalamus is also thought to have a role in generating cluster headaches given their seasonal periodicity and timing during the night, though the molecular mechanisms are unresolved. While there is a lack of clarity about the mechanisms leading to generation of cluster headaches, botulinum toxin could affect all pathways at the end of the cluster headache pathophysiologic cascade by inhibiting neurotransmitter release and subsequent pain initiation, as well as decreasing peripheral sensitization of nociceptive sensory nerve fibers. This makes botulinum toxin an attractive treatment option.
Given the periodic and often predictable nature of episodic cluster headaches,29 and the fact that most who suffer from cluster headaches have the episodic form,30 botulinum toxin should be considered in episodic cases as well. This is highlighted by the fact that some patients may respond within 1 to 2 weeks of treatment.16,20,24 A patient-tailored approach is appropriate and should be addressed by future studies. The risk-benefit ratio of injecting botulinum toxin into the SPG for cluster headaches should be given strong consideration due to the associated risk of serious adverse events,17 perhaps due to need for general anesthesia from the trauma of injection itself. A more recent follow-up study showed safety in performing a new technique of SPG injection requiring only local anesthesia.31 However, using treatment paradigms that do not require SPG injection appears to be beneficial15,16,23,24 and safe,15 which may negate the need to perform a more invasive procedure.

Conclusions
This systematic review and data quality analysis demonstrate the dearth of data on botulinum toxin in cluster headache management. However, there are some conclusions that can be drawn. There is low-quality evidence that botulinum toxin improves cluster attack frequency by up to 50%; the evidence is mainly limited by the size of the studies and lack of control groups for comparison. Adequate pain response to treatment may not need direct injection through the SPG, which appears to have more risk of adverse events. There appears to be evidence that a pathophysiologic link between botulinum toxin's inhibition of pain neurotransmitter release and the molecular underpinnings of the cluster headache syndrome explains the possible utility of botulinum toxin in treatment of cluster headaches. Future studies should include both episodic and chronic cluster headaches, differentiate patients with active headaches at the time of enrollment, and evaluate different treatment paradigms and outcomes, which are guided by the studies reviewed here. There is clear evidence that further prospective, blinded, randomized studies are warranted and that off-label use of botulinum toxin in cluster headaches should be considered.

Acknowledgments
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References