

OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program.

[Aurora SK](#), [Dodick DW](#), [Diener HC](#), [Degryse RE](#), [Turkel CC](#), [Lipton RB](#), [Silberstein SD](#).

Source

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Abstract

OBJECTIVE:

Chronic migraine (CM) is a prevalent and disabling neurological disorder. Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program assessed efficacy and safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with CM. This secondary analysis assessed patients who received all five treatment cycles and completed the study.

MATERIALS AND METHODS:

PREEMPT (two phase III studies: 24-week double-blind, placebo-controlled [DBPC], parallel-group phase, followed by 32-week open-label [OL] phase) evaluated the efficacy and safety of onabotulinumtoxinA in CM (≥ 15 days/month with headache lasting ≥ 4 h a day). Patients were randomized (1:1) to onabotulinumtoxinA or placebo every 12 weeks for two cycles, followed by onabotulinumtoxinA for three cycles. Multiple headache symptom measures were evaluated. Results for the completer (five cycles) subgroup of patients are reported.

RESULTS:

Of 1384 total PREEMPT patients, 1005 received all five treatment cycles (513 received onabotulinumtoxinA only [onabotulinumtoxinA/onabotulinumtoxinA (O/O)] and 492 received two cycles of placebo then three cycles of onabotulinumtoxinA [placebo/onabotulinumtoxinA (P/O)]). Demographics were similar between treatment groups. At Week 56, after all patients were treated with onabotulinumtoxinA, there continued to be significant between-group differences favoring the O/O vs P/O group for the following headache symptom measures: LS mean change from baseline in frequencies of headache days (-12.0 O/O, -11.1 P/O; $P = 0.035$), migraine days (-11.6 O/O, -10.7 P/O; $P = 0.038$), and moderate/severe headache days (-11.0 O/O, -10.1 P/O; $P = 0.042$). For other measures (cumulative hours of headache on headache days, frequency of headache episodes, and percentage with severe Headache Impact Test (HIT)-6 score, and total HIT-6 and Migraine-Specific Quality of Life Questionnaire scores), there were also large mean improvements from baseline. The percent of patients with a $\geq 50\%$ reduction from baseline in frequency of headache days was significantly greater for the onabotulinumtoxinA-only group at Week 56 (69.6% O/O, 62.8% P/O; $P = 0.023$). The treatment-related adverse event rate was 28.5% for onabotulinumtoxinA vs 12.4% for placebo in the DBPC phase and 34.8% for patients treated with onabotulinumtoxinA for all five cycles throughout the 56-week trials.

CONCLUSIONS:

This subgroup analysis demonstrated improvements with onabotulinumtoxinA treatment (five cycles) vs placebo (two cycles)/onabotulinumtoxinA (three cycles) for multiple headache symptom measures and suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes. These findings demonstrate the continued need and cumulative benefit over time with continued prophylaxis, an important and clinically pragmatic observation for clinicians and patients.

[Headache](#). 2013 Sep;53 Suppl 2:54-61. doi: 10.1111/head.12185.

OnabotulinumtoxinA for the Treatment of Headache.

[Ashkenazi A](#), [Blumenfeld A](#).

Source

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Abstract

Botulinum toxin, a potent muscle relaxant, has been found to have analgesic effects in patients with various pain syndromes. Both in vitro and in vivo studies showed the ability of the toxin to block the release of pain neurotransmitters, such as substance P, glutamate, and calcitonin gene-related peptide. The effect of the toxin, and specifically of one of its serotypes, botulinum neurotoxin type A, on headaches, has been extensively studied. This serotype is available in the United States in 3 forms, including as onabotulinumtoxinA. Data from clinical trials confirmed the efficacy, safety, and tolerability of onabotulinumtoxinA in the prophylactic treatment of chronic migraine, the most severe and debilitating type of migraine, in adults. The drug was approved by the Food and Drug Administration for this indication in 2010. The drug was not found to be effective for episodic migraine or tension-type headache. Noncontrolled studies suggest the efficacy of the toxin for headache associated with craniocervical dystonia. Proper injection technique and appropriate patient selection are essential for achieving positive results after treatment with onabotulinumtoxinA. The recommended injection paradigm combines a fixed site/fixed dose and follow the pain approaches, with the toxin injected to multiple sites of the head and neck, at a total dose of 155U-195U. The treatment is given at intervals of 12 weeks on average. The efficacy of onabotulinumtoxinA for some headaches, its long duration of action, and its favorable adverse effect profile make it a viable treatment option for the appropriate headache patients. The drug may be particularly suitable for patients who cannot tolerate, or are not compliant with, the daily intake of oral headache preventive drugs.

[J Med Econ](#). 2013 Jul;16(7):877-87. doi: 10.3111/13696998.2013.802694. Epub 2013 May 22.

The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK.

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Source

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Abstract

BACKGROUND:

Although chronic migraine is associated with substantial disability and costs, few treatments have been shown to be effective. OnabotulinumtoxinA (Botox, Allergan Inc., Irvine, CA) is the first treatment to be licensed in the UK for the prophylaxis of headaches in adults with chronic migraine. This study aims to evaluate the cost-effectiveness of onabotulinumtoxinA in this indication in the UK.

METHODS:

A state-transition (Markov) model was developed comparing onabotulinumtoxinA to placebo. Efficacy data and utility values were taken from the pooled Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical trials program (n = 1384). Estimates of resource utilisation were taken from the International Burden of Migraine Study (IBMS), and stopping rules were informed by published medical guidelines and clinical data. This study estimated 2-year discounted costs and quality-adjusted life years (QALYs) from the UK National Health Service perspective.

RESULTS:

At 2 years, treatment with onabotulinumtoxinA was associated with an increase in costs of £1367 and an increase in QALYs of 0.1 compared to placebo, resulting in an incremental cost-effectiveness ratio (ICER) of £15,028. Treatment with onabotulinumtoxinA reduced headache days by an estimated 38 days per year at a cost of £18 per headache day avoided. Sensitivity analysis showed that utility values had the greatest influence on model results. The ICER remained cost-effective at a willingness to pay threshold of £20,000-£30,000/QALY in the majority of scenario analyses as well as in probabilistic sensitivity analysis, where onabotulinumtoxinA was cost-effective on 96% of occasions at a threshold of £20,000/QALY and 98% of occasions at £30,000/QALY.

CONCLUSION:

OnabotulinumtoxinA has been shown to reduce the frequency of headaches in patients with chronic migraine and can be considered a cost-effective use of resources in the UK National Health Service. The uncertainties in the model relate to the extrapolation of clinical data beyond the 56-week trial.

[CNS Drugs](#). 2012 Aug 1;26(8):717-23. doi: 10.2165/11208930-000000000-00000.

OnabotulinumtoxinA (BOTOX®): a guide to its use in preventing headaches in adults with chronic migraine.

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Source

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Abstract

Intramuscular onabotulinumtoxinA (onaBoNTA; BOTOX®) is indicated for headache prophylaxis in adults with chronic migraine. According to pooled results from two large trials, treatment with up to five cycles of onaBoNTA (155-195 units/cycle) at 12-week intervals was effective in reducing headache symptoms, decreasing headache-related disability and improving health-related quality of life in patients with chronic migraine. OnaBoNTA was generally well tolerated in these trials, with an adverse event profile that was consistent with that of the neurotoxin when injected into head and neck muscles.

[Neurology](#). 2011 Oct 11;77(15):1465-72. doi: 10.1212/WNL.0b013e318232ab65. Epub 2011 Sep 28.

OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine.

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Source

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Abstract

OBJECTIVE:

To assess the effects of treatment with onabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA) on health-related quality of life (HRQoL) and headache impact in adults with chronic migraine (CM).

METHODS:

The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program (PREEMPT 1 and 2) included a 24-week, double-blind phase (2 12-week cycles) followed by a 32-week, open-label phase (3 cycles). Thirty-one injections of 5U each (155 U of onabotulinumtoxinA or placebo) were administered to fixed sites. An additional 40 U could be administered "following the pain." Prespecified analysis of headache impact (Headache Impact Test [HIT]-6) and HRQoL (Migraine-Specific Quality of Life Questionnaire v2.1 [MSQ]) assessments were performed. Because the studies were similar in design and did not notably differ in outcome, pooled results are presented here.

RESULTS:

A total of 1,384 subjects were included in the pooled analyses (onabotulinumtoxinA, n = 688; placebo, n = 696). Baseline mean total HIT-6 and MSQ v2.1 scores were comparable between groups; 93.1% were severely impacted based on HIT-6 scores ≥ 60 . At 24 weeks, in comparison with placebo, onabotulinumtoxinA treatment significantly reduced HIT-6 scores and the proportion of patients with HIT-6 scores in the severe range at all timepoints including week 24 ($p < 0.001$). OnabotulinumtoxinA treatment significantly improved all domains of the MSQ v2.1 at 24 weeks ($p < 0.001$).

CONCLUSIONS:

Treatment of CM with onabotulinumtoxinA is associated with significant and clinically meaningful reductions in headache impact and improvements in HRQoL.

CLASSIFICATION OF EVIDENCE:

This study provides Class 1A evidence that onabotulinumtoxinA treatment reduces headache impact and improves HRQoL.

[Nat Rev Neurol](#). 2012 Feb 14;8(3):162-71. doi: 10.1038/nrneuro.2012.13.

Chronic migraine--classification, characteristics and treatment.

[Diener HC](#), [Dodick DW](#), [Goadsby PJ](#), [Lipton RB](#), [Olesen J](#), [Silberstein SD](#).

Source

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Abstract

According to the revised 2nd Edition of the International Classification of Headache Disorders, primary headaches can be categorized as chronic or episodic; chronic migraine is defined as headaches in the absence of medication overuse, occurring on ≥ 15 days per month for ≥ 3 months, of which headaches on ≥ 8 days must fulfill the criteria for migraine without aura. Prevalence and incidence data for chronic migraine are still uncertain, owing to the heterogeneous definitions used to identify the condition in population-based studies over the past two decades. Chronic migraine is severely disabling and difficult to manage, as affected patients experience substantially more-frequent headaches, comorbid pain and affective disorders, and fewer pain-free intervals, than do those with episodic migraine. Data on the treatment of chronic migraine are scarce because most migraine-prevention trials excluded patients who had headaches for ≥ 15 days per month. Despite this lack of reliable data, a wealth of expert opinion and a few evidence-based treatment options are available for managing chronic migraine. Trial data are available for topiramate and botulinum toxin type A, and expert opinion suggests that conventional preventive therapy for episodic migraine may also be useful. This Review discusses the evolution of our understanding of chronic migraine, including its epidemiology, pathophysiology, clinical characteristics and treatment options.

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An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions

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Abstract

Botulinum toxin (Botox) is an exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from the cholinergic nerve end plates leading to inactivity of the muscles or glands innervated. Botox is best known for its beneficial role in facial aesthetics but recent literature has highlighted its usage in multiple non-cosmetic medical and surgical conditions. This article reviews the current evidence pertaining to Botox use in the head and neck. A literature review was conducted using The Cochrane Controlled Trials Register, Medline and EMBASE databases limited to English Language articles published from 1980 to 2012. The findings suggest that there is level 1 evidence supporting the efficacy of Botox in the treatment of spasmodic dysphonia, essential voice tremor, headache, cervical dystonia, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and rhinitis. For chronic neck pain there is level 1 evidence to show that Botox is ineffective. Level 2 evidence exists for vocal tics, trigeminal neuralgia, dysphagia and post-laryngectomy oesophageal speech. For stuttering, ‘first bite syndrome’, facial nerve paresis, Frey's syndrome, oromandibular dystonia and palatal/stapedial myoclonus the evidence is level 4. Thus, the literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With ongoing research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as ‘the poison that heals’.

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Introduction

Botulinum toxin (Botox) is a protease exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from cholinergic nerve endings causing inactivity of muscles or glands. Its effects are transient and may be graded by varying the dose and frequency of administration. Botox is one of the most potent naturally occurring biological poisons and in the past has been responsible for many accidental deaths prior to its discovery in medicine. Its first medical use was to treat strabismus in 1980. Nine years later, the cosmetic effects of the toxin on wrinkles were noted, but it was only in 2002, following Food and Drug Administration approval, that Botox gained widespread popularity as an alternative to cosmetic surgery.¹

Recently, the therapeutic uses of Botox have expanded exponentially to include a wide range of medical and surgical conditions. This has been aided by a greater understanding of its underlying physiology as well as improved efficacy and safety. This review examines the evidence on Botox usage in non-cosmetic conditions of the head and neck.

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Methods

The Cochrane Controlled Trials Register, Medline and EMBASE databases were searched from 1980 to 2012. The medical subject heading search terms were ‘botox’ and ‘larynx’ or ‘dysphonia’ or ‘dystonia’ or ‘tremor’ or ‘oral’ or ‘myoclonus’ or ‘temporomandibular’ or

‘sialorrhoea’ or ‘bruxism’ or ‘oesophagus’ or ‘dysphagia’ or ‘speech’ or ‘face’ or ‘autonomic nervous system’ or ‘sweating’ or ‘torticollis’ or ‘pain’ or ‘migraine’ or ‘headache’ or ‘myalgia’ or ‘neuralgia’ or ‘nose’ or ‘rhinitis’. A total of 997 English language abstracts were reviewed and 88 relevant articles identified. Further references were obtained through their bibliographies. Evidence levels, based on those suggested by the Oxford Centre for Evidence-Based Medicine (Table 1),² are shown in the text inside []. The highest level of evidence pertaining to Botox treatment for each of the ENT conditions is presented in Table 2.

Table 1
Levels of evidence based on those suggested by the Oxford Centre for Evidence-Based Medicine

Level of evidence	Type of study
1a	Systematic review (SR) (with homogeneity) of randomised controlled trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
2a	All or none
2b	SR (with homogeneity) of cohort studies
2c	Individual cohort study (including low quality RCT e.g. $in vitro$ follow-up)
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series, case reports and poor quality cohort or poor quality case-control study
5	Expert opinion without explicit critical appraisal, or based on physiology/biochemistry

*This refers to a systematic review that is free of ascertainment bias (heterogeneity)

[Table 1](#)

Levels of evidence based on those suggested by the Oxford Centre for Evidence-Based Medicine

Table 2
Levels of evidence for the role of Botox in various head and neck conditions

Condition	Highest level of evidence
Laryngeal	
Spasmodic dysphonia ^{1,2}	1a
Essential voiceless ³	1a
Strabismus ⁴	4
Vocal cord ^{5,6}	1b
Pain	
Headache ^{7,8,9,10}	1a
Cervical dystonia/spasmodic torticollis ¹¹	1a
Masticatory spasm ^{12,13}	1b
Chronic neck pain ¹⁴ (non-traumatic)	1a
Impaired swallowing ^{15,16}	1b

[Table 2](#)

Levels of evidence for the role of Botox in various head and neck conditions

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Results and discussion

Laryngeal conditions

Spasmodic dysphonia

Spasmodic dysphonia is due to inappropriate glottic closure or opening due to spasm of intrinsic laryngeal muscles. Symptoms include hoarseness and strangled speech breaks (adductor type) or hypophonia and breathy voice (abductor type).³ A meta-analysis of 30 randomized controlled trials (RCTs) involving Botox therapy in adductor spasmodic dysphonia revealed an improvement to about one standard deviation across the dependent voice-related Quality of Life (QoL) variables studied [1a].^{4,5} A subsequent RCT also confirmed the beneficial effects of Botox

in spasmodic dysphonia with the greatest improvements present in those patients who were most profoundly impaired [1b].⁶ In addition, a recent prospective study ($n = 133$) has demonstrated a mean Voice Handicap Index improvement of 9.6% following laryngeal Botox injection in patients with spasmodic dysphonia.⁷

Essential voice tremor

Essential voice tremor is characterized by rhythmic activation of mainly the intrinsic laryngeal muscles. The voice is affected by breaks in pitch, diminished fluency and arrests. It naturally accompanies the ageing process, but may also occur with spasmodic dysphonia.⁸ Electromyography (EMG)-guided Botox injection into the thyroarytenoid muscles was shown to have beneficial effect in a RCT ($n = 13$) [1b],⁹ in a prospective crossover study ($n = 10$) [3b]¹⁰ and a case report [4].¹¹

Stuttering or stammering

This refers to a disorder of speech-motor control in which the flow of speech is disrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases, with occasional involuntary silent pauses, collectively caused by poor coordination between lingual, labial, laryngeal and respiratory muscles. There is only one case series that has shown that intralaryngeal Botox injection improves fluency in speech therapy failures so its value in treating this disorder is questionable and requires further research [4].¹²

Vocal tics (Gille de la Tourette syndrome)

Repetitive dyskinetic movements of the laryngeal musculature lead to the production of embarrassing speech known as vocal tics. This is commonly seen in Gille de la Tourette syndrome. There is one RCT showing that Botox injections into the thyroarytenoid muscles is efficacious in reducing the frequency and urge of vocal and motor tics ($n = 18$) [2b], but the patients did not report an overall benefit from the treatment.¹³⁻¹⁵ Again, further research is mandated to assess the efficacy of Botox for vocal tics.

Pain

Headache

Numerous multicentre double-blind placebo-controlled trials support the use of Botox as a prophylactic therapy for migraine [1a].¹⁶⁻¹⁸ The technique involves injections into muscles innervated by the facial or trigeminal nerves (e.g. procerus, corrugator, frontalis, temporalis and suboccipital), specific sites of pain distribution or a combination of both.¹⁹ Significant reductions from baseline were observed in patients in the Botox trial arm with regard to headache and migraine days, cumulative hours of headache and frequency of moderate/severe headache days. A recent meta-analysis confirmed these beneficial effects of Botox but only in the treatment of chronic daily headaches and chronic migraines (>15 episodes per month) [1a]. Adverse effects

including blepharoptosis, skin tightness, paraesthesias, neck stiffness, muscle weakness and neck pain can occur at injection sites but these were minimal and transient.²⁰

Cervical dystonia or spasmodic torticollis

This refers to sustained neck muscle contraction resulting in involuntary movements of the head and neck associated with significant cervical pain and abnormal cervical postures. It can be primary or secondary to other neurological disorders.²¹ The evidence supporting the use of Botox in the treatment of cervical dystonia consists of two Cochrane systematic reviews of 13 (677 participants for Botox A) and three (308 participants for Botox B) high-quality RCTs, respectively [1a].^{22,23} These meta-analyses showed that single injection of Botox is effective (as evident from both objective and subjective rating scales) and can be safely repeated if necessary. Since then, there have been further RCTs confirming the efficacy and safety of Botox in the treatment of cervical dystonia in both previously treated as well as Botox-naive patients [1b].²⁴ It is worth noting that Botox not only reduces abnormal movements and contractures but can also prevent secondary degenerative changes of the cervical spine and associated radiculopathy.^{25,26}

Masticatory myalgia

Masticatory pain can be explained by chronic nociceptive irritation of the tendons and fascias of the masseter, temporalis and medial pterygoid muscles.^{27,28} There are three RCTs showing Botox to be more effective than placebo (saline) in reducing masticatory myalgia [1b].²⁹⁻³¹ The most recent of these three RCTs also evaluated with EMG the action potentials of the masseter and temporalis muscles and showed that these decreased by nearly 80% on day 14, and by 25% on day 28 following Botox injection.³⁰ Botox causes a disuse atrophy of the affected muscle which relieves tension, improves aerobic metabolism and enables decompression of afferent nociceptive neurons through reduction of substance P-mediated neurogenic inflammation.^{31,32}

Chronic neck pain (no benefit with Botox)

Several studies have assessed the role of intramuscular Botox injections in chronic neck pain; however, no significant beneficial effect has been demonstrated. A recent Cochrane systematic review of nine trials (503 participants) showed that Botox alone was no better than the placebo (saline) for patients with subacute or chronic neck pain and concluded that the available evidence does not support the use of Botox either as a monotherapy or in combination with any other treatment in patients with subacute or chronic neck pain [1a].³³

Trigeminal neuralgia

The role of Botox in the treatment of drug-refractory trigeminal neuralgia has been evaluated in three studies ($n = 15$, $n = 12$, $n = 8$, respectively).³⁴⁻³⁶ All three studies (including a low-quality RCT) found Botox to be an effective treatment with the majority of the patients reporting a reduction or even disappearance of the pain [2b].³⁴⁻³⁶ Botox was found to be effective in combination with pharmacotherapy, prior to considering more invasive therapies such as surgery or gamma knife radiosurgery.³⁴ As such, Botox is a particularly valuable treatment for elderly patients and those with adverse anaesthetic comorbidities.^{37,38}

First bite syndrome

This is the development of facial pain after the first bite of each meal and is seen after surgery in the parapharyngeal space, especially deep lobe parotidectomy.³⁹ It is probably due to autonomic dysfunction of salivary myoepithelial cells. Intraparotid Botox injection was found to significantly decrease symptom severity and improve the patients' QoL in a case series of five patients and a case report [4].^{40,41}

Oesophageal conditions

Oesophageal speech post-laryngectomy

Tracheoesophageal puncture in laryngectomy patients allows excellent quality speech development in most cases. The procedure involves cricopharyngeal myotomy and valve placement. However, postoperative pharyngo-oesophageal spasm can cause failure of tracheoesophageal speech and dysphagia.⁴² Traditionally, this was treated with dilation of the pharyngo-oesophageal segment (POS), pharyngeal myotomy and/or pharyngeal neurectomy.⁴³ More recently, EMG-guided Botox administration that chemically denervates the cricopharyngeus muscle facilitating tracheoesophageal speech and relieving dysphagia has been reported. There are several prospective⁴⁴⁻⁴⁷ and retrospective outcomes research studies⁴⁸ assessing the efficacy of Botox using both subjective (videotaped recordings) and objective (videostroboscopy) outcome measures [2c]. In corroboration, the largest and most recent prospective study consisting of 34 laryngectomized patients showed Botox therapy to be effective in POS voice restoration, especially when combined with speech therapy [2c].⁴⁴ The effects of Botox were shown to be long-lasting with only one patient needing to be re-injected every three months.⁴⁴ These results are promising but further, higher quality studies are needed to establish the true value of Botox in oesophageal speech post-laryngectomy.

Dysphagia

Incoordination of cricopharyngeal contractions at the initiation of swallowing can result in dysphagia, especially in the elderly population. EMG-guided Botox injections either percutaneously⁴⁹ or endoscopically⁵⁰ to the cricopharyngeus muscle were found to be effective in the treatment of dysphagia in a number of prospective and retrospective outcomes research studies [2c].⁵¹⁻⁵³ Effective toxin administration can predict a successful surgical outcome following cricopharyngeal myotomy.^{51,54} Again, like with oesophageal speech post-laryngectomy, these results are promising but further, higher quality studies are needed before the true value of Botox in dysphagia is determined.

Oral conditions

Sialorrhoea

Sialorrhoea may occur in neurological and other akinetic disorders such as Parkinson's disease and cerebral palsy. There are several RCTs where the efficacy of Botox injections to the parotid

and/or submandibular glands in such patients has been demonstrated [1b].⁵⁵⁻⁵⁷ The effects last 3–6 months and can be repeated. Injections can also be used for sialorrhoea caused by salivary fistulas and sialadenitis.⁵⁸

Temporomandibular joint disorders

Spasm of the lateral pterygoid muscles may cause temporomandibular joint (TMJ) disc displacement anteriorly resulting in exquisite pain and clicking. The evidence supporting the use of Botox in the treatment of such TMJ disorders includes multiple RCTs [1b].^{29,31,59} However, injection of Botox into the lateral pterygoid muscle may cause a ‘fixed’ smile due to diffusion into the superficial facial muscles.⁶⁰

Bruxism

This is characterized by non-functional contact of the mandibular and maxillary teeth resulting in clenching or tooth grinding due to repetitive, unconscious contraction of the masseter and temporalis muscles.⁶¹ There is one RCT ($n = 30$) which has shown Botox to be efficacious in reducing myofascial pain symptoms in bruxers compared with control patients receiving saline placebo injections²⁹ with a second one currently underway [1b].⁶²

Oromandibular dystonia

This disorder is characterized by involuntary, action-induced, tonic or clonic spasms of the masticatory, lingual and pharyngeal musculature. Symptoms include dysphagia, dysarthria, bruxism and temporomandibular joint subluxation. There are case series and case reports [4] showing favourable effects of Botox injections into the lateral pterygoid, anterior belly of digastric, masseter and temporalis muscles.^{63,64} Thus, further higher quality studies are needed to establish the true role of Botox in the treatment of oromandibular dystonia.

Palatal and stapedius myoclonus

Palatal myoclonus is characterized by involuntary palatal contractions, causing clicking tinnitus due to the action of soft palate muscles on the membranous Eustachian tube. Similarly, stapedius myoclonus can cause clicking tinnitus due to the contractions of the stapedius muscle. There are two case reports, one for each type of myoclonus where the use of Botox has been shown to be beneficial in relieving the patients’ symptoms [4]. For palatal myoclonus, Botox was injected in the soft palate under EMG guidance,⁶⁵ while for stapedius myoclonus, Botox was placed trans-tympanically into the middle ear on a piece of gelfoam.⁶⁶ In the latter case, the beneficial effects of Botox lasted for four months.

Facial conditions

Blepharospasm

Involuntary contraction of the eyelid muscles typically occurs bilaterally and in patients over 60 years. The orbicularis oculi muscle is most commonly implicated, but upper facial muscles can also be affected. The therapeutic use of Botox in blepharospasm was first described in 1985⁶⁷ and it has since become the treatment of choice.⁶⁸ There are three RCTs demonstrating the superiority of Botox over placebo [1b].⁶⁹⁻⁷¹ A recent Cochrane systematic review has concluded that doing more RCTs to prove the effectiveness of Botox over the placebo (saline) would be unethical due to the high efficacy and obvious benefits of Botox in treating blepharospasm.⁷²

Hemifacial spasm

This is characterized by unilateral, recurrent, involuntary movements of the muscles innervated by the facial nerve. It is usually due to compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar artery.⁷³ The first study to assess Botox in hemifacial spasm was in 1986.⁷⁴ Since then, there have been several studies, including one RCT which showed Botox to be an effective and safe treatment.⁷⁵ This RCT involved 11 patients and clearly demonstrated the beneficial effect of the Botox over the placebo [1b].

Facial nerve paresis

Botox may be used to induce therapeutic ptosis, thereby protecting the cornea during the acute phase of facial nerve paresis. This is achieved by transcutaneous injection into Mueller's muscle and the levator palpebrae superioris. There are two case series of therapeutic chemodenervation with Botox of these muscles comprising three and 10 patients, respectively.^{76,77} Both showed that Botox administration is beneficial in preventing damage as well as healing of the cornea [4]. In addition, there is one case series of 30 patients showing Botox to reduce synkinesis in aberrant facial nerve regeneration following facial nerve paresis.⁷⁸ In that study, Botox was injected to several synkinetic muscles of patients with facial nerve paresis and all 30 patients experienced improvement after treatment [4].

Nasal conditions

Rhinitis

In a RCT of 39 patients with allergic rhinitis, Botox therapy provided better symptomatic control than steroid injections into each inferior turbinate, both in terms of the duration and degree of symptoms [1b].⁷⁹ In another RCT of 20 patients with idiopathic (vasomotor) rhinitis, topical application of Botox on a sponge significantly reduced rhinorrhoea compared with placebo (saline) but nasal congestion remained unchanged.⁸⁰ Furthermore, in a study of 38 patients with idiopathic rhinitis, Botox displayed a similar degree and duration of efficacy with regard to hypersecretion symptoms to ipratropium bromide.⁸¹ Middle and inferior turbinate injections of Botox were shown to be a highly effective, safe and simple intervention in a RCT of 30 patients with vasomotor rhinitis [1b].⁸² Hence, the role of Botox seems promising in the treatment of allergic and idiopathic rhinitis though several limiting factors prevent its widespread use. These include the mode of administration which can be associated with the requirement of specialized skills and the potential for significant pain (particularly with injection to the inferior and/or middle turbinates) in addition to its high cost.⁸³

Autonomic conditions

Frey's syndrome

This typically occurs after parotid surgery and is caused by aberrant regeneration of postganglionic parasympathetic fibres innervating sympathetic cholinergic sweat glands. The result is sweating, flushing and piloerection while eating (gustatory sweating).⁸⁴ Several case series have demonstrated the efficacy of Botox in Frey's syndrome [4].⁸⁵⁻⁹⁰ The procedure involves injecting the areas of gustatory sweating identified by an iodine-starch test. Further research is needed to assess the efficacy of Botox as a treatment for Frey's syndrome.

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Conclusion

The literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to Otorhinolaryngology and Head & Neck Surgery. With ongoing research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.