The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Botulinum A for treating masseteric hypertrophy (MH) and temporomandibular disorders (TMD) in adults aged 18 and over

PAC recommendations

Botulinum toxin is recommended for:

The treatment of masseter hypertrophy in adults aged 18 and over where:

- Symptoms result in functional issues (e.g. spasm and pain, limited mouth opening), and
- Failed or lack of response to conservative measures (over a three month period), e.g. physiotherapy, orthodontic interventions (bite adjustments or teeth splints where relevant), and appropriate pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and
- Quality of life is affected significantly due to constant pain, restriction in mouth opening.

The treatment of temporomandibular disorders (TMD) in adults aged 18 and over where:

- Symptoms result in functional issues (e.g. spasm and pain, limited mouth opening), and
- The spasm is localised (not diffuse), and
- Failed or lack of response to conservative measures (over a three month period), e.g. physiotherapy, orthodontic interventions (bite adjustments or teeth splints where relevant), and appropriate pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and
- Quality of life is affected significantly due to constant pain, restriction in mouth opening.

Botulinum toxin is not recommended for treatment of masseteric hypertrophy for solely cosmetic reasons.

Key points

Masseteric hypertrophy (MH) is generally an asymptomatic condition, involving overdevelopment of the masseter muscle and causing a squaring of the jawline, but for a small group of patients it is associated with pain and functional disorder. It may be associated with temporomandibular disorder (TMD) and shares similar features. TMD refers to a group of conditions involving the temporomandibular joint (TMJ), masticatory muscles, and associated structures.

Most trials involving MH conducted thus far have involved the use of botulinum neurotoxin type A (hereafter referred to as BoNT-A) for cosmetic facial sculpting, and as such do not include data on outcomes such as resolution of pain. Studies looking at the cosmetic effect of BoNT-A have however demonstrated a measurable reduction in muscle mass after the intervention.

There is a paucity of good quality evidence supporting the use of BoNT-A for the treatment of MH when it gives rise to adverse symptoms, however published case reports have described a beneficial effect for patients in whom it causes significant functional loss and pain.

A variety of treatment options for MH (including pharmacotherapy, physiotherapy and orthodontic devices) have been described, but none have been demonstrated to be effective in all patients. Surgical resection of the masseter is invasive, has the greater potential for serious side effects, a higher initial cost, and is not suitable for all patients, but is a permanent solution which is unlikely to need repeating, and is most consistently effective. BoNT-A is less invasive, has fewer side effects, is less expensive in the short term, and can be performed as an outpatient procedure (with appropriate specialist training), which may improve patient experience, but has not been proven to have long-term efficacy and might need repeating on more than one occasion to obtain a sustained response, leading to increased long-term costs.

It has been suggested that BoNT-A treatment of MH may have an additional positive benefit by stopping subconscious triggers such as bruxism or jaw-clenching, preventing a return of symptoms.

Although there is a lack of good quality evidence to support the use of BoNT-A for these indications, a pragmatic approach to funding could be considered where MH/TMD is causing significant pain and loss of function, where other treatment modalities (e.g. pharmacotherapy, orthotic appliances and surgery where appropriate) have been tried and failed, as no effective current standard treatment is suitable for these patients.

Background

Masseteric hypertrophy (MH) is an overdevelopment of the masseter muscles, which attach to the mandible and are involved in moving the jaw. It develops as an enlargement of the jaw muscles and may be either unilateral or bilateral. It may be idiopathic in origin but may also be triggered by habits such as bruxism or clenching of the jaw.

Symptomatic masseteric hypertrophy appears to be comparatively uncommon. For the majority of affected individuals, this hypertrophy is benign, associated with problems that are solely cosmetic in nature.[1] Consequently, the bulk of the published evidence relates to the use of BoNT-A for facial sculpting and does not assess the resolution of symptoms such as pain or bruxism. Some trials have specifically excluded patients with history of temporomandibular joint disorder.[2]

There is a degree of crossover between MH and TMD. TMD is a fairly broad term used to describe a group of conditions involving the temporomandibular joint (TMJ), masticatory muscles, and associated structure.[3] MH alone can cause pain and spasm. In some affected individuals, the hypertrophied muscle can lead to an imbalance between opening and closing muscles of the jaw, an alteration of mandibular movements, limitation of mouth opening, and elevated pressure in the temporomandibular joints which can generate severe pain and mimic TMD.[4] Some patients suffer from tooth breakage requiring complex dental repairs. In addition, MH may be associated with hypertrophy of other muscles such as the temporalis, which can in turn be associated with other painful conditions such as recurrent headaches.

Various treatment modalities have been suggested for management of MH, which are broadly the same as treatments used for management of TMD. They include:[1]

- Pharmacotherapy (opioid analgesics, anti-inflammatory agents, muscle relaxants, antidepressants and anxiolytics)
- Physiotherapy
- Dental restoration and orthodontic devices (including bite adjustments or the use of splints on the teeth)
- Surgical interventions (intra-oral and extra-oral surgical reduction of masseter size, removal of mandibular angle, neurectomy of the masseteric nerve, and resection of the buccal fat pad)
- Radiofrequency volumetric reduction
- Botulinum toxin

Historically, surgical methods (including resection of either the masseter or the mandible) have been used as successful long-term treatments for MH. Unlike the use of BoNT-A, which causes muscular atrophy,

surgical excision of part of the masseter reduces the number of muscle cells, leading to a sustained effect. It is a resource-heavy surgical procedure and may not be appropriate in all patients. It has been reported to be difficult to assess the amount and depth of muscle resection during surgical excision, which is complex and may result in postoperative complications, including bleeding, haematoma, facial nerve damage, asymmetry and the inability to chew.[5] It is more expensive in the short term as the initial procedure is associated with a higher cost, however it is unlikely to need repeating.

Radiofrequency (RF) ablation is another treatment that has been in use since approximately 2007. One clinical trial comparing the two treatments suggested that RF ablation may be associated with similar effectiveness and a more sustained response than to BoNT-A. Whether it should be considered as a treatment option has not been covered in this document.[5]

Injection of BoNT-A into the masseter muscle is generally considered a less invasive modality and has gained favour as a treatment option, but there is little good supporting evidence, and optimal dose and duration of treatment has not yet been determined. A Cochrane review published in 2013 failed to identify any adequate studies regarding the use of BoNT-A for the management of MH (even from a cosmetic perspective) and as such could not give an opinion,[1] however a number of case reports have demonstrated a beneficial effect in patients for whom MH causes pain and disability.

BoNT-A causes atrophy of the muscle and consequently a decrease in volume, through interference with the neurotransmitter mechanism and muscular paralysis. Some trials have reported a 22% to 35% reduction in muscle volume.[6] The actual number of muscle cells is not affected and there is the potential for the effect to wear off, although again figures are inconsistent. For some patients, effects are long-lasting; one paper describes “consistent atrophy” for 25 months after injection,[7] and others mention that for some, the effect is curative.[4] These may however be the exception, rather than the rule. The mechanics of the intervention suggest that the localised, dose-dependent paralysis achieved with BoNT-A typically lasts from three to six months, and the effect is reversed chiefly by re-innervation of the muscle.[3] In some patients, muscle re-hypertrophy may thus occur within six months. It has been suggested that for a sustained response, treatment may need to be repeated on more than one occasion for some patients, although the precise number of repeat treatments has not been determined.[8]

It has been noted that bruxism and tooth clenching are unconscious habits associated with MH that may not be effectively treated with medications. Some authors suggest that the resulting muscle paralysis after intramuscular injections of BoNT-A may help to stop the habit of tooth grinding/clenching, reducing the likelihood of muscle re-hypertrophy once the therapeutic effect of BoNT-A has worn off.[4]

BoNT-A potentially fits in as a treatment option for those patients where there has been a failed or inadequate response to the conservative, non-invasive treatments listed above, provided an adequate trial of these (e.g. a three month period) has been performed. Although potentially of shorter duration of action, BoNT-A is less invasive than surgical interventions, associated with fewer long-term side effects, and less expensive in the short term. The potential need for repeated treatments will increase the long-term cost.

Evidence

In some of the papers listed below, it is unclear whether the authors have looked to establish treatment effectiveness in patients with symptomatic MH/TMD or achieve a solely cosmetic effect.

In addition, some authors have considered both MH and TMD; where crossover exists, the information has been placed under masseteric hypertrophy.

Masseteric hypertrophy

In 2013, a Cochrane Systematic Review of botulinum toxin for MH was written by Fedorowicz et al[1] as an update to a review previously published in 2009 by Al-Muharraqi. The authors note that surgery has historically been the standard treatment for cosmetic reduction of MH, but injection of BoNT-A into the muscle, which is generally considered to be a less invasive modality, has more recently been advocated.

In their plain-language summary, the authors go into detail of the condition, noting: "masseter muscle hypertrophy occurs as a soft enlargement of the jaw muscles near the angle of the lower jaw and seldom presents a major health problem. However, in some individuals the swelling can be associated with pain or may be so large that it causes facial disfigurement. Symptoms such as pain can be treated with muscle relaxants and may also include bite adjustments or involve the use of splints on the teeth. Surgical reduction of the jaw muscle or injections of BoNT-A directly into the muscle are other treatment options. When BoNT-A is injected into a muscle it causes interference with the neurotransmitter mechanism producing selective loss of muscle function and a subsequent decrease in the mass of the muscle."

Limitation of mouth opening has been reported in some cases, particularly where the muscles are focally dystonic with tension in the region of the hypertrophied muscle; midline deviation has also been observed, as well as masseteric spasm, and it has been suggested that the hypertrophied muscles of the jaw can lead to increased pressure in the temporomandibular joints, which can generate severe pain and mimic TMD.

Fedorowicz et al mention that a range of treatment options for masseter hypertrophy have been reported, with variable degrees of success and failure, such as pharmacotherapy (with anxiolytics, muscle relaxants and antidepressants); dental restorations, occlusal adjustments and orthotic appliances); radiofrequency volumetric reduction; surgery (including surgical reduction of masseter size, removal of mandibular angle, neurectomy, and resection of the buccal fat pad); and BoNT-A injections into the muscle.

This review was to assess the efficacy and safety of BoNT-A compared to placebo or no treatment, for the management of benign bilateral MH. The authors considered only randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing intra-masseteric injections of BoNT-A versus placebo administered for cosmetic facial sculpting. The authors initially retrieved 683 unique references to studies, but 660 were excluded for being non-applicable. They then assessed 23 full text articles for eligibility, and all of these studies were excluded from the review.

The authors acknowledged that "the use of BoNT-A injections might appear to have certain advantages over surgery", but they did not find any high-quality studies that evaluated the effectiveness and potential side effects of it for the management of benign MH, and that well-designed randomised controlled trials are needed. They stated that a large number of references to trials were produced, so the lack of relevant RCTs/CCTs as well as any robust evidence to support or refute the treatment's effectiveness "proved to be somewhat disappointing".

An older paper published in 2001 by Von Lindern et al discussed a case series of seven patients where BoNT-A was considered as an alternative treatment to the then-dominant conservative and surgical measures for the treatment of hypertrophy of the masseter and temporal muscles.[7] Although only the abstract was available, so the degree to which the authors were involved isn't clear, they say treatment involved targeted, "sometimes electromyographically controlled" intramuscular injection of botulinum into the affected muscles, and marked inactivity atrophy occurred in seven patients over the course of three to eight weeks. This atrophy remained constant over a follow-up period of up to 25 months, and no side effects were observed. It isn't stated whether the entire cohort was limited to seven patients, or only seven out of a larger group were successfully treated. They do however consider the minimal invasiveness to imply this technique has an advantage over conventional surgical therapy, and treatment with BoNT-A can be regarded as a sensible alternative to surgery in cases of hypertrophy of the masseter and/or temporal muscles.

In December 2016, Pihut et al conducted a prospective outcome study looking to determine the efficacy of intramuscular BoNT-A for treating masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headaches.[9] This did not involve cosmetic use of BoNT-A as the 42 patients recruited (between 2009 and 2014 at a single centre) were only included in the study if they met a number of criteria including masseter muscle pain and increased masticatory muscle tension. Their results showed a decrease in the number of referred pain episodes including a decrease in pain

in the temporal region bilaterally and a reduction of analgesic drug intake. The authors concluded that intramuscular BoNT-A was an efficient method of treatment for masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache.

A paper published in 2016 by Graziano et al looked at the hypertrophy of both the masseter and the temporalis muscle, examining a case series of 15 patients treated at their hospital, in conjunction with a review of the literature.[8] The authors noted that this association of conditions is a rare clinical entity, with variable causative factors, such as bruxism, temporomandibular disorders, malocclusion and others, and causing cosmetic problems, pain, and functional impairment. They analysed 15 patients (treated between 2000 and 2013) for temporalis and/or masseteric muscle hypertrophy, five of whom were treated with surgical reduction of the muscle, and the remaining ten with BoNT-A (one of whom also had a "bite" which is taken to refer to a device worn to aid in muscle stability). One patient in particular who had "a marked bilateral swelling of the temporalis and masseteric region" complained of recurrent headaches.

The paper is of limited quality as details of the patients treated surgically were not subsequently provided, and there did not appear to be any discussion of the two treatments in comparison. Similarly, the authors noted the possible complications of "this procedure" but fail to differentiate between surgical and medical treatments; they describe external scarring, damage to the mandibular or temporal branches of the facial nerve, change in bite strength, speech disturbance, muscle pain, facial asymmetry, and prominent zygoma. They did however note that "perhaps the biggest limitation of BoNT-A therapy is that the effects of treatment wear off within six months and the original pathological condition returns".

The authors concluded that treatment with BoNT-A could be an effective option compared to conservative treatment or surgical intervention, although their review of the literature showed that this is only a temporary treatment and "surgery still remains the best option". They advise that treatment must be repeated every four to six months for two to three consecutive years before having stable benefits, although the addition of a "bite treatment" allowed them to achieve more lasting and stable results over time without a recurrence of symptoms between the treatments.

In January 2015, Wei et al published the results of a randomised open-label trial looking at ways of prolonging the duration of masseter muscle reduction by adjusting the masticatory movements (after treatment with BoNT-A).[10] They noted that until this point, few reports had discussed how to prolong the duration of its effectiveness. Ninety-eight patients were recruited and randomly and equally divided into two groups, with one group being "instructed to strengthen their masticatory effort during the denervated atrophic stage of the masseter", and the other group given no advice. All patients were treated with BoNT-A, and when the masseter muscle began to recover, patients in both groups were instructed to reduce their chewing. The authors concluded that "purposely strengthening masticatory muscle movement during the denervated atrophic stage of the masseter can prolong the duration of masseter re-hypertrophy". It isn't clear whether the treatments were purely cosmetic or had some medicinal intent.

A prospective study by To et al was published in 2001 in the British Journal of Plastic Surgery, with the authors looking to evaluate the effect of BoNT-A on masseteric muscle hypertrophy by using ultrasound and electromyography.[11] It was a small open-label study involving only five patients (nine hypertrophic muscles in total, as some patients had bilateral symptoms), but all five showed a good response, with the maximal effect of a 31% reduction in muscle bulk seen three months after treatment. Six muscles had a sustained stable response one year after injection, with three muscles needing a second injection to maintain the atrophy. The authors suggested that this showed BoNT-A may be a safe alternative method of treating masseteric muscle hypertrophy, but that the effect may be temporary and further intramuscular injection may be required to maintain atrophy. It is not clear whether these patients were treated on a cosmetic or functional basis, and there was no discussion of whether any other health benefits (e.g. reduction in bruxism or headaches) were observed.

A similar paper looking to measure any reduction in masseter volume was published in 2003, by Kim et al, who presented the results of an open-label study looking to evaluate the effects of BoNT-A on masseteric

hypertrophy using computed tomography.[6] They noted that "a paucity of reports exist on the use of BoNT-A injections as an alternative non-invasive treatment for masseteric hypertrophy." Eleven patients with masseteric hypertrophy were administered intramuscular BoNT-A, and any changes in masseteric muscle volume before and 12 weeks after injection were evaluated using computed tomography. Nine of the 11 subjects showed a mean reduction of approximately 22% in the masseteric muscle volume; the remaining two patients are not discussed. This was likely to be a purely cosmetic study, as the authors noted "nine subjects showed aesthetically good results with a grade of good or excellent at 12 weeks after treatment." The authors of the Cochrane review also determined that this paper could not be included in their meta-analysis as it lacked a control group.

In 2005, Mischkowski et al published details of a case series of eight patients treated with BoNT-A for MH between 2000 and 2004 (where one patient had bilateral symptoms, and the others were unilateral).[12] No details were given as to whether the patients had functional symptoms or whether the treatments were cosmetic. The authors stated that a significant improvement of facial asymmetry was caused by "chemo-denervation" with botulinum, and subsequent reduction of the hypertrophic muscle mass could be achieved in all cases. Complications during the injection, side effects, signs of intoxication, and therapy failure were not observed. The authors concluded that their results showed agreement with other published literature that BoNT-A can be considered as the therapy of choice in MH. This was one of the 23 cases mentioned by Cochrane but was excluded as it was not a clinical trial.

A number of studies looked at the change in bite force a patient may experience as a result of BoNT-A administration. In 2007, Kim *et al* looked at the change of maximum bite force (MBF) after BoNT-A injection for treating MH.[13] They conducted a non-blinded study in just seven patients to evaluate the change in the maximum bite force, and found the difference in MBF between the pre-injection and two, four, and eight week post-injection time points was statistically significant, but that any difference had disappeared by 12 weeks. The authors of the Cochrane study evaluated this paper but ruled it out as it had a non-relevant study design.

Kim et al conducted a similar open trial in 2009, also noting that BoNT-A can cause muscle weakness.[14] They conducted an open-label study in 30 volunteers to measure any change in MBF after BoNT-A injection into the masseter muscle, and to evaluate the influence of a booster/repeated injection. They noted that MBF was significantly lower after the booster injection of BoNT-A, but that it gradually recovered in a predictable pattern, and the degree of discomfort experienced by the subjects had little effect on normal mastication.

Most studies evaluated for this document either had no control group, or compared the treatment to placebo/saline, but one paper looking at a comparison with another form of treatment was located.[5] A randomised, open-label comparative study of the efficacy and safety of radiofrequency (RF) ablation and BoNT-A in treating MH was published in May 2014 by Huang *et al*, although it is not clear whether the 24 patients recruited were treated on a cosmetic or functional basis. The authors discussed that there had as yet been no comparative studies between RF ablation and BoNT-A. They noted that MH can be treated with surgical methods, but it is difficult to assess the amount and depth of resection of the masseter muscle during surgical excision, which is complex and may result in postoperative complications, including bleeding, hematoma, facial nerve damage, asymmetry and the inability to chew. In this paper, patients were randomly divided into two groups, with equal numbers treated with either radiofrequency (RF) ablation (which the authors describe as having been in use since approx. 2007 with favourable clinical results) or BoNT-A. Treatments were not without side effects – in the BoNT-A injection group, the main local adverse effects were difficulties chewing hard food, speech disturbance and pain at the injection sites, although these were transient, usually lasting between one and four weeks after the injection. Facial asymmetry and prominent zygoma were also observed. In the RF ablation treatment arm, marked swelling was observed in the treatment area within one to two weeks, but this disappeared two weeks later.

The authors assessed the outcome of treatment with ultrasound measurement and clinical photographs, prior to treatment and at six and 12 months post. In the group treated with botulinum, masseteric

muscle thickness decreased to the lowest point six months after the injections but then increased until 12 months after injection. However, in the group treated with RF ablation, muscle thickness decreased steadily over the 12 months following surgery. The main advantages of injection with BoNT-A were an easy procedure with fast postoperative recovery; in addition, they concluded it was safe, with no evident complications occurring within two years of the injection. The authors concluded that both injection with BoNT-A and RF ablation therapy are safe and effective treatment options for MH, but the effect of RF ablation on the thickness of the masseter muscle may be much larger than that obtained following injection with BoNT-A.

Temporomandibular Dysfunction (TMD)

In August 2015, Chen et al also conducted a systematic review of RCTs of BoNT-A therapy for TMD.[15] The authors seem to have come to similar conclusions to the Cochrane authors; they located five relevant study trials, involving 117 participants. Two trials revealed a significant between-group difference in myofascial pain reduction, another trial that compared BoNT-A with fascial manipulation showed equal efficacy of pain relief on TMD, while the remaining two trials showed no significant difference between the botulinum and placebo groups. Unfortunately, the authors found considerable variations in study methods and evaluation of results, so a meta-analysis could not be performed, and no consensus could be reached on the therapeutic benefits of BoNT-A in TMD. They also recommended that more rigorous designs of trials should be carried out in future studies.

In September 2019, Machado et al published a systematic review and meta-analysis of BoNT-A for painful TMD in the Journal of Pain.[16] Specific MH was not included, but the authors did describe the pain as "usually involving the masticatory muscles", of which the masseter is one. The authors included 12 RCTs that compared botulinum to other inactive or active interventions (including placebo, behavioural strategies, occlusal splints and "pharmacologic measures" which aren't further defined). Most of the studies included participants with a clinical diagnosis of TMD and bruxism, with previous treatment failure.

BoNT-A was not associated with a significant increase in the risk of adverse events and appeared to be well tolerated. Unfortunately, the results were not promising; the authors found that BoNT-A was slightly more effective than placebo for pain reduction at one month, however there were no significant differences at three and six months. The authors report that "botulinum toxin A was similar to no treatment for pain reduction at three and six months." It was more effective than conventional treatment and low-level laser therapy for pain reduction at one, six and 12 months, but less effective than facial manipulation for pain reduction at three months. They evaluated the quality of the evidence as being low, and the results were insufficient to support the use of BoNT-A for painful temporomandibular disorders; they advised that high quality RCTs are needed to increase confidence in effect estimates.

In July 2003, Chikhani et al conducted an analysis of the literature and published (in French) a paper discussing bruxism, TMD and BoNT-A.[4] The authors describe how tooth grinding and tooth clenching are involuntary habits that result in hypertrophy of the masseter and temporalis muscles, with an imbalance between opening and closing muscles of the jaw, leading to an alteration of mandibular movements and elevated pressure in the temporomandibular joints which can generate severe pain. Intramuscular injections of BoNT-A allow balance between the muscles to be re-established, with relief of pain, and to stop the habit of tooth grinding/clenching. Although the authors state "botulinum toxin is effective, according to our experience on many parameters" and that one single session of injections is curative for two thirds of patients, it is not clear to what degree the authors were involved in delivering treatment as they did not discuss how many patients were involved, over what timeframe, or what long-term follow-up had occurred. It should be noted that a number of other authors describe a need for repeat injections to maintain a successful reduction of hypertrophy. This paper was one of the one of the 23 located by the Cochrane authors, but was discounted as the characteristics of the participants did not meet their study criteria.

A recent paper, published in February 2019 by Villa et al, discussed their retrospective study looking to evaluate improvement in quality of life after BoNT-A injection for TMD in general.[17] They included 28 patients diagnosed with TMD in their study, all of whom had myofascial pain, and received BoNT-A injections in the temporalis and masseter muscles. Patients answered two validated questionnaires (OHIP-14 and TMJ-QoL) alongside a visual analogue scale before the injection, at one month after the injection and at three months after the injection. The authors evaluated the relationship between QoL and factors such as bruxism, age, sex and body mass index.

All patients reported significant improvements in their QoL. The authors concluded that overall, QoL in patients with TMD improved significantly at one and three months after BoNT-A injections, and injection in the masticatory muscles of patients with TMD can be a useful supportive therapy to control pain and improve QoL. This study only appears to have looked at a time period of three months, so from these results the long-term sustainability of therapeutic effect cannot be determined.

In April 2017, Patel et al conducted a randomised controlled pilot study on the use of Xeomin® (Incobotulinum toxin A) to manage temporomandibular joint disorder, involving dysfunction of the temporomandibular joint and associated muscles (including the masseter), causing pain with chewing, limitation of jaw movement, and pain.[18] They hypothesised that chemodenervation of the "muscles of mastication" with BoNT-A would decrease the stress on the temporomandibular joint and improve pain associated with TMD.

Twenty patients were randomized to either BoNT-A or saline injection of the masticatory muscles, and a patient-reported pain scale was recorded at four week intervals following injection for 16 weeks. Those patients who received saline injection initially were assessed for reduction in pain at the first four week interval and rolled over into the treatment arm if they still showed significant pain. Pre-injection pain scores were similar between patients, and while there was a statistically significant reduction in pain score in the placebo group at one month, there was an overall larger drop in average pain scores in those patients injected with BoNT-A initially. All patients initially injected with placebo crossed over into the BoNT-A group. Similar results were seen when examining the composite masticatory muscle tenderness scores. There was no significant change in usage of pain medication.

A number of papers looking at utilising BoNT-A in dental medicine were identified.

One paper published in the Journal of Dental Research in September 2019 by Munoz Lora et al critically reviewed the uses of BoNT-A in oral medicine and found it effective for trigeminal neuralgia, and probably effective in TMD and bruxism.[19] Only the abstract is available, but they do not appear to have assessed any of their own patients, instead conducting a review of the published literature.

Another group of authors (Park et al) also looked at the use of a BoNT-A in dentistry and oral and maxillofacial surgery, publishing their paper in September 2016.[20] They similarly appear to have conducted a review of the published literature, rather than conducted any of their own trials, for this paper. The authors describe how BoNT-A has been used mainly in the treatment of TMD, and the hypertrophy and hyperactivity of the masticatory muscles, along with use as a therapeutic option to relieve pain and help in functional recovery from dental and oral and maxillofacial surgery. They describe how TMD patients are usually given BoNT-A into the adjacent masticatory muscles such as the masseter and temporalis muscles, which has successfully improved parafunction such as clenching as well as bruxism and TMD symptoms. Although the therapeutic effect of BoNT-A is temporary and relatively safe, it is essential to have knowledge about related anatomy, as well as the systemic and local adverse effects of medications that are applied to the face. In their conclusion, they wrote "Although there have been a number of preliminary studies on BoNT-A, most clinical studies have only reported the successful cases, and research studies showing a high level of scientific evidence have been very rare."

In 2007, Ihde et al looked to determine whether BoNT-A was safe and effective in treating patients with cervical dystonia and maxillofacial conditions, although their aim was to determine whether or not it may be used prophylactically in patients undergoing dental implant therapy.[21] They did not perform a trial themselves but performed a systematic search of the literature for other RCTs evaluating patients

treated with BoNT-A as an adjunct to dental implant therapy, maxillofacial conditions including TMD, and cervical dystonia. They concluded that BoNT-A appears relatively safe and effective in treating chronic facial pain associated with "masticatory hyperactivity", but also noted that randomized clinical trials are warranted to determine the safety and efficacy of BoNT-A in maxillofacial conditions such as bruxism.

Dose and administration

No BoNT-A products are presently licensed for masseteric hypertrophy or TMD.[22-26]

The optimal dose has not been established. A variety of doses have been used in the studies, although a large number of abstracts were not specific about what dose was administered, and there is some variability inherent in the preparation used (see below). The commonest doses stated were 20 units(U), 25U, 30U and 35U per masseter, generally administered into two to three (but up to five) sites per individual muscle. Higher doses have been used, but no precise detail was given on these. Dysport® would realistically be expected to require higher dosing than Botox® or Xeomin®.

It is not always clear which type of BoNT-A was used in each trial. In a number of clinical trials, the preparations were not listed by brand name but rather by chemical name, as "onabotulinum" (equivalent to Botox®), "abobotulinum" (≡ Dysport®) and "incobotulinum" (≡ Xeomin®). These names indicate the degree to which the formulation contains accessory proteins, meaning they are not all equivalent on a dose-for-dose basis. While Botox® and Xeomin® have demonstrated comparable efficacies with a 1:1 conversion ratio, and have demonstrated therapeutic equivalence in different indications, it has been suggested that a Botox® to Dysport® conversion ratio of ≤1:3 should be considered the most appropriate.[27]

The brands Bocouture® and Azzalure® are also available, but it is not clear what type of toxin these are classified as, although Bocouture® is free of complexing proteins and thus similar to Xeomin®. Azzalure® nor Bocouture® are only licensed for cosmetic use and not for medicinal purposes.[25,26]

The long-term effectiveness of BoNT-A has not been adequately studied. Trials have followed patients up for varying amounts of time. Data suggests that a single treatment may be sufficient to be curative for some patients, but that others may require retreatment. Based on the way the intervention works, it has been suggested likely that that the effect may wear off within six months.[3] The authors of one combined case report and literature review published in 2016 advised that treatment must be repeated every four to six months for two to three consecutive years before having stable benefits, although the addition of a "bite treatment" (orthodontic device) allowed them to achieve more lasting and stable results over time without a recurrence of symptoms between the treatments.[8] An older study (n=9) published in 2001 showed that some patients sustained a stable response one year after injection, but some needed a second injection to maintain the atrophy (interval not specified).[14]

It has been suggested that a suitable schedule would involve the patient receiving the intervention, then follow-up reviews by the specialist at three months and nine months. Patients would be discharged following the nine month review, with any recurrence of hypertrophy requiring a new GP referral.[28] However, published evidence suggests that re-hypertrophy may occur after six months, so a second review at six months may be more appropriate.

Tariff status and commissioning responsibility

Botulinum toxin is listed as a high cost drug excluded from National Tariff.[29] CCGs are the responsible commissioner for this indication.

Cost impact estimate

It is assumed that between 20-35 units would be required per masseter muscle per treatment course (i.e. 40-70 units if both masseters are treated), although the optimal dose has not been established. All brands of botulinum toxin type A vials currently on the UK market are intended for single use,[22-26] therefore the

pricing below involves whole vials. It is likely that no more than a single vial (max 100 units of Botox® or Xeomin®, or 300 units of Dysport®) would be used per treatment.

It is anticipated that the treatment would be administered at an outpatient appointment. Day case costs are given for comparison purposes.

Note: Cost impact estimates below are indicative only. Cost impact estimates use the list price for each drug. Actual drug costs may be lower as most are available to the NHS at a lower cost via the Commercial Medicines Unit contract framework. Activity costs used may vary between providers.

Administered as an outpatient:

	Dysport 300 unit	Botox 50 unit	Xeomin 50 unit	Botox 100 unit	Xeomin 100 unit
Drug cost	£92.40	£77.50	£72.00	£138.20	£129.90
Outpatient activity costs*	£147.00	£147.00	£147.00	£147	£147.00
Cost per treatment	£239.40	£224.50	£219.00	£285.20	£276.90
Cost per patient per year (2 treatments)**	£478.80	£449.00	£438.00	£570.40	£553.80

*Outpatient treatment function code 144, Maxillo-facial surgery,[29] includes only the cost of the initial visit. Follow-up review appointments will be required, but the cost of these will be offset by the cost of follow-up procedures needed with other interventions.

**Trials have not established the number of treatments that may be required; however any loss of effect appears to generally occur around 6 months so it is anticipated that a maximum of two treatments are likely per year for most patients.

Administered as a day case:

	Dysport 300 unit	Botox 50 unit	Xeomin 50 unit	Botox 100 unit	Xeomin 100 unit
Drug cost	£92.40	£77.50	£72.00	£138.20	£129.90
Day case activity costs**	£645.00	£645.00	£645.00	£645.00	£645.00
Cost per treatment	£737.40	£722.50	£717.00	£783.20	£774.90
Cost per patient per year (2 treatments)	£1474.80	£1445.00	£1434.00	£1566.40	£1549.80

** Admitted patient care and outpatient procedure price. CA85A Minor, Mouth or Throat Procedures, 19 years and over.[29]

A business case submitted in 2016 to Bedfordshire and Luton Joint Prescribing Committee for the use of BoNT-A by a Consultant Oral and Maxillofacial Surgeon at the Luton & Dunstable Hospital NHS Trust estimated that around ten patients per year may require treatment.[28] Based on the Bedfordshire CCG population of between 448,000 (2016) and 455,000 (2018), this works out as approx. Two patients per 100,000 population.[29]

Treatment with BoNT-A is intended as an alternative to surgery, however long-term efficacy and persistence of effect remains unknown. For comparison purposes, maxillofacial surgery (resection of masseter muscle or mandible) is likely to cost between £1830 and £8512 (HRG codes CA94Z and CA91A respectively), depending on severity and complexity; it is however anticipated that this would be a single procedure and would not require repeating.[30]

BoNT-A comes as single-use vials. The most appropriate size vial should be chosen depending on the dose required; options include 50, 100, 125, 200, 300 and 500 unit vials, although not all brands are available in all vial sizes. They may also not be bioequivalent. Prices taken from the BNF are as on the page below:[31]

Botulinum toxin A preparation and strength	Manufacturer	Cost/vial*	Cost/unit
Bocouture 50-unit powder for solution for injection vial	Merz Pharma UK Ltd	£72.00	£1.44
Botox 50-unit powder for solution for injection vial	Allergan Ltd	£77.50	£1.55
Xeomin 50-unit powder for solution for injection vial	Merz Pharma UK Ltd	£72.00	£1.44
Bocouture 100-unit powder for solution for injection vials	Merz Pharma UK Ltd	£229.90	£2.30
Botox 100-unit powder for solution for injection vial	Allergan Ltd	£138.20	£1.38
Xeomin 100-unit powder for solution for injection vial	Merz Pharma UK Ltd	£129.90	£1.30
Azzalure 125-unit powder for solution for injection vial	Galderma (UK) Ltd	£64.00	£0.51
Botox 200-unit powder for solution for injection vial	Allergan Ltd	£276.40	£1.38
Xeomin 200-unit powder for solution for injection vial	Merz Pharma UK Ltd	£259.80	£1.30
Dysport 300-unit powder for solution for injection vial	Ipsen Ltd	£92.40	£0.31
Dysport 500-unit powder for solution for injection vials	Ipsen Ltd	£154.00*	£0.31

*Price quoted in the BNF is for two vials; this is the cost for a single vial.

Health economy impact

There is no effective current standard treatment which is suitable for these patients. It is anticipated that this intervention may potentially reduce overall costs due to reduced hospital outpatient appointments, avoidance of physiotherapy, and reduction in dental treatment for injuries caused by bruxism. The intervention may reduce drug costs as resolution of MH may lead to a resolution of pain and TMD symptoms. It is likely that custom-made orthodontic equipment (e.g. orthodontic or bite raising devices, which similarly have a limited lifespan) will also no longer be required.

Options considered by PAC

- Do not recommend funding for botulinum toxin for any patients with masseteric hypertrophy or TMJ disorders due to lack of evidence of efficacy and cost effectiveness.
- Recommend funding for patients who have failed on conservative treatments and where there is significant impact on QoL.

Acknowledgements

Greater Manchester botulinum toxin commissioning policy, Version 1.0 – February 2018.
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Bedfordshire and Luton Joint Prescribing Committee (JPC) Guidance on the use of Botulinum Toxin Type A (Revised Guidance – Updated June 2017)

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Document history

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Appendix 1: Assessment against ethical and commissioning principles

1. Treatment assessed

Botulinum A for treating masseteric hypertrophy (MH) and temporomandibular disorders (TMD) in adults aged 18 and over

2. East of England Priorities Advisory Committee Recommendation

Botulinum toxin is recommended for:

2.1 The treatment of masseter hypertrophy in adults aged 18 and over where:

- Symptoms result in functional issues (e.g. spasm and pain, limited mouth opening), and
- Failed or lack of response to conservative measures (over a 3-month period), e.g. physiotherapy, orthodontic interventions (bite adjustments or teeth splints where relevant), and appropriate pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and
- Quality of life is affected significantly due to constant pain, restriction in mouth opening

2.2 The treatment of TMJ disorders in adults aged 18 and over where:

- Symptoms result in functional issues (e.g. spasm and pain, limited mouth opening), and
- The spasm is localised (not diffuse), and
- Failed or lack of response to conservative measures (over a 3-month period), e.g. physiotherapy, orthodontic interventions (bite adjustments or teeth splints where relevant), and appropriate pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and
- Quality of life is affected significantly due to constant pain, restriction in mouth opening

2.3 Botulinum toxin is not recommended for treatment of masseteric hypertrophy for solely cosmetic reasons.

3. Clinical effectiveness

There is a lack of robust evidence supporting the use of BoNT-A for the treatment of MH/TMJ when these conditions rise to functional symptoms. However, this treatment option could be considered where MH/TMJ dysfunction is causing significant pain and loss of function, where other treatment modalities (e.g. pharmacotherapy and orthotic appliances) have been tried and failed as no effective current standard treatment is suitable for these patients.

4. Cost effectiveness

There is no evidence for the cost effectiveness of the use of BoNT-A for the treatment of MH/TMJ when these conditions result in functional symptoms, however costs may be offset by a reduction in costs associated with supportive treatments such as analgesics, and an improvement in the patients quality of life.

5. Equity

No issues identified

6. Needs of the community

The number of eligible patients is likely to be small. This treatment offers an option for patients with refractory symptoms for whom there no effective current standard treatment.

7. Need for healthcare (incorporates patient choice and exceptional need)

A small group of patients who do not respond standard treatments would benefit from this treatment.

8. Policy drivers

None

9. Disinvestment

None