

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

GUIDANCE ON THE USE OF BOTULINUM TOXIN TYPE A

(Update history:- Revised and updated June 2017, October 2018, December 2019, March 2021)

March 2021 update:

NB: A local amendment to the PF guidance, NO.51 has been agreed (March 2021) by BLMK CCG, stating that patients do not have to have tried Iontophoresis before being considered eligible for botulism toxin A therapy ([see bulletin 294 - Iontophoresis commissioning statement](#))

Dec 2019 Update:

With reference to EoEPAC recommendation for Disease induced hypersalivation (Indication no.13 in EoEPAC document attached below), please note the publication of NICE TA605 – Xeomin (botulinum neurotoxin type A for the treatment of sialorrhoea. October 2019

<https://www.nice.org.uk/guidance/ta605>

Oct 18 Guidance

The East of England Priorities Advisory Committee (PAC) have issued an updated Guidance Statement entitled: Botulinum Toxin Type A (BTA) : Evidence review and commissioning recommendations (Dec 15). This new document supersedes the previous recommendations that were issued in September 2013.

As per the previous guidance, **the JPC agreed to support a modified version of the EoE PAC Guidance.**

The locally agreed modifications are highlighted below, followed by the EoE PAC guidance statement.

General Point:

The JPC agreed that where an indication within the EoE PAC guidance had a “negative unless exceptional circumstances” recommendation, that in such incidences, clinicians can request treatment via the Individual Funding Route (IFR).

Summary of Locally agreed JPC modifications to the EoE PAC recommendations (for specified indications below)

Indication	JPC recommendations
Chronic anal fissure in adults	Positive with Local modification: Positive recommendation. Approved for use only after topical GTN or diltiazem have been unsuccessful (or are inappropriate) in healing chronic anal fissures and when surgery would be the next treatment option.

Hyperhidrosis	Positive – as per Beds and Herts Priorities Forum (PF) Interim Guidance It has been agreed locally to adopt the Beds & Herts Priorities Forum Guidance Interim No 51 on Hyperhidrosis instead of the EoE PAC recommendations. (Oct 2017) Guidance-51-hyperhidrosis-october-2017-BHPF-BCCG-v1.1.pdf (cscsu.nhs.uk) (NB: This guidance specific to hyperhidrosis supersedes the EoE PAC hyperhidrosis guidelines recommendations) Update March 2021 NB : A local amendment to the PF guidance, NO. 51 has been agreed (March 2021) by BLMK CCG , stating that patients do not have to have tried iontophoresis before being considered eligible for botulinum toxin A therapy. (see Bulletin 294 – Iontophoresis Commissioning statement)
<u>Spasticity treatment in paediatric cerebral palsy</u>	Local agreement to amend the wording under “Evidence” Section of the table on page 10 of PAC guidance to state: “NHSE commission use when used by a Specialist Centre. CCGs commission use when used by a non-specialist centre”. This new wording replaces the PAC wording that states “ This indication is currently commissioned locally for treatment through approved specialist centres.
Masseteric Hypertrophy (request for cosmetic reasons)	Negative policy (as per EoEPAC recommendations)
Pain associated with Masseteric hypertrophy (See JPC Bulletin 235 - agreed April 16)	Positive – Local agreement to support the use of Botulinum toxin A for the treatment of pain associated with Masseteric hypertrophy as outlined below. - To support the use of Botulinum Toxin A for the treatment of pain associated with Masseteric Hypertrophy when Botulinum Toxin A when it is used as per the agreed set of criteria below:
	<u>Criteria for Treatment</u> - Painful and clinical (including radiological) enlargement of masseter muscles which may be unilateral or bilateral and - Failed or lack of response to conservative measures (over a 3 month period), for example, soft diet, relaxation, avoid teeth clenching, appropriate analgesics, and bite raising appliance and - Quality of life affected significantly, due to constant pain, restriction in mouth opening and facial deformity - Patients to be reviewed by the Specialist at 3 months and 9 months after receiving the Botulinum Toxin A injection. - Patients will be discharged following the 9 month review. Any recurrence of Masseteric hypertrophy, will require a new GP referral.

Summary of locally agreed JPC Recommendations for Additional Indications not included in the updated EoE PAC guidance:

Indication	JPC Recommendations
Idiopathic Toe Walking	This indication was not listed in the previous EoE PAC document; however it was listed as a JPC approved local amendment. This indication is not included in the newly updated EoE PAC guidelines however, it was agreed to retain the previous local agreement that states: <i>“A review of the literature suggests that this treatment can be effective, although randomised controlled trials specifically in the idiopathic toe walking area are lacking. The evidence comes mainly from case reports/series’ and review articles. Some of the evidence is old and some is restricted to conference abstracts (trials not fully published). [33] There is insufficient evidence available to agree a policy position on the use of botulinum toxin A for the treatment of idiopathic toe walking. Requests for treatment for this indication should continue to be considered on an individual basis via the CCG Individual Funding Request Team.”</i>
Focal Limb Dystonia (Upper and Lower Limb) (See JPC Bulletin 234 – agreed April 16)	The JPC reviewed this indication in April 16 (Bulletin 234) and agreed the following recommendations: To support the use of Botulinum Toxin A for the treatment of Focal Limb Dystonia for both upper and lower limb dystonia. (Approval for use in lower limb dystonia was agreed With the proviso that an audit of its use would be carried out and the results presented to the committee in 12 months’ time). The use of Botulinum Toxin A is for use by the hospital specialist only.
To induce Ptosis (temporary and long term) (See JPC Bulletin 244, approved February 2017)	JPC Recommendations:- - To support use in the acute setting i.e. in corneal patients to induce temporary ptosis to prevent corneal perforations. - To support use in the chronic setting i.e. in ectropion patients who are not suitable for surgery due to other co-morbidities and who fit the following patient selection criteria:- - Patients with reduced mental capacity e.g. dementia, learning difficulties. - Patients taking NOACS or other anticoagulants which cannot be stopped temporarily for surgery, for whom there would be an increased risk of retrobulbar haemorrhage (and subsequent visual loss) with surgery. - Patients with physical constraints e.g. spinal/ back problems, who cannot lie in one position for the duration of surgery. The above recommendations are subject to administration of the Botulinum toxin being charged to CCGs using the following: - The Luton & Dunstable Hospital – Outpatient Procedure tariff - All other Trusts – Outpatient Appointment tariff
<u>Cervical Dystonia - Use of Botulinum Toxin B (Bulletin 225)</u> October 2018 – The JPC review its previous position with regards the use of Botulinum Toxin B and a decision was taken to archive Bulletin 225. Any request to use botulinum B should be submitted to the CCG Individual Funding Request (IFR) panel.	

GUIDANCE STATEMENT

Botulinum toxin type A (BTA): Evidence review and commissioning recommendations

Summary of recommendations for specified indications

Note: PAC **does not recommend** the use of botulinum toxin for cosmetic use.

Indication	Proposed PAC recommendations
1. Chronic anal fissure in adults	Positive
2. Severe blepharospasm in adults	Positive
3. Hemi-facial spasm in adults	Positive
4. Cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults	Positive
5. Laryngeal dystonia (spasmodic dystonia)	Negative unless there is an exceptional clinical circumstance.
6. Hidradenitis suppurativa	Negative
7. Mechanical neck disorders	Negative
8. Focal spasticity in adults in upper and lower limb	Positive
9. Hyperhidrosis	See separate PAC policy regarding management of hyperhidrosis for recommendations regarding the place in therapy of BTA.
10. Dysphagia and achalasia	Positive for dysphagia caused by achalasia in patients at high risk of perforation during pneumatic dilatation treatment or aspiration. Negative for dysphagia resulting from any other condition.
11. Overactive bladder	Positive
12. Spasticity treatment in paediatric cerebral palsy (now commissioned by NHSE)	Positive
13. Disease induced hypersalivation (NOT drug induced)	Positive
14. Correction of squint (strabismus) in paediatrics	Negative unless there is an exceptional clinical circumstance.
15. Hirschsprung's disease	Positive
16. Raynaud's disease	Negative unless exceptional clinical circumstance.
17. Masseteric hypertrophy	Negative
18. Migraine	Positive in line with NICE technology appraisal guidance [TA260]

Background

Botulinum toxins cause neuromuscular blockade by inhibiting the calcium-ion mediated release of acetylcholine at the motor nerve terminals, resulting in a diminished endplate potential and subsequent flaccid paralysis of the affected muscles. The paralysis persists until new nerve terminals form, usually within 2 to 4 months. Botulinum A toxin is given by local injection and has been used in the treatment of hemifacial spasm, blepharospasm, spasmodic torticollis, lower limb spasticity in children with cerebral palsy, and upper limb spasticity associated with stroke in adults. Botulinum A toxin is also used for the management of strabismus and hyperhidrosis.

Table 1 includes the current licensed medical indications for the various brands of botulinum toxin A¹⁻³

Table 1: BTA product licensed indications (does not include cosmetic uses)¹⁻³

Product	Licensed indications						
	Ble-pharospasm	Hemi-facial spasm	Idiopathic cervical dystonia	Hyper-hidrosis Axillary only	Chronic migraine	Focal spasticity	Bladder dysfunction
Botox®	3	3	3	3	3	3	3
Dysport®	3	3	3	6	6	3	6
Xeomin®	3	6	3	6	6	3	6

The following NICE guidance has been issued in relation to conditions where botulinum toxin may have a place in therapy.

- Migraine, Technology Appraisal Guidance (TA260), issued June 2012.
- Spasticity in children and young adults with non-progressive brain disorders, Clinical Guideline 145 (CG145), issued July 2012.
- Urinary incontinence in neurological disease, (CG148), issued August 2012.
- Lower urinary tract symptoms in men, (CG97), Issued May 210; updated June 2015
- Urinary incontinence, (CG171), issued September 2013.
- Multiple Sclerosis (CG186), issued October 2014.
- Stroke Rehabilitation (CG162), issued June 2013.
- Stroke (CG68), issued July 2008.

This document reviews the evidence and provides commissioning recommendations for the use of BTA.

Safety

Botulinum toxin type A and B products have rare but serious risks of adverse effects. In March 2013, the Medicines and Healthcare products Regulatory Agency advised that all patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties.⁴ They should be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.⁵

Botulinum toxins prevent the release of acetylcholine at neuromuscular or other cholinergic junctions and reversibly denervates muscles or eccrine glands.

- Spread reactions - including muscle weakness, dysphagia, and aspiration - have been reported rarely with all products that contain botulinum toxin.
- Extreme caution is needed on administration of products that contain botulinum toxin to patients who have neurological disorders, or a history of dysphagia or aspiration.
- Only physicians with appropriate experience (including use of the required equipment) should administer products that contain botulinum toxin.
- Patients or caregivers should be informed about the risk of spread of toxin, and should be advised to seek immediate medical care if problems with swallowing or speech develop, or if respiratory symptoms arise.
- Units of botulinum toxin are not interchangeable from one product to another.
- Recommended administration techniques and specific dosing guidance (including the recommendation to use the minimum effective dose and titrate according to individual need) should be followed.⁵

Table 2: Evidence review and detailed recommendations for the use of BTA

Indication	Evidence	PAC recommendations
1. Chronic anal fissure in adults Anal fissure is an ulcer in the squamous epithelium of the anus located just distal to the muco-cutaneous junction and usually in the posterior midline. It typically causes pain during defecation and for one to two hours afterwards. The most consistent finding in typical fissures is hypertonia of the internal anal sphincter, which is so severe that the pain caused by fissure is thought to be due to ischemia. Relief of the spasm has been associated with relief of pain and healing of the fissure without recurrence. The main surgical response is sphincterotomy which can lead to incontinence. Medical therapies include glyceryl trinitate (GTN), diltiazem cream and BTA.	A NICE evidence summary (ESU014) published in June 2013 included evidence from two systematic reviews, including a Cochrane review and four further randomised controlled trials (RCTs). The summary suggests that BTA injection is no better or worse than topical GTN (mostly 0.2% ointment) or isosorbide dinitrate, and no better than placebo or lidocaine at healing anal fissure and is less effective than surgery. However all medical therapies including BTA, do not appear to be associated with a risk of permanent incontinence.^{6,7} The overall fissure healing rate estimated in the 2012 Cochrane review was approximately 67.5% after botulinum toxin type A injection.⁶ A study by Yiannakopoulou et al suggested recurrence rates after BTA injection ranged from 0% (24-month follow-up) to 52.5% (5-year follow-up) depending on the length of follow-up.^{7,8} The recurrence rate after a fissure had healed following treatment with BTA was 50% in a randomized controlled trial and 40% in a case series.⁷ BTA injection appeared well tolerated, with temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients being the main adverse effects reported.⁷	Positive
2. Severe blepharospasm in adults Blepharospasm is a focal dystonia characterized by chronic intermittent or persistent involuntary eyelid closure due to spasmodic contractions of the orbicularis oculi muscles. Each spasm can last for a few seconds to a few minutes. The exact cause of blepharospasm is unknown. Many patients also have spasms of other facial, oromandibular, pharyngeal, laryngeal, or cervical muscles and when adjacent body regions are involved this form of segmental dystonia is referred to as cranial-cervical dystonia. Severe blepharospasm can be very disabling and embarrassing.	A Cochrane review published in 2004, found no high quality randomised controlled trials (RCTs) that met their inclusion criteria. It was concluded that the available studies showed that BTA was highly effective and safe for treating blepharospasm (90% of patients benefited), and that the large effect size meant that it would probably be unethical to perform further placebo controlled studies.⁹ NHS Choices currently recommends patients with blepharospasm should contact their GP to discuss the possibility of BTA treatment.¹⁰ NHS Scotland accepts BTA for the symptomatic management of blepharospasm in adults.¹¹	Positive

Indication	Evidence	PAC recommendations
3. Hemi-facial spasm in adults Hemi-facial spasm (HFS) is a condition characterised by involuntary paroxysmal contractions of muscles innervated by the facial nerve. Although HFS is not dangerous it usually causes significant cosmetic and functional disability. Its severity ranges from a slight unilateral blinking with no involvement of the lower hemiface, to intense spasm of the lower hemiface and neck with one eye closed and a progressive facial weakness. HFS may interfere with the patient's professional and social life and have important health and economic implications. It is a chronic disease and recovery is rarely spontaneous.	A Cochrane review found one small RCT of 11 patients meeting its inclusion criteria. The findings of the single eligible study supported the findings of larger less high quality studies with significant improvements from treatment of hemi-facial spasm with BTA. The conclusion was that all of the studies available suggested that BTA is safe and effective for the treatment of HFS.¹²	Positive
4. Cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults	A Cochrane review concluded that BTA is effective and safe for treating cervical dystonia.¹³ A DARE systemic review concluded that there is convincing evidence for the role of botulinum (A&B) in the treatment of pain associated with cervical dystonia. However, there is a risk of adverse events, particularly at higher doses.¹⁴ A review for the American Academy of Neurology concluded that botulinum (A&B) is established as safe and effective for the treatment of cervical dystonia.¹⁵ NHS Scotland accepts BTA for the symptomatic management of cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.¹¹	Positive

Indication	Evidence	PAC recommendations
5. Laryngeal dystonia (spasmodic dystonia)	Only one study in the literature met the inclusion criteria for a Cochrane review as it reported a treatment/no treatment comparison. It reported significant beneficial effects for fundamental frequency (Fo), Fo range, spectrographic analysis, independent ratings of voice severity and patient ratings of voice improvement. The Cochrane review concluded that the evidence from RCTs supporting the effectiveness of botulinum toxin for management of spasmodic dysphonia is deficient. The lack of supporting evidence from RCTs results in an inability to draw unbiased generalized conclusions regarding the effectiveness of botulinum toxin for all types of spasmodic dysphonia.¹⁶ A review for the American Academy of Neurology concluded that laryngeal dystonia (spasmodic dysphonia) generally presents as adductor type (ADSD) and less frequently as abductor type of spasmodic dysphonia (ABSD). Botulinum toxin is probably effective for the treatment of ADSD. There is insufficient evidence to support a conclusion of effectiveness for botulinum treatment in ABSD.¹⁶ It was not possible to establish if BTA or botulinum type B was used in the studies above.	Negative BTA use not supported unless there is an exceptional clinical circumstance.
6. Hidradenitis suppurativa	There is currently no available evidence to confirm the effectiveness of BTA in hidradenitis suppurativa and the rationale for the use of BTA in hidradenitis suppurativa is unclear.	Negative BTA use not supported due to lack of evidence.
7. Mechanical neck disorders	A Cochrane review concluded that in participants with chronic neck disorders with or without radicular findings or headache, there was moderate evidence from five high quality trials that BTA intramuscular injections had similar effects to saline in improving pain (pooled SMD: -0.39, 95%CI - 1.25 to 0.47), disability or global perceived effect.¹⁷	Negative BTA use not supported due to lack of clinical efficacy.

Indication	Evidence	PAC recommendations
8. Upper and lower limb in adults including focal spasticity associated with stroke	The SMC has accepted BTA (Botox™ or Dysport™) for use within NHS Scotland for focal spasticity, including the treatment of wrist and hand disability due to upper limb spasticity associated with stroke in adults. The use of BTA for lower limb including ankle disability is not recommended by the SMC.¹⁸⁻²⁰ In a placebo-controlled study, BTA was significantly superior to placebo in terms of the disability assessment scale and efficacy was maintained across repeated injections in an open-label extension study with a duration of one year.¹⁸ The Royal College of Physicians conducted a systematic review concerning the use of BTA in patients with upper or lower limb spasticity in 2009. In most of the papers reviewed, patients had spasticity secondary to stroke, but there were also subjects with MS or general neurological conditions in the studies considered. The guidance did not limit itself to patients with spasticity secondary to stroke and recommended BTA treatment for patients with focal or multifocal spasticity where there is a dynamic spastic component (as opposed to contracture) and there are anticipated functional gains. Please refer to the guidance for more detailed recommendations.²¹ In controlled clinical trials patients with focal upper limb spasticity associated with stroke were followed for 12 weeks after single treatment with BTA. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 units over 54 weeks. If it is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished. Re-injections should not occur before 12 weeks.¹	Positive BTA should be considered for all patients, including those with stroke, with focal or multifocal spasticity where there is a dynamic spastic component (as opposed to contracture) and there are anticipated functional gains in line with Royal College of Physician guidance.
9. Hyperhidrosis	See separate PAC policy regarding management of hyperhidrosis and recommendations regarding the place in therapy of BTA.²² The Cochrane Skin Group has also concluded that BTA is effective, although injections are painful; they last for six to eight months after which they need to be repeated.²³ A NICE Clinical Knowledge Summary regarding hyperhidrosis, suggests BTA as a possibly treatment option, although the guidance does confirm that the treatment is not available at all secondary care providers and is often only available via private clinics.²⁴	Positive BTA should be considered in the management pathway for hyperhidrosis as per PAC recommended pathway.

Indication	Evidence	PAC recommendations
10. Dysphagia (including dysphagia caused by achalasia) Dysphagia is the medical term for swallowing difficulties and has several underlying causes including achalasia, gastro-oesophageal reflux disease and gastro-oesophageal cancer as well as being a complication of several neurological disorders.²⁵ Achalasia is an oesophageal motility disorder, of unknown cause, which results in increased lower oesophageal sphincter (LOS) tone and symptoms of difficulty in swallowing. It affects approximately 600 people in the UK.²⁶ Treatments are aimed at reducing the LOS tone. Current endoscopic therapeutic options include pneumatic dilation (PD) or botulinum toxin injection (BTX).²⁷	A Cochrane review published in 2013 included six studies involving a total of 178 participants with primary achalasia. Two studies were excluded from the meta-analysis of remission rates on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference in remission between PD or BTA treatment within four weeks of the initial intervention.²⁷ There was also no significant difference in the mean oesophageal pressures between the treatment groups; weighted mean difference for PD of -0.77 (95% CI -2.44 to 0.91, P = 0.37). Data on remission rates following the initial endoscopic treatment was available for two studies at six months and three studies at 12 months. At six months, 22 of 29 PD participants were in remission compared to seven of 27 in the BTA group; whilst at 12 months 33 of 47 PD participants were in remission compared to 11 of 43 BTA participants. No serious adverse outcomes occurred in participants receiving botulinum, whilst PD was complicated by perforation in three cases.²⁷ The World Gastroenterology Organisation (WGO) recommends BTA as a treatment alternative only in patients with achalasia who have a high risk of poor surgical outcome and mortality. The WGO does not make any specific recommendation with respect to the use of BTA for other causes of dysphagia.²⁸ A Cochrane review which aimed to assess the impact of BTA on upper oesophageal sphincter function and effectiveness for swallowing difficulties in patients with neurological disorders, failed to identify any eligible trials for inclusion in the analysis.²⁹ There is limited evidence for the use of BTA in patients with dysphagia due to causes other than achalasia at this time.	Positive for dysphagia caused by achalasia BTA should be approved for use in patients with achalasia at high risk of perforation during pneumatic dilatation treatment or aspiration. Repeat injection of BTA can be administered when the clinical effect of a previous injection diminishes and the treating physician in consultation with the patient deems it necessary. Re-treatment can occur every 3-4 months and some patients may delay re-treatment up to 6 months. Negative for dysphagia resulting from any other condition

Indication	Evidence	PAC recommendations
II. Overactive bladder	NICE CG148, August 2012 on urinary incontinence in neurological disease states - offer bladder wall injection with BTA to adults with spinal cord disease (e.g. SCI or MS) and with symptoms of an overactive bladder (OAB) or with urodynamic investigations showing impaired bladder storage, and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated. Ensure that patients who have been offered continuing treatment with repeated BTA injections have prompt access to repeat injections when symptoms return.³⁰ NICE CG97, originally published in May 2010 and updated in June 2015 on lower urinary tract symptoms in men, – recommends that consideration should be given to offering bladder wall injection with BTA to men with detrusor over activity only if their symptoms have not responded to conservative management and drug treatments and the man is willing and able to self-catheterise.³¹ NICE CG171, September 2013 on urinary incontinence: the management of urinary incontinence in women says - bladder wall injection with BTA should be offered after an multidisciplinary team review (MDT) to women with OAB caused by proven detrusor over activity that has not responded to conservative management (including OAB drug therapy).³² A Cochrane review identified nineteen studies. Most patients in the studies had neurogenic OAB, but some included patients with idiopathic OAB. All studies demonstrated superiority of BTA to placebo. Lower doses of BTA (100 to 150 U) appeared to have beneficial effects, but larger doses (300 U) may have been more effective and longer lasting, but with more side effects. Sub-urothelial injection had comparable efficacy to intra-detrusor injection. The effect of BTA may last for a number of months and is dependent upon dose and type of toxin used. Patients receiving repeated doses do not seem to become refractory to BTA. BTA appeared to have beneficial effects in OAB that quantitatively exceeded the effects of intra-vesical res-iniferatoxin. Intra-vesical BTA appeared to be reasonably safe; however, one study was halted due to a perceived unacceptable rate of urinary retention.³³	Positive BTA should be approved for use subject to failure of both non-pharmacological and pharmacological interventions. Re-treatment Patients should be considered for reinjection for urinary incontinence due to neurogenic detrusor over activity when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection. In phase 3 clinical studies, the median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis. Limited data are available beyond 2 treatments. No urodynamic data beyond 2 treatments and no histopathological data after repeated treatment are currently available. Patients should not receive multiple treatments in the event of limited symptomatic improvement.¹

Indication	Evidence	PAC recommendations
I 2. Spasticity treatment in paediatric cerebral palsy (Lower and upper limb)	This indication is currently commissioned locally for treatment through approved specialist centres. The studies are mainly in patients with spasticity of upper limb post stroke. NICE CG145, July 2012 on spasticity in children and young people general treatment principles are: Consider BTA treatment in children and young people in whom focal spasticity of the upper limb is: • impeding fine motorfunction, • compromising care and hygiene, • causing pain, • impeding tolerance of other treatments, such as orthoses, • causing cosmetic concerns to the child or young person. Consider BTA treatment where focal spasticity of the lower limb is: • impeding gross motorfunction, • compromising care and hygiene, • causing pain, • disturbing sleep, • impeding tolerance of other treatments, such as orthoses and use of equipment to support posture, • causing cosmetic concerns to the child or young person. A Cochrane review of the use of BTA in lower limb spasticity in children with cerebral palsy in January 2009 showed that injection of BTA into muscle causes local muscle weakness and so may help counter spasticity. This review found that published, controlled evidence was weak as they identified three controlled trials involving only a small number of children (two to 11 years). Children receiving a single course of injections of BTA (Botox®, 3 to 8 µg/kg or Dysport®, 15 µg /kg) into the calf muscle tended to have an improved pattern of walking (gait) compared with inactive injections (placebo). Both BTA injections and lightweight walking plaster casts below the knee (for four to six weeks) produced similar significant improvements in gait. Some calf pain was reported among the 26 children injected with BTA and parents reported inconvenience with wearing casts and weakness of legs following removal.³⁴ A Cochrane review of the use of BTA in upper limb spasticity in children with cerebral palsy in 2010 showed that BTA injected into muscles reduces muscle tightness. When used in conjunction with occupational therapy, the aim of BTA injections in the arms and hands is to improve movement and function in treated limbs. This review demonstrated improvements on a range of measures with the combined treatment. In the absence of significant side effects, injection of BTA has been identified as a safe and effective treatment for upper limb spasticity when used in combination with occupational therapy in children.³⁵	Positive BTA should be approved for spasticity treatment in paediatric cerebralpalsy for both upper and lower limbs. Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.¹ Botulinum is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. Botulinum is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.¹

Indication	Evidence	PAC recommendations
I3. Hypersalivation caused by disease and not drug induced There are a range of conditions that may cause hypersalivation e.g. Parkinson's disease.	30 children with cerebral palsy or neurodegenerative disorder were injected with either BTA or botulinum toxin B under ultrasound guidance into the parotid and submandibular glands on both sides. All injections were well tolerated without general anaesthesia. Drooling severity at baseline and reduction of sialorrhea during treatment was measured using a parent's questionnaire and rated using the Teacher Drooling Scale (TDS). Reduction of sialorrhea was achieved two weeks after injection, with a positive effect lasting about three to four months in most children. 83% showed a good response to botulinum toxin after first injection, but only in 50% treatment was continued. There were no significant differences between BTA or B. Side effects were observed in five children with viscous saliva and in one child a unilateral parotitis was observed.^{36,37} Below is a summary of a search of 15 studies found on BTA in the treatment of sialorrhea in human subjects. One controlled trial found that BTA caused significant reductions in patients' severity and frequency of drooling compared with placebo. Another found significant saliva reductions in the treatment group receiving the highest dose of BTA but found no subjective improvement compared with the placebo group. A third study comparing BTA with placebo found significant improvements in subjective and objective measures of drooling in the treatment group. A fourth controlled trial found significant reductions from baseline levels of drooling after patients received BTA injections. Similar efficacy was found between the botulinum and scopolamine treatment groups.	Positive BTA should be approved for treatment of disease induced hypersalivation.
I4. Correction of squint (strabismus) in paediatrics	Strabismus is a condition in which the eyes are out of alignment; one eye may turn inwards, outwards, upwards or downwards. Strabismus may develop in childhood or may be acquired as an adult. Treatment options include eye therapy, glasses, prisms, occlusion, BTA or surgery, to reduce the deviation of the eyes. Currently there is no clear recommendation on the use of BTA in the treatment of strabismus.³⁸ The Royal College of Ophthalmologists recommend BTA as a possible treatment option in childhood strabismus under certain circumstances.³⁹ A Cochrane review found four RCTs that compared BTA to another treatment or to no treatment. The results showed no prophylactic use for BTA in sixth nerve palsy, poor effect in adult horizontal strabismus without binocular use of the eyes, and no difference in response for retreatment of infantile esotropia or acute onset esotropia. It was not possible to determine dose effect because of the different types and doses of BTA used in each trial. Complications from the use of BTA (Botox™ or Dysport™) included transient ptosis and vertical deviation and combined rates for these complications ranged from 24% to 55.54%. This review identified a need for more RCTs to provide further reliable evidence on the effective use of botulinum toxin for the treatment of strabismus.³⁸	Negative BTA should not be approved for correction of squint in paediatric patients unless there is an exceptional clinical circumstance.

Indication	Evidence	PAC recommendations
I5. Hirschsprung's disease Hirschsprung's disease is characterised by an absence of ganglion cells in the distal bowel, beginning at the internal sphincter and extending proximally. The resulting ganglionic segment of the colon fails to relax, causing a functional obstruction. Presentation is commonly in the first 28 days of life (neonatal period), with delayed passage of meconium and abdominal distension. However, about 12% of patients present again in childhood with intractable constipation (not responsive to laxatives) and failure to thrive, with about a third of these presenting with enterocolitis.⁴⁰	Koivusalo et al have reported on their experiences with the use of BTA (Botox, 3-6IU/kg) in 16 patients, of which eight had Hirschsprung's disease (HD) and eight had internal sphincter achalasia (ISA). Median ages were 3.8 years (0.4-9.3) for HD and 8.1 years (range 1.5-11.4) for ISA. Seven HD patients had previous colo-anal pull-through (CAPT), and one had total colon aganglionosis (TCA) colectomy and ileo-anal J-Pouch anastomosis. Indication for botox injection treatment (BIT) was anal outlet obstruction (n = 11) with soiling and recurring HD-associated enterocolitis (n = 5) and in one patient (HD, TCA) soiling with enterocolitis (n = 1). Before receiving BTA, all patients underwent anorectal manometry, rectal biopsies and barium enema. The effect was evaluated after two months and BTA injections were repeated if necessary. Effect was scored as follows: 0 no, 1 little, 2 significant effect and 3 symptoms disappeared. Median follow-up was 19 months (range 3-43). The median number of injections was two per patient (range 1-4) and the median Botox dose was 80 U (range 40-100). Scores of BIT effect were 3 or 2 in five (31%) and 0 or 1 in 11 (69%). After adjunctive treatment modalities (myectomy n = 1, CAPT n = 1, adjusted ACE/laxative treatment), the end result was good or satisfactory in 11 (69%) but remained poor in five (31%) patients. Patient age, diagnosis, anorectal resting pressure or findings in barium enema were not correlated with BTA injection efficiency score (R range -0.06 to 0.39, P = 0.12-0.91). The authors concluded that although successful in some patients, the role of BTA remains undetermined. It is difficult to predict which patients will profit from BTA. Continuing other treatment modalities after BTA may improve the results.⁴¹ Patrus et al conducted a retrospective review of 22 patients with Hirschsprung's disease treated over ten years. Patients had previously undergone pull-through surgery and had received a median number of 2 BTA injections (range, 1-23). The number of hospitalizations for obstructive symptoms significantly decreased from pre-injection (median, 1.5; interquartile range [IQR], 1-3) to post injection (median, 0; IQR, 0-1) (P = 0.0003). The number of injections was lower in children with a recto-sigmoid transition zone (median, 1 injection; IQR, 1-3.5) than in those with long-segment disease (median, 3 injections; IQR, 1-15) (P = 0.04). Eighty percent of patients had a good response to the first dose of BTA, and 69% of them required additional injections. There were no short-term or long-term complications related to botulinum toxin. The authors concluded that BTA should be strongly considered in the management algorithm for postoperative obstructive symptoms in children with Hirschsprung's disease.⁴²	Positive BTA should be approved for use in Hirschsprung's disease subject to the following inclusion and end of treatment criteria. Criteria for initiating therapy: Ongoing constipation and recurrent enterocolitis despite continuing medical treatment of constipation. Criteria proposed for stopping therapy: Effectiveness of this treatment to be monitored regularly on an out-patient basis, if partially successful or not successful after first injection, dose may be considered to be repeated. If repeated dose is unsuccessful then treatment is to be discontinued. The effects of botulinum is transient and may wear off, hence treatment may need to be repeated every 3-6 months.

Indication	Evidence	PAC recommendations
16. Raynaud's disease Raynaud's phenomenon is a common condition that affects the blood supply to certain parts of the body – usually the fingers and toes.⁴³ It is often referred to as Raynaud's syndrome, Raynaud's disease or just Raynaud's. Raynaud's is usually triggered by cold temperatures, anxiety or stress. The condition occurs because blood vessels go into a temporary spasm, which blocks the flow of blood. This causes the affected area to change colour to white, then blue and then red, as the blood flow returns. Other symptoms include numbness, pain, and pins and needles and can last from a few minutes to several hours. There are two types of Raynaud's: ○ Primary – when the condition develops by itself (this is the most common type). ○ Secondary – when it is caused by another health condition. Most cases of secondary Raynaud's are associated with conditions that cause the immune system to attack healthy tissue (autoimmune conditions), such as rheumatoid arthritis and lupus. CONTINUED OVERLEAF	BTA has been suggested as a possible treatment in patients with Raynaud's disease, however the exact mechanism remains unknown and available evidence is limited to small studies and case reports.⁴⁴⁻⁴⁹ In a report published as a conference abstract in November 2014, seven patients with Raynaud's phenomenon who had experienced poor response to other treatment alternatives received a cumulative total dose of between 30–60 units of botulinum toxin injected into the palmar aspect of the hand. 30 minutes after infiltration, three patients felt no improvement; two assessed slight improvement and two very important improvement. At the patients' one-week and thirty-day follow-up visits two patients did not perceive any change and four experienced great amelioration. A decrease in pain was noted in all of the cases. Three patients presented digit ulcers at baseline visit; ulceration healing was noted in all of them, two of them one week after the injection and the other one, one month after. Three patients reported mild "weakness" after being injected and one reported slight thenar-eminence pain that lasted a few days. None of the patients suffered any systemic complications related to the toxin.⁴⁶ In another extremely small randomised controlled trial, ten patients with severe Raynaud (i.e. history of digital infarcts or ulcerations, standard therapy failure, or impending digital amputation) were randomized to receive BTX injections into either the left or right hand, while the contralateral hand was injected with saline. The patient and the assessor were both blinded to the randomization scheme. A total of 10 U (0.2 mL) of BTX was injected into each of four sites of the palmar hand (40U/hand, 0.8 mL), followed by 30 minutes of gentle massage. The contralateral hand was injected similarly with equivalent volumes of sodium chloride (NaCl). The primary outcome in this study was digital pulp temperature. Temperatures of each finger were recorded using a thermometer at baseline and for cold recovery time in 3-minute intervals after a 20-second 48°C ice-bath immersion. At the 6-week follow-up visit, temperature measurements were repeated. One patient withdrew secondary to needle phobia, and one patient was lost to follow-up, resulting in seven women and one man, ages 26 to 70 with a mean age of 46 years. CONTINUED OVERLEAF	Negative

Indication	Evidence	PAC recommendations
16. Raynaud's disease continued Secondary Raynaud's can severely restrict the blood supply, so it carries a higher risk of complications, such as ulcers, scarring and even tissue death (gangrene) in the most serious cases. However, severe complications are rare. Raynaud's phenomenon is a common condition. It affects up to 20% of the adult population worldwide. There may be as many as 10 million people with the condition in the UK.⁴³ Primary Raynaud's usually begins in between 20-40 years of age. Secondary Raynaud's can develop at any age, depending on the cause. Raynaud's is slightly more common in women than men.	There was a significant increase in digital pulp temperatures of the hands treated with BTX six weeks post-injection from baseline as compared with the saline-injected hands. The mean temperature difference was 1.30 degrees centigrade C (95% confidence interval 0.23-2.36, P value 0.018). There was no statistically significant difference in cold recovery times between the digits of treatment and control hands.⁴⁷ In a case report published in 2004, a 52 year old woman with severe resting pain of fingers and hands and multiple ulcerations on the digits due to Raynaud's syndrome in conjunction with Rheumatoid arthritis received a cumulative dose of 100IU BTA injected in small doses (10-20iu per site) into the palmar side of the hand. An improvement of blood flow to the digits was noted within 30 minutes of injection. In addition, the patient verbalized considerable, immediate improvement in resting finger and hand pain that has continued. The only adverse effect noted was mild, non-limiting, bilateral thenar muscle weakness, likely exaggerated by baseline muscle weakness secondary to prior fusion of the joints in these digits. Three months after BTA was administered, three of the six digital ulcers on the patient's right hand resolved completely with partial healing of two additional ulcers. Some worsening of an ulcer on the right fifth digit was noted, but the patient recalled minor trauma to that location after initial treatment; however, pain in the digit, which was substantial before treatment, had completely resolved. In addition, all three digital ulcers on the left hand healed entirely, and to date, no new ulcers have developed on either hand.⁴⁸ A retrospective study focused on patient outcomes was performed on 19 patients diagnosed with Raynaud's phenomenon. Patients suffered from chronic ischemic hand pain. All patients had vascular studies to rule out occlusive disease. 50 to 100 units of Botox were injected into the palm around each involved neurovascular bundle. Pre injection and post injection laser Doppler scanning was performed on most patients to measure blood flow.	Negative

Indication	Evidence	PAC recommendations
16. Raynaud's disease continued	Sixteen of 19 patients (84%) reported pain reduction at rest. Thirteen patients reported immediate relief; three reported more gradual pain reduction over 1 to 2 months. Three patients had no or minimal pain relief. Tissue perfusion results demonstrated a marked change in blood flow (-48.15% to 425%) to the digits. All patients with chronic finger ulcers healed within 60 days. Most patients [n = 12 (63%)] remained pain-free (13 to 59 months) with a single-injection schedule. Four patients (21%) required repeated injections because of recurrent pain.^{49,50}	Negative
17. Masseterichypertrophy Benign masseter muscle hypertrophy is an uncommon clinical phenomenon of uncertain aetiology, which is characterised by a soft swelling near the angle of the mandible. The swelling may on occasion be associated with facial pain and can be prominent enough to be considered cosmetically disfiguring. Varying degrees of success have been reported for some of the treatment options for masseter hypertrophy, which range from simple pharmacotherapy to more invasive surgical reduction. Injection of botulinum toxin type A into the masseter muscle is generally considered a less invasive modality and has been advocated for cosmetic sculpting of the lower face.⁵¹	A Cochrane review published in 2013 failed to identify any adequate studies regarding the use of BTA for the management of masseteric hypertrophy. There is limited evidence for the use of BTA in masseteric hypertrophy at this time.⁵¹ The use of BTA in masseteric hypertrophy is considered to be a cosmetic indication and therefore its use is not recommended.	Negative

Indication	Evidence	PAC recommendations
18. Migraine	NICE has recommended botulinum toxin type A as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least eight days are with migraine) that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. ⁵²	Positive

Document history

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Consultation process	EoE clinicians via PAC members
QA process	Katie Smith – Director of East Anglia Medicines Information Service, 26th June 2015 v3.1 8th December 2015

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