New Medicine Assessment

Botulinum Toxin Type A

For treatment of primary idiopathic hyperhidrosis and secondary hyperhidrosis

Recommendation: RED for the following indications:

- As an option for the management of severe primary idiopathic hyperhidrosis of the axillae, which does not respond to self-care strategies and topical treatment with 20% aluminium chloride antiperspirant (minimum 6 weeks), and where the cause is not due to social anxiety disorder.
- As an option for the management of severe secondary hyperhidrosis of the axillae, which does not respond to self-care strategies and topical treatment with 20% aluminium chloride antiperspirant (minimum 6 weeks), where the cause is not due to social anxiety disorder, and where the primary condition has been optimally managed as far as reasonable to alleviate the hyperhidrosis.

In order to reduce the potential for antibody formation which reduces the effectiveness of treatment, inject the lowest effective dose at the longest clinically indicated interval.

Summary of supporting evidence:

- There is a general lack of robust evidence available – problems with the small scale of trials and prevalence of bias.
- There is moderate-quality evidence of a large statistically significant effect of botulinum toxin on axillary hyperhidrosis symptoms, compared with placebo.
- The FDA and EMEA have approved the use of botulinum toxin for axillary hyperhidrosis.
- There is a lack of quality evidence for the efficacy and safety of botulinum toxin for hyperhidrosis in areas other than the axilla.
- The side effect profile for use of botulinum toxin in palmar, plantar and craniofacial regions is less favourable than for its use in the axillary regions.
- Few serious or severe adverse effects have been seen across the studies.
- Products that contain botulinum toxin are associated with the risk of serious adverse reactions due to distant spread of toxin.
- Safety and effectiveness is not established in patients under the age of 18.
- Botulinum toxin has been used for a range of other indications over many decades.
- Further studies are required comparing botulinum toxin with other treatments, rather than placebo, for hyperhidrosis.
- A well-conducted, adequately powered, RCT of botulinum toxin (with anaesthesia) compared with iontophoresis for palmar hyperhidrosis is needed. The cost of botulinum toxin plus anaesthesia is considerably higher than the cost of iontophoresis; therefore, cost-effectiveness would also need to be assessed.
- Analysis suggests iontophoresis is the most cost-effective option for axillary hyperhidrosis in an NHS setting, followed by botulinum toxin.19

Details of Review

Name of medicine (generic & brand name)**:**

Botulinum Toxin type A (Botox)

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport)

Strength(s) and form(s):[1]

Botox 50 unit powder for solution for injection vials

Botox 100 unit powder for solution for injection vials

Botox 125 unit powder for solution for injection vials

Botox 200 unit powder for solution for injection vials

Botox 300 unit powder for solution for injection vials

Botox 500 unit powder for solution for injection vials

Dysport 300 unit powder for solution for injection vials

Dysport 500 unit powder for solution for injection vials

Dose and administration:

Botox2

50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart.
The recommended injection volume for intradermal injection is 0.1-0.2 ml.

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.

Clinical improvement generally occurs within the first week after injection and persists for 4-7 months.
Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating healthcare practitioner deems it necessary. Injections should not be repeated more frequently than every 16 weeks.

Dysport3

The recommended initial dosage is 100 units per axilla. If the desired effect is not attained, up to 200 units per axilla can be administered for subsequent injections. The maximum dose administered should not exceed 200 units per axilla.
The area to be injected may be determined beforehand using the iodine-starch test. Both axillae should be cleaned and disinfected. Intradermal injections at ten sites, each site receiving 10 units, i.e., to deliver 100 units per axilla, are then administered.

The maximum effect should be seen by week two after injection. In many cases, the recommended dose will provide adequate suppression of sweat secretion for approximately 48 weeks. The time point for further applications should be determined on an individual basis according to clinical need. Injections should not be repeated more frequently than every 12 weeks. There is some evidence for a cumulative effect of repeated doses so the time of each treatment for a given patient should be assessed individually.
The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

BNF therapeutic class / mode of action:

Neurotoxins (botulinum toxins)

Licensed indication(s):[2,3]

Botox:[2]

- Symptomatic treatment of focal spasticity
- Symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- Prophylaxis of headaches in adults with chronic migraine
- Management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics
- Management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- Temporary improvement in the appearance of severe facial lines when the severity of the facial lines has an important psychological impact in adult patients

Dysport:[3]

- Symptomatic treatment of focal spasticity
- Symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- Management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics

For more detailed narrative on indications please refer to the product literature.

Whilst other brands of botulinum toxin type A are available, not all are licensed for treatment of hyperhidrosis.

Proposed use (if different from, or in addition to, licensed indication above):

For the treatment of primary idiopathic hyperhidrosis and secondary hyperhidrosis

Course and cost:

Axillae

Botox, Botulinum toxin type A 50 unit vial = £77.50

Botox, Botulinum toxin type A 100 unit vial = £138.20

Assuming 100 units every 4-7 months:

Annual cost per patient using **Botox** = Approx £138 - £465

Dysport, Botulinum toxin type A 300 unit vial = £92.40

Dysport, Botulinum toxin type A 500 unit vial = £154 (price listed as 2 vials at £308)

Assuming 200-400 units every 3-12 months:

Annual cost per patient using **Dysport** = Approx £92 - £616

NHS indicative prices taken from BNF October 2021.

Current standard of care/comparator therapies:

Self-care products:4

- Antiperspirant (axillary)
- Underarm pads (axillary)
- Moisture-wicking socks (plantar)
- Absorbent soles (plantar)
- 20% aluminium chloride hexahydrate preparations such as roll-on antiperspirants and sprays (axillary, plantar, palmar, craniofacial)
- Management of anxiety

Specialist care:4

- Higher strength aluminium salts (up to 50%), and topical glutaraldehyde or formaldehyde may be used.
- Topical glycopyrrolate may be useful for primary craniofacial hyperhidrosis (off-label indication).
- Oral antimuscarinics, such as oxybutynin and glycopyrronium bromide decrease sweat secretion by competitive inhibition of acetylcholine at the muscarinic receptors near eccrine sweat glands (off-label indications).
- Iontophoresis
    - The sites of hyperhidrosis are immersed in warm water (or a wet contact pad may be applied) through which a weak electric current is passed. This introduces charged ions into the skin which inhibits the function of the sweat glands in that area.
    - It is mainly suitable for the palms and soles, as treatment of the axillae is less practical.
    - If unsuccessful, glycopyrronium bromide (an antimuscarinic agent) may be added to the water.
    - Maintenance treatment is typically required at intervals of 1–4 weeks, as recurrence of symptoms, is common after stopping treatment.
    - Adverse effects include transient discomfort, erythema, and vesicle formation at the treatment site.
- Botulinum A toxin (See section 'Relevant NICE guidance')
- Surgery
    - Localized resection of eccrine sweat glands can be carried out using local anaesthesia and is useful for small areas of axillary hyperhidrosis.
    - Endoscopic thoracic sympathectomy (ETS) may be offered if other measures are ineffective or not tolerated.

Options available privately:

- miraDry (medical device which uses thermolysis to destroy the sweat glands)[11]

Relevant NICE guidance:

NICE CKS Hyperhidrosis 2018

Botulinum A toxin[4]

- Botulinum toxin is delivered by multiple intradermal injections to the affected areas.

- It acts by inhibiting acetylcholine release from the sympathetic cholinergic nerve terminals that innervate sweat glands.
- Botulinum toxin is licensed for the treatment of axillary hyperhidrosis and may also be used for palmar, plantar, and craniofacial hyperhidrosis (treatment is more painful in these areas). The effect may last for 6–9 months.
- Adverse effects include pain during injections and compensatory sweating. Transient muscle weakness and loss of fine motor control have also been reported.

NICE Interventional Procedures Guidance

Endoscopic thoracic sympathectomy for primary hyper hidrosis of the upper limb (2014)[5]

Transcutaneous microwave ablation for severe primary axillary hyperhidrosis (2017)[6]

NICE Evidence Summary

Hyperhidrosis: Oral glycopyrronium bromide (2013)[7]

Hyperhidrosis: Oxybutynin (2017)[8]

NICE CG159[9]

Social anxiety disorder: recognition, assessment and treatment (2013)

- Do not offer botulinum toxin to treat hyperhidrosis (excessive sweating) in people with social anxiety disorder. This is because there is no good-quality evidence showing benefit from botulinum toxin in the treatment of social anxiety disorder and it may be harmful.

Background and context

Hyperhidrosis (Hh) is a disorder of uncontrollable, extreme, episodic, unexpected sweating beyond what's considered "normal" or is necessary to maintain thermal homeostasis or as a reaction to stress. Individuals with Hh may sweat four or five times more than "average."

There are two main categories of Hh: Primary idiopathic hyperhidrosis and secondary hyperhidrosis.

Patients with Hh can have excessive sweating either over localized areas (called focal areas) or over the entire body (generalized). Typically, primary idiopathic hyperhidrosis is focal in nature while secondary hyperhidrosis is more likely to manifest as generalized sweating.

Focal areas commonly affected by primary Hh include the soles, palms, axillae, craniofacial region, groin, buttocks, or other distinct body regions. Combinations of focal areas are commonly seen. For example, research shows that 81% of axillary hyperhidrosis sufferers indicate that they sweat excessively from three or more additional focal areas.

While primary Hh is a condition unto itself, secondary hyperhidrosis symptoms are due to one of a large number of underlying medical conditions, including endocrine disorders, neurological problems, use of certain drugs, cancer, chronic infections, dermatologic syndromes, and conditions associated with excess catecholamine discharge. Occasionally, hyperhidrosis can be related to eating (gustatory sweating) or secondary to parotid surgery or diabetes. Secondary Hh may also occur as a side effect of a medication.[10]

Treatment begins with self-help and straightforward treatments (e.g. antiperspirants) progressing to more complex treatments such as Iontophoresis, Botulinum toxin anticholinergics, miraDry and surgery.[11]

Botulinum toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.[2] In the case of the sweat glands it turns them off to reduce sweating.[11]

Summary of evidence

Summary of efficacy data in proposed use:

EMEA

Scientific Conclusions and Grounds for Amendment of the Summary of Product Characteristics for Botox Presented by the EMEA 2003[12]

The pivotal trial plus its open extension demonstrates that Botox in the 50U/axial dose is efficacious in the symptomatic treatment of primary axillar hyperhidrosis. It is acknowledged that the recommended dose did not result from a dose-finding study but rather from a confirmatory study (the pivotal trial). The choice of dose used in the pivotal trial was based on common practice of off-label use. The dose proved to be efficacious with an acceptable safety profile. The efficacy and safety of Botox, on repetitive use for primary axillary hyperhidrosis is not firmly established by direct data. However, taking into consideration the large database generated by the use in other indications and the lack of evidence to the contrary, it is accepted that the Benefit/Risk of Botox for long-term use is favourable. It is also important to recognise that Botox duration of effect in primary hyperhidrosis is longer than in focal dystonia's, which would imply a very long (several years) clinical trial if efficacy of repetitive injections was to be established by such a clinical study.

Intradermal injection of Botox, 50 U per axilla in a placebo-controlled clinical trial setting reduced mean sweat production to physiological levels within one week of administration and benefit was maintained on average for 30.6 weeks. These clinical findings, along with the high levels of

patient satisfaction with treatment, were consistently statistically significantly superior to those seen with placebo.

Canadian Agency for Drugs and Technologies in Health

Botulinum Toxin for Treating Primary Focal Hyperhidrosis in Adult Patients: Clinical Effectiveness[13]

One health technology assessment, one randomized controlled trial, and one non-randomized study were identified regarding the clinical effectiveness of botulinum toxin for treating primary focal hyperhidrosis in adult patients. No systematic reviews were identified. Furthermore, no studies focusing on the working adult population were identified.

The health technology assessment by Wade et al. aimed to determine the most effective treatments for refractory primary hyperhidrosis in secondary care.19 Overall, the authors concluded that there was moderate quality evidence that botulinum toxin injections, compared to placebo, had a statistically significant effect on axillary hyperhidrosis symptoms. The randomized controlled trial by Lueangarun et al. aimed to evaluate the efficacy and safety of a topical botulinum toxin A liposomal cream in patients with primary axillary hyperhidrosis.[14] Compared to the liposomal vehicle cream alone, topical botulinum toxin A liposomal cream significantly improved sweat reduction and patient satisfaction outcomes. Lastly, the non-randomized study by Baker et al. compared the initial effectiveness of botulinum toxin A injections, 1% topical glycopyrrolate and 2% topical glycopyrrolate in patients with axillary hyperhidrosis.[15] Overall, there was a significant improvement in treatment outcomes with botulinum toxin A compared to 1% glycopyrrolate spray, but no difference in treatment outcomes between botulinum toxin A and 2% glycopyrrolate spray.

Follow up Studies

Lynch at al 2020[16]

In this single-centre series, all patients attending for axillary botox, with five or more years of follow-up, were prospectively included. QOL was assessed in all patients using the validated assessment tool, the modified Dermatology LifeQuality Index (DLQI). Standard statistical methods were utilised with data reported as mean (± standard deviation). A total of 75 patients (83% female) met the inclusion criteria with 67% completing the DLQI assessment. Follow-up ranged from 5 to 10 years with a mean age of 37.6 years (± 8.82). The mean number of treatments over the study period was 12 (±3.1). Mean overall post-treatment DLQI score was 1.6 (± 2.01). This represented a significant improvement in patient QOL (p=<0.0001) associated with long-term botox application. This statistical significance was identified consistently across all components of the DLQI tool.

Rosen et al 2017[17]

Australian study on efficacy and patient satisfaction with botulinum toxin A in primary axillary hyperhidrosis with evaluation of possible prognostic factors. Examined 10 years of electronic records at a private Sydney dermatology clinic for patients 12 years or older that had been treated with onabotulinumtoxin A (100 U) for axillary hyperhidrosis of at least 6-months duration that had failed 20% topical aluminium chloride. Patients were contacted retrospectively by telephone and were asked to answer a nine-question survey. A total of 192 (96%) reported at least moderate satisfaction (score≥2 or 50% improvement). The median effect duration was 7 months. None of the assessed prognostic factors was statistically significantly associated with satisfaction score or duration, including age (P= 0.13, P= 0.74), gender (P= 0.74, P= 0.67), sweating elsewhere (P= 0.85,P= 0.51), family history (P= 0.25,P= 0.48) and failed treatment prior(P= 0.531,P= 0.976). Thirteen (6.5%) patients reported compensatory sweating. A total of 143 patients had at least two treatments and were able to be assessed. A total of 123 (86%) patients reported subsequent treatments lasting the same amount of time or longer. Using our scale, 194 (97%) patients reported at least some improvement in life quality. A total of 85 (42.5%) patients felt that

onabotulinumtoxin A had ‘changed their life’. No prognostic factors appeared to influence quality of life.

Systematic reviews

Cochrane: Interventions for the treatment of Frey’s syndrome (Review) 2015[18]

Unable to establish the efficacy and safety of the different methods used for the treatment of Frey's syndrome. RCTs are urgently needed to assess the effectiveness of interventions for the treatment of Frey's syndrome.

Wade et al 2017[19]

A systematic review and value-of-information analysis of the interventions for hyperhidrosis in secondary care. Fifty studies were included in the effectiveness review: 32 randomised controlled trials (RCTs), 17 non-RCTs and one large prospective case series. Most studies were small, rated as having a high risk of bias and poorly reported. The interventions assessed in the review were iontophoresis, botulinum toxin (BTX), anticholinergic medications, curettage and newer energy-based technologies that damage the sweat gland (e.g. laser, microwave).

There is moderate-quality evidence of a large statistically significant effect of BTX on axillary hyperhidrosis symptoms, compared with placebo. Twenty-three studies of BTX administered by subcutaneous injection were included. Thirteen studies were randomised trials and 10 were non-randomised studies. Risk of bias was considered to be high across all reported outcomes in 14 studies. Studies were published between 1997 and 2016; the BTX used in the earlier studies may not have the same effectiveness and adverse event profile as newer formulations. Most studies used BTX-A and only two used botulinum toxin type B (BTX-B). Five studies used Botox®, three studies used Dysport®, one study used both brands and 14 studies did not state which brand was used. When stated, the most common dosage of BTX-A was 50 U, although some studies used dosages as high as 250 U. Studies of BTX-B used dosages of 2500 U or 5000 U. More than two-thirds of the studies focused on treatment for axillary hyperhidrosis exclusively and about a third focused on palmar hyperhidrosis.

None of the studies reported serious or severe adverse events related to the intervention. The most common treatment-related events reported included injection site pain and compensatory sweating. Overall, there is moderate-quality evidence of a large effect of subcutaneous BTX on symptoms of axillary hyperhidrosis in the short and medium term (up to 16 weeks), and of a small to moderate positive effect on quality of life in the short term, compared with placebo. There is low-quality evidence to suggest that BTX is associated with higher patient satisfaction in the short to medium term, as well as a higher incidence of non-severe adverse events, notably injection site pain and CS, compared with placebo.

There is very low-quality evidence suggesting that BTX injections have a small positive effect on palmar hyperhidrosis symptoms compared with placebo or no treatment, although there is some very low-quality evidence to suggest a high incidence of adverse events with BTX-B (5000 U). The evidence for an effect of BTX injections for palmar hyperhidrosis on quality of life is insufficient. As stated previously, there is very low-quality evidence to suggest that iontophoresis is less effective than BTX injections at reducing palmar hyperhidrosis symptoms in the short term and that the duration of effect is shorter than with BTX.

There is very low-quality evidence regarding the relative effectiveness of BTX injections to the axillae compared with curettage and no evidence of a difference in longer-term effectiveness, and low-quality evidence suggesting a higher incidence of adverse events in patients undergoing curettage.

There was weak but consistent evidence for iontophoresis for palmar hyperhidrosis. Evidence for other interventions was of low or very low quality. For axillary hyperhidrosis cost-effectiveness results indicated that iontophoresis, BTX, medication, curettage and ETS (endoscopic thoracic sympathectomy) was the most cost-effective sequence (probability 0.8), with an incremental cost-

effectiveness ratio of £9304 per quality-adjusted life-year. Uncertainty associated with study bias was not reflected in the economic results.

Patients and clinicians attending an end-of-project workshop were satisfied with the sequence of treatments for axillary hyperhidrosis identified as being cost-effective. All patient advisors considered that the Hyperhidrosis Quality of Life Index was superior to other tools commonly used in hyperhidrosis research for assessing quality of life.

The evidence for the clinical effectiveness and safety of second-line treatments for primary hyperhidrosis is limited. This meant that there was insufficient evidence to draw conclusions for most interventions assessed and the cost-effectiveness analysis was restricted to hyperhidrosis of the axilla.

Galadari et al 2020[20]

A systematic review of the literature to identify evidence on the treatment approaches and outcomes associated with abobotulinumtoxinA (aboBoNT-A) (Dysport) treatment of hyperhidrosis. Of 191 unique articles identified, 23 were considered relevant (3 observational studies, 10 nonrandomized controlled trials, and 10 randomized controlled trials). These articles provided data on axillary, palmar, and forehead hyperhidrosis, compensatory hyperhidrosis of the back, Frey syndrome, and diabetic gustatory sweating. All studies reported that aboBoNT-A reduced sweating and no serious adverse events were observed. Patient satisfaction was high and improvements to quality of life were observed after aboBoNT-A treatment for axillary and palmar hyperhidrosis. The review was sponsored by Ipsen who manufacture Dysport.

Obed et al 2021[21]

Meta-Analysis of treatment and quality-of-life outcomes for hyperhidrosis. Including randomized controlled trials of botulinum toxin injections compared with placebo for patients with primary or secondary focal hyperhidrosis. Eight studies met the inclusion criteria (n=937). Overall, risk bias was mixed and mostly moderate. Botulinum toxin injections showed reduced risk in comparison with placebo for the gravimetric quantitative sweat reduction of > 50 %from baseline (risk difference: 0.63, 95% CI 0.51 to 0.74). Additionally, improvements were seen for disease severity and quality-of-life assessments evaluated by Hyperhidrosis Disease Severity Score reduction of ≥2 points (risk difference: 0.56, 95% CI 0.42 to 0.69) and mean change in Dermatology Life Quality Index (mean difference: -5.55,95% CI-7.11 to-3.98). The acquired data were insufficient to assess for long-term outcomes and limited to an eight-week follow-up period. Further studies assessing BTX in comparison with first-line treatments for hyperhidrosis are warranted.

Summary of safety data:

EMEA

Scientific Conclusions and Grounds for Amendment of the Summary of Product Characteristics for Botox Presented by the EMEA 200312

The safety profile of this treatment was remarkably benign, with no serious treatment related adverse event seen among over 440 exposures to treatment, no statistically significant difference in overall adverse events compared with placebo and no change of adverse event profile with repeat exposures. Therefore, the benefit-risk profile of Botox in the proposed indication can be considered as favourable.

The safety database to support repeat intermittent use of Botox and the suitability of the safety parameters recorded in the pivotal study is small, when taken together with the supportive data it is considered to be adequate since the dose used is well in the range of the established indications and the safety profile seen in the pivotal trial does not suggest that in primary hyperhidrosis there are any specific side-effects.

Summary of Product Characteristics[2,3]

Special warnings and precautions for use

- Contraindicated if known hypersensitivity to botulinum toxin type A or to any of the product excipients
  Contraindicated if presence of infection at the proposed injection site(s).
- Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.
    - The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.
- Patients treated with therapeutic doses may also experience exaggerated muscle weakness.
- Dysphagia has also been reported following injection to sites other than the cervical musculature.
- Use with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders.
- Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions.
- As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.
- There have been reports of adverse events following administration of BOTOX involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.
- New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to botulinum toxin injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.
- Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of treatment by inactivating the biological activity of the toxin. Results from some studies suggest that injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

  Undesirable effects

  Primary hyperhidrosis of the axillae

System Organ Class	Preferred Term	Frequency
Nervous system disorders	Headache, paraesthesia	Common
Vascular disorders	Hot flushes	Common
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis (non axillary sweating), abnormal skin odour, pruritus, subcutaneous nodule, alopecia	Common
Musculoskeletal and connective tissue disorders	Pain in extremity	Common
	Muscular weakness, myalgia, arthropathy	Uncommon
General disorders and administration site conditions	Injection site pain	Very common
	Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia, injection site reactions	Common

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000)

Increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

FDA[22]

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in paediatric patients under age 18.

Strengths and limitations of the evidence:

Strengths

- There is moderate-quality evidence of a large statistically significant effect of botulinum toxin on axillary hyperhidrosis symptoms, compared with placebo.
- The FDA and EMEA have approved the use of botulinum toxin for axillary hyperhidrosis.
- Few serious or severe adverse effects have been seen across the studies.

- Botulinum toxin has been used for a range of indications over many decades.

Limitations

- Lack of robust evidence available – problems with the small scale of trials and prevalence of bias.
- Studies use different botulinum toxin products, and some do not stipulate which product was used.
- There is a lack of quality evidence for the efficacy and safety of botulinum toxin for hyperhidrosis in areas other than the axilla.
- Further studies are required comparing botulinum toxin with other treatments for hyperhidrosis.
- A well-conducted, adequately powered, RCT of botulinum toxin (with anaesthesia) compared with iontophoresis for palmar hyperhidrosis is needed.
- Safety and effectiveness not established in patients under the age of 18.

Summary of evidence on cost effectiveness:

First line treatment for axillae, palmar and plantar hyperhidrosis after identifiable triggers have been modified:

Aluminium chloride 20% solution (roll on antiperspirant)

- Driclor = £4 for 20ml
- Anhydrol Forte = £2.50 for 60ml

Prices taken from drug tariff online Oct 2021

Apply once daily at night, adapt frequency to symptoms.

Annual cost highly unpredictable due to variations between patients in site and frequency of use.

Iontophoresis for axillae, palmar, plantar and facial hyperhidrosis:[23]

With or without glycopyrrolate powder for solution for iontophoresis (drug tariff = £327 for 3g)

Treatments can be needed up to weekly in order to control symptoms.

Machines are available for patients to purchase and use at home.

Oral antimuscarinics for generalised hyperhidrosis:

- Glycopyrronium tablets (unlicensed indication) are prohibitively expensive.
- Propantheline bromide (licensed for hyperhidrosis) 15mg tablets = £21 for 112
    - 15 mg 3 times a day, dose to be taken at least one hour before food and 30 mg, dose to be taken at bedtime; maximum 120 mg per day.
    - Non formulary in Lancashire and South Cumbria
- Oxybutynin (unlicensed for hyperhidrosis) 2.5mg and 5mg tablets = £1.50 for 56
    - RCTs use the standard release formualtions8
    - Dose variable depending on symptom and tolerability
    - 2.5mg - 20mg daily = £0.75 - £6 per month

Botulinum toxin type A:

Prevalence unquantified and data for Botox prescribing is diffuse across the indications.

Prescribing and risk management issues:

MHRA alert October 2007[24]

Botulinum toxin products: rare but serious risks
Products that contain botulinum toxin are associated with the risk of serious adverse reactions

due to distant spread of toxin. Spread reactions including muscle weakness, dysphagia, and aspiration - these 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.

Summary of product characteristics[2]
The recommended dosages and frequencies of administration of BOTOX should not be exceeded due to the potential for overdose, exaggerated muscle weakness, distant spread of toxin and the formation of neutralising antibodies. Initial dosing in treatment naïve patients should begin with the lowest recommended dose for the specific indication.

Prescribers and patients should be aware that side effects can occur despite previous injections being well tolerated. Caution should therefore be exercised on the occasion of each administration.

Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Availability and frequency of availability of treatment varies across Trusts and geographical regions. Patient information provided needs standardising.
Financial implications of the intervention:
Cost of administration and anaesthesia not incorporated into this review.
Service Impact Issues Identified:
Impact on dermatology services needs considering in light of current pressures.
Equality and Inclusion Issues Identified:
None identified
Cross Border Issues Identified:
The **Pan Mersey APC** recommends no more than TWO TREATMENT SESSIONS per YEAR of Botulinum Toxin Type A Injection by specialists for the treatment of severe axillary hyperhidrosis that has not responded to treatment with topical antiperspirants or other antihidrotic treatment, as

a potential alternative to surgery (RAG rated red).[25]

The **Greater Manchester Medicines Management Group** (GMMMG) recommends the use of Botulinum toxin for the following forms of hyperhidrosis, with specific initiation and continuation criteria for each condition:[26]

- Severe primary hyperhidrosis of the axillae
- Severe primary palmar or plantar hyperhidrosis
- Severe primary craniofacial hyperhidrosis
- Frey's syndrome

The Greater Manchester Combined Authority policy statement on hyperhidrosis recommends the use of Botox in line with GMMMG guidance.[27]

Legal Issues Identified:

None identified

Media/ Public Interest:

None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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