Hyperhidrosis treatment with Botulinum Toxin for Axillary Hyperhidrosis

Policy

In accordance with the licensing, treatment with Botulinum Toxin A will only be funded for the management of **severe** (HDSS score of 3 or 4) **axillary hyperhidrosis**, provided first-line treatment (topical therapy) and/or iontophoresis have failed or are contraindicated.

These polices have been approved by the eight Clinical Commissioning Groups in North West London (NHS Brent CCG, NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith and Fulham CCG, NHS Harrow CCG, NHS Hillingdon CCG, NHS Hounslow CCG and NHS West London CCG).

Background

Hyperhidrosis (ICD-10 Code: R61) refers to excessive/enhanced sweating beyond that which is required to return body temperature to normal[1]. It can be generalised or focal, primary or secondary. Primary focal hyperhidrosis is the most common type [2], is idiopathic, and develops in previously healthy people. It typically affects the axillae, palms, soles of feet (plantar) and face (craniofacial) [2-5], areas principally involved in emotional sweating [2]. It is thought to affect >2.5% of the population[5]. It usually has its onset in childhood or adolescence[4], but can occur at any age. Palmar and plantar hyperhidrosis may be present at birth.

Secondary generalised hyperhidrosis involves the entire body, and is due to an underlying condition, most often an infectious, endocrine or neurological disorder; or may be simply drug-induced[4]. It develops due to dysfunction of the central or peripheral nervous system[2]. Secondary focal hyperhidrosis involves specific areas of the body, but is also caused by an underlying condition (e.g. neurological disorders, intrathoracic neoplasms, or compensatory hyperhidrosis).

The **Hyperhidrosis Disease Severity Scale** (HDSS) (http://www.sweathelp.org/pdf/HDSS.pdf) provides a qualitative measure of the severity of the patient's condition, and allows tailoring of treatment[6]. A score of 1 or 2 indicates mild or moderate hyperhidrosis. A score of 3 or 4 indicates severe hyperhidrosis. A one- point improvement in HDSS score post-treatment has been associated with a 50% reduction in sweat production and a 2-point improvement with an 80% reduction[6].

Recommended treatment approaches

Type of hyperhidrosis	First-line therapy	Second-line therapy (options)	Comment
Mild axillary, palmar, and plantar hyperhidrosis (HDSS score of 2)	• Topical treatments - aluminium chloride-based (AC) & other • Consider treating any underlying anxiety, which may be an exacerbating factor	• Iontophoresis • Botulinum toxin A (BTX-A)**	**unlicensed indication
Severe axillary, palmar, and plantar hyperhidrosis (HDSS score of 3 or 4)	• Topical treatments – AC & other • Consider treating any underlying anxiety, which may be an exacerbating factor	• Iontophoresis^ • **BTX-A** *^ • Local surgery (axillary) and ETS should only be considered after failure of all other treatment options	• * **licensed indication only for severe axillary hyperhidrosis**, but evidence exists for benefit of treatment for palmar and plantar hyperhidrosis • ^Canadian expert statements suggest considering these first-line
Craniofacial hyperhidrosis	• Topical treatments – AC & other • Consider treating any underlying anxiety, which may be an exacerbating factor	• Oral anti-cholinergic medications^ • BTX-A** ^	• **unlicensed indication • ^Canadian expert statements suggest considering these first-line
Generalised hyperhidrosis	• Treatment of underlying condition	• Oral anti-cholinergic medications	BTX-A not indicated
§ based on Guidelines for the primary care treatment and referral of focal hyperhidrosis (9), an evidence-based review (22), US and Canadian expert consensus statements (6, 8), and internet-based guidelines (23)			

Evidence base for treatment

Secondary hyperhidrosis

Management of **secondary generalised or focal hyperhidrosis** should be directed at looking for an underlying cause, and managing that appropriately[7]. Oral anti- cholinergics may also be used[8,9].

Primary focal hyperhidrosis

Various medical, surgical and electrical therapies exist for **primary focal hyperhidrosis**. However, for many, the efficacy is short-term or they are associated with unacceptable side effects[1]. A step-by-step approach is recommended for treatment. Local treatment options with few and minor side effects should be tried first[2,7,9]

First-line treatment (primary care)

- 20% aluminium chloride (AC) hexahydrate in alcohol solution e.g. aluminium salts in OTC anti-perspirants[2,3,7,9]
- Consider treating any underlying anxiety, which may be an exacerbating factor[7]
- If that fails – refer to dermatologist/ secondary care[9]

Secondary care treatment options

- Modified topical therapy:
  - emollients, topical corticosteroids, different strengths of aluminium salts (up to 50%), and topical glutaraldehyde or formaldehyde
  - topical glycopyrrolate (an antimuscarinic agent) can be prepared by special order manufacturers, and may be useful for primary craniofacial hyperhidrosis
  - efficacy and tolerability vary widely[10].

- Iontophoresis [2,3,7]
  - The sites of hyperhidrosis (hands, feet) are immersed in warm water (or a wet contact pad may be applied e.g. for the axillae) through which a weak electric current is passed
  - In more severe cases of hyperhidrosis affecting plantar and palmar areas, glycopyrronium bromide (an antimuscarinic agent) as a 0.05% solution can be added to the water [11], but adverse effects are common
  - Some people seem to gain considerable symptom relief. Most report an improvement after 6-10 sessions. Maintenance treatment is usually required at 1-4-week intervals.

Background (continued)

- Botulinum toxin A (BTX-A) (*Botox*®)
  - BTX-A blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intradermally, BTX-A produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating [12]
  - BTX-A is the best-studied treatment to date for focal hyperhidrosis, and local intradermal injections of BTX-A have been used since 1996 as a minimally invasive treatment for focal hyperhidrosis, with numerous studies documenting safety, efficacy, effectiveness, and extremely high levels of patient satisfaction, especially when other treatment options have proven ineffective
  - It is only **licensed** for the treatment of **severe axillary hyperhidrosis** that is inadequately managed by /**unresponsive** to topical agents [11,13,14]
  - *Effectiveness*: BTX-A effectively treats axillary hyperhidrosis [1,5,10,13-16]. In a 52-week, multicentre, double-blind study comparing BTX-A with placebo for treatment of severe primary axillary hyperhidrosis, published in 2007 (15), a 2- point improvement on the 4-point HDSS was reported in 75% of subjects in the 75- U and 50-U BTX-A groups and in 25% of the placebo group (p <0.001). In a single- centre, randomised, parallel, open-label, 12-week study[10] which compared the efficacy and safety of BTX-A with 20% AC for the treatment of primary focal axillary hyperhidrosis, 92% of subjects in the BTX-A group (n=25) achieved treatment response at week 4, compared with 33% of the subjects in the AC group
  - *Duration of effectiveness*: effectiveness is of limited duration, and repetitive treatments are necessary. In a 52-week, multicentre, double-blind study comparing BTX-A with placebo for treatment of severe primary axillary hyperhidrosis, published in 2007 (15), the median duration of effect was 197 days, 205 days, and 96 days in the 75-U BTX-A, 50-U BTX-A, and placebo groups, respectively[15]. An audit by Moffat et al in 2008 [17,] which aimed to determine treatment durability by active follow-up of patients over 24 months, suggests that patients experience a gradual return of symptoms between 6 and 24 months. A minority do not require re-treatment at this time[17]
  - *Other anatomic sites*: while BTX-A is also used routinely off-label for other anatomic sites[5], the procedure may be more difficult and painful at these sites [7]. It has been shown to be effective for treatment of primary *palmar* hyperhidrosis [1,7,16,18]. It may also be helpful for *gustatory sweating*[16], and *plantar*, and *craniofacial* hyperhidrosis[7]. Other indications (forehead sweating, truncal sweating) are only anecdotally reported [16]
  - *Paediatric patients*: while the product information states that safety and effectiveness of BTX-A have not been established for the treatment of hyperhidrosis in paediatric patients under age 18[12], there is some evidence to suggest the efficacy of BTX-A in primary palmar hyperhidrosis in children [7,19], with a mean duration of effect of 7 months in one study of nine patients[19]
  - *Safety*: BTX-A is reported to be well-tolerated [5,10,13,16] including in children [19]. The most frequently reported adverse events (3-10% of adult patients) following injection of *Botox*® in double-blind studies included injection site pain and haemorrhage, non-axillary sweating (compensatory sweating), infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety [12]
  - *Patient satisfaction*: BTX-A is reported to produce high levels of patient satisfaction [5,10,15,16]
  - *Cost-effectiveness*: the cost-effectiveness of BTX-A compared to other treatments has yet to be established [20,21]
- Surgery [2,3,7]
  - Local surgery (axillary; resection of sweat glands) and endoscopic thoracic sympathectomy (ETS) should only be considered if other treatment options have failed or have not been tolerated[6;] complications may be permanent and significant
  - ETS involves video-assisted laparoscopic division of the sympathetic chain over the neck of the ribs under general anaesthesia, usually by a vascular surgeon. It is mainly indicated as a last resort for severe palmar, axillary, and sometimes craniofacial hyperhidrosis. Lumbar sympathectomy is not used for plantar hyperhidrosis because of the risk of sexual dysfunction.
- Oral medication
  - Oral anti-muscarinics, such as glycopyrronium bromide (which needs to be imported[7] and oxybutinin, may be used, but their use is limited by adverse effects; other options include: clonidine, diltiazem, benzodiazepines
  - Systemic therapies are mainly used in treatment of generalised hyperhidrosis

References

Patient information

http://www.bad.org.uk/site/829/default.aspx

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