Botulinum toxin A for the treatment of primary hyperhidrosis

Background

Condition

Sweating is a process that naturally allows the body’s temperature to be regulated and maintained as well as providing grip in the hands and feet. It is controlled by the autonomic nervous system (1), (2). Eccrine and apocrine glands are the two types that produce sweat in response to temperature changes or emotional stress (3). Eccrine glands cover most of the body, including the palms and soles and apocrine glands develop in areas abundant in hair follicles such as the scalp, armpits (axillae) and groin.

Hyperhidrosis can be defined as a disorder of excessive sweating out of proportion with thermoregulatory requirements, usually in response to thermal or emotional stimuli, or physical activity (4). As there is no standardised definition of ‘excessive sweating’, clinicians base their diagnoses in part on measures to estimate how hyperhidrosis affects a patient’s quality of life.

Hyperhidrosis can cause wetness and staining of clothes, sweaty hands, inability to grip objects and odour. This can lead to worry about changing clothes and may lead individuals to avoid making friends, interacting with other people, work or leisure, which in turn, can lead to depression, loneliness and lack of confidence (1).

Types of hyperhidrosis

Idiopathic (primary) hyperhidrosis has no known cause and affects hands (palmar), feet (plantar) and armpits (axillary) (1). There is some evidence for a genetic abnormality as affected individuals have similarly affected first -degree relatives (5;6).

Generalized (secondary) hyperhidrosis can occur as a result of endocrine abnormalities, medications, malignancies, infections or neurological diseases and can affect the face, scalp, back, neck, groin, legs and buttocks on both sides of the body equally (3;5;7).

Epidemiology

Hyperhidrosis affects both males and females aged between 18 to 54 years and can begin in childhood or adolescence (8). If idiopathic hyperhidrosis occurs in childhood, the areas that are mostly affected are the palms, whereas axillary hyperhidrosis is more common in adolescents (1).

Prevalence of hyperhidrosis ranges approximately from 2% to 4% worldwide (9;10). In the United States it is estimated by one study that the prevalence is 2.9%, with 50% of this group having axillary hyperhidrosis. In the United Kingdom it is estimated that 1% of the population is affected by this condition (7).
Most individuals with severe hyperhidrosis have palmo-plantar hyperhidrosis, 15% to 20% have combined palmar-axillary hyperhidrosis, 5% to 10% have isolated axillary hyperhidrosis and less than 5% have craniofacial hyperhidrosis (11).

Interventions

Interventions to treat hyperhidrosis can be divided into five categories: topical pharmacological agents, iontophoresis, systemic agents, botulinum toxin injections and surgical techniques.

**Topical pharmacological agents**: used as first line treatment, aluminium chloride is applied to axillae, palms and soles and is thought to induce changes to eccrine glands with repeated use and a reversible blockage of sweat ducts (1;12). Although commonly used, such treatments can be irritating to the skin and can stain clothing (1). Topical anticholinergic drugs can also be used for idiopathic facial sweating. Topical glycopyrrolate may be used for axillary and palmar hyperhidrosis (1).

**Iontophoresis**: areas of the body that are affected are immersed in water through which a very weak current is passed (13). This technique is effective if hyperhidrosis affects palmar and plantar regions, but can be used to treat axillary areas, although treatment in axillary areas may not be effective (14). Treatment needs to be repeated regularly for the effect to be sustained (4). Treatment can be effective but can be time-consuming and can lead to skin discomfort, skin redness and blister formation. Variations of this technique include dissolving drugs in tap water such as glycopyrrolate (15) or botulinum toxin (16). Dry use of current without water has also been used (1).

**Systemic agents**: can be used to treat axillary, palmar and plantar hyperhidrosis.

Diazepam (Valium) can be used if sweating is related to anxiety. Fluoxetine (Prozac) has also been used in addition to psychiatric care as a therapeutic agent for social anxiety disorder (14).

Systemic anticholinergic drugs such as propantheline, glycopyrrolate, oxybutynin and benztropine are effective because they act on acetylcholine, which is the pre-glandular neurotransmitter for sweat secretion (14). Anticholinergics can cause adverse effects including xerostomia, mydriasis, cycloplegia and bowel and bladder dysfunction. High doses are usually required to inhibit sweating but can lead to unpleasant and intolerable effects including dry mouth, blurred vision, urinary retention, constipation and tachycardia (4).

Non-steroidal anti-inflammatory agents, calcium channel blockers, sedatives and tranquilizers have also shown to be effective in treating palmar and plantar hyperhidrosis. Reports of individuals showed benefit from the use of clonidine (antidepressant) but larger trials are lacking and all systemic agents carry with them risk of side effects (14;17).

**Surgery**: surgical treatments are available for patients with hyperhidrosis who fail to respond to other treatments. These procedures include:

**Tissue excision**: involves excision of axillary sweat glands, is usually permanent, and has 50%-90% effectiveness. Adverse effects include infection, bleeding, delayed healing, flap necrosis, hypertrophic and constrictive scarring.
Retrodermal curettage: involves removal or destruction of axillary sweat glands, or disruption of the neurovascular supply to the glands, usually with 90% efficacy. Adverse effects include infection, superficial skin erosions, paraesthesiae, ecchymoses, haematomas, seromas, fibrotic bands, and skin retractions.

Laser ablation: performed in the UK since 2009, this procedure involves destruction of sweat glands destroyed by laser (7). This procedure is effective in patients with axillary hyperhidrosis. It can cause infection, and takes two weeks to recover.

Endoscopic thoracic sympathectomy: involves destruction of sympathetic ganglia that cause sweat glands to produce excessive sweat via excision or clamping. It is effective for axillary, palmar and facial hyperhidrosis, with moderate risk of recurrence. It can cause compensatory hyperhidrosis and patient dissatisfaction, gustatory sweating, phantom sweating, Horner syndrome, wound infection, neuropathic complications, pneumothorax and cardiac arrest (4;7).

Botulinum toxin: Botulinum toxin type A (Botox, Dysport) is a potent protein produced by the Clostridium botulinum bacterium. Originally licensed in the European Union in 1994 to treat muscle dystonias, botulinum toxin has also been licensed since 24th September 2012 to treat axillary hyperhidrosis (1;18;19). Subdermal injection of botulinum toxin reduces sweating, which is mediated through blockage of presynaptic acetylcholine release from cholinergic fibres of the sympathetic nervous system (18).

Objective

To carry out a rapid evidence review summarising the effects and effectiveness of local Botulinum Toxin type A (Botox A) injections in people with primary idiopathic hyperhidrosis of the axillar, plantar, palmar and craniofacial body regions. No economic evaluation will be done.

Methods

Criteria for selecting studies

Types of studies

English language summaries of research evidence were included in the first instance such as: systematic reviews; health technology assessments; evidence based clinical guidelines; rapid evidence reviews; and evidence based commissioning policies. Where these were absent or of low methodological quality, randomised controlled trials (RCTs) were included.

Types of participants

Adults who have been diagnosed with primary idiopathic hyperhidrosis of the axillar, plantar, palmar and craniofacial body regions.

Types of interventions

Botox A injections.

Types of outcome measures
Primary: Sweat production.

Secondary: Improvement in chronic cutaneous conditions such as skin maceration, dermatitis, fungal infections and secondary microbial conditions; quality of life (QOL); adverse effects.

**Exclusion criteria**

Secondary hyperhidrosis, Frey’s syndrome, Botulinum Toxin type B therapy.

**Search methods for identification of studies**

The following sources were searched:

Bibliographic databases: Cochrane Library 2013 Issue 1 (all databases); MEDLINE (Ovid) 1946 - Jan week 4 2013; EMBASE (Ovid) 1980 - 2013 week 4 and CRD Databases (DARE and HTA Database) up to Jan 2013. Index and text words were used which encompassed the intervention (Botox A) and the population (primary hyperhidrosis). Filters for systematic reviews and RCTs were applied to the searches of MEDLINE and EMBASE.

Internet sites: TRIP Database up to Jan 2013; NHS Evidence (Jan 2013); NICE and web sites of commissioning organisations.

Citation checking: the reference lists of existing reviews were examined for relevant studies.

No language or date restrictions were applied to the searches. Search strategies for MEDLINE, EMBASE and the Cochrane Library are presented in Appendix 1.

**Study selection**

Decisions on which papers to include were taken by two reviewers working independently. Uncertainties were resolved with the other reviewer.

**Data collection**

Data were extracted by two reviewers working independently and put into the Summary of Findings tables. Uncertainties were resolved with the other reviewer. The Summary of Findings tables are presented in Appendices 4 and 5.

**Critical appraisal and quality assessment**

Systematic reviews were critically appraised using the AMSTAR checklist. The PRISMA checklist was used to assess completeness of reporting.

RCTs were critically appraised using the SIGN checklist. The CONSORT statement was used to assess completeness of reporting.

The Oxford Centre for Evidence Based Medicine grading system was used to rate the level of evidence for each included report of studies (refer to Appendix 3).

**Results**
Results of searches

143 references were identified. After excluding 129 references which were either duplicate references (57), not relevant or not the correct study design (72), 14 full text papers were obtained. After further exclusion of seven papers on the basis of study design, seven papers met the inclusion criteria as follows: one evidence review (20); one systematic review of safety of the intervention (21); four trials (18;22-24) and one on-going Cochrane review (1). All trials related to primary axillary hyperhidrosis. The flow diagram of results from the search strategy are presented in Appendix 2.

Findings

Effectiveness

Systematic reviews

No systematic reviews of effectiveness were identified.

One evidence based review was identified which, although lacking a quantitative summary of primary studies, adopts some systematic review principles so as such represents a reasonable summary of the research to date (20). It scored medium AMSTAR and PRISMA assessments and the findings are summarised in Appendix 4. The methodology is reported in a companion paper on Botox A for the treatment of spasticity (25).

The Naumann review included five trials which were relevant to hyperhidrosis. Two class I trials related to axillary hyperhidrosis (26;27); and two class II trials (28;29) and one class III trial (30) to palmar hyperhidrosis (classification of studies was based on the American Academy of Neurology). All studies compared Botox A injections of various preparations and brands with placebo and measured sweat production as the primary outcome. The detailed summary of the findings of the Class I and II trials are presented in Appendix 5. No studies were included for plantar or craniofacial hyperhidrosis.

The included trials relating to axillary hyperhidrosis were of reasonable methodological quality and the results appear to be reliable. Those relating to palmar hyperhidrosis are relatively small and of lower methodological quality.

In summary, the evidence from this review indicates that Botox A is effective and safe for axillary hyperhidrosis. However, it appears to be of indeterminate or of limited effect for palmar hyperhidrosis. It should be borne in mind that many of the included trials are sponsored by the drug manufacturers and the study investigators deliver Botox therapy.

Trials

A search was conducted for trials which were not included in the Naumann review. Reports of four trials were identified all of which related to axillary hyperhidrosis (18;22-24) with one specifically related to quality of life measures (31).

The largest trial (22) (n =322) assessed the efficacy and safety of two doses of Botox A injections (75 U and 50 U). It found that Botox A produced significant reductions in the severity of primary axillary...
hyperhidrosis, as evaluated by subject assessments of efficacy (Hyperhidrosis Disease Severity Scale (HDSS)), physician assessments of efficacy (gravimetry), and subject reported measures (Dermatology Life Quality Index (DLQI)). It appeared that 50 U of Botox A was a reasonable starting dose for treating most subjects with axillary hyperhidrosis. The data also suggested that one or two treatments were typically sufficient to manage a subject’s hyperhidrosis through one year. Furthermore, Botox A therapy produced meaningful clinical and health related quality of life (HRQOL) benefits in subjects whose condition affected their daily activities. Botox A therapy was well tolerated even after repeated administration and had a safety profile similar to that of placebo. However, the trial had important methodological limitations which should be borne in mind. The method of randomization, sequence generation and concealment of the sequence from the investigators (allocation concealment) were not reported. All of these are important safeguards against bias.

As smaller trial (n=18) compared Botox type A injections with placebo (23). It found the active treatment group had an average reduction in sweat production of 91.6% at two weeks (from 5.03 ml/min/m² to 0.42 ml/min/m², P < .05). Average sweat reduction over five months was 88.2%. At the end of the study only one of 12 Botox A treated patients had returned to baseline sweat production. This trial also had significant methodological weaknesses. For instance, there were more participants in the treatment group (n=12) than the placebo group (n=6). Baseline characteristics of the participants were not fully reported therefore it is difficult to ascertain whether both groups were the same at the beginning of the study and no information regarding the method of randomization was reported.

Another trial conducted a within group comparison of Botox A with placebo in 13 participants (24). Three weeks after treatment, the mean difference in ninhydrin staining between botox A treated and placebo-treated axillae was -34.5% (P < 0.001), after eight weeks -36.9% (P < 0.001) and after 13 weeks -28.4% (P < 0.001). Subjective rating of sweat production was evaluated on a visual analogue scale (0, no sweating, to 100, most severe sweating). Three weeks after treatment the difference between the botox A treated and placebo-treated axillae was -56.5% (P < 0.001), after 8 weeks -67.4% (P < 0.001) and after 13 weeks -62.5% (P < 0.001). No serious side effects were observed. The trial did not report measures to safeguard against bias. For instance, information concerning allocation concealment, intention-to-treat analysis or blinding. Also, the characteristics of the study population were not given therefore it is not possible to tell whether participants were the same at the beginning of the trial.

The trial which reported quality of life measures for severe axillary hyperhidrosis compared Botox A with placebo in 320 participants (31). At baseline, 151 of 242 (62.3%) patients in the Botox A group and 40 of 78 (52%) patients in the placebo group reported spending only 15 minutes or less per day treating their hyperhidrosis. Following treatment, this percentage was significantly greater in the Botox A group than the placebo group at every follow-up visit (P ≤ 0.001). In the Botox A group, the percentage of patients spending less than 15 minutes per day treating their hyperhidrosis increased to 82.5% at week one, remained above 85% through week 12, and was 78.8% at week 16 post-treatment. There was no report of methods of blinding in this trial.
Safety / adverse effects

One systematic review was identified (21) which included three trials relevant to hyperhidrosis. It scored medium to low AMSTAR and PRISMA assessments. No quality assessment of the included studies was performed to assess risk of bias, neither was reporting of detailed characteristics of included studies, which means it is not possible to assess whether the included studies are relevant to the review question. Therefore, the validity and applicability of the results cannot be gauged. The findings of the systematic review are summarised in Appendix 4.

The review found no treatment related severe adverse events (as defined by original investigators).

Mild to moderate adverse events (as defined by original investigators) were significantly greater in the treated group compared with control (- 24.7% v 15.0%, p<0.001).

There was significantly greater frequency of reporting of focal weakness in the treatment group in patients with blepharospasm and cervical dystonia compared with controls (- 0.25, 95% CI 0.07-0.44). The two studies included for hyperhidrosis showed no difference between treatment and control.

There was no significant difference between treatment and control groups for pain, (0.01, 95% CI -0.02-0.03), headache (-0.09, 95% CI -0.22-0.05), back, neck pain or soreness (0.02 95% CI -0.07-0.03), ptosis (0.10 95% CI -0.02-0.22) or ‘other’ adverse events (0.00 95% CI -0.04-0.05).

Overall, the findings suggest that Botox A is safe and well tolerated however it is important to consider the methodological limitations mentioned previously.

Conclusions

Based on the largest and most methodologically robust trials, Botox type A injections appear to be effective for axillary hyperhidrosis. The evidence for effectiveness for palmar hyperhidrosis is unclear. No trials were identified for plantar and craniofacial hyperhidrosis.

All of the trials are subject to significant methodological limitations, the most important being lack of reporting about method of randomisation, allocation concealment and blinding. Also, most are sponsored by a drug company with some investigators declared having either a financial interest in the sponsor or practicing Botox.

Evidence from a systematic review and trials suggest Botox is safe and well tolerated.
Appendix 1. Search strategies.

Systematic reviews

Ovid MEDLINE(R) 1946 to January Week 4 2013

1 Sweating/ (5365)
2 exp Hyperhidrosis/ (2707)
3 (perspir* or sweat*).ti,ab. (15734)
4 hyperhidrosis.ti,ab. (2181)
5 (excessive or idiopathic).ti,ab. (143388)
6 1 or 3 (18132)
7 5 and 6 (810)
8 2 or 4 (3301)
9 7 or 8 (3854)
10 exp Botulinum Toxins/ (10958)
11 botox.ti,ab. (1106)
12 10 or 11 (11067)
13 9 and 12 (484)
14 limit 13 to "reviews (maximizes specificity)" (7)

Ovid Embase 1980 to 2013 Week 04

1 Sweating/ (14862)
2 exp Hyperhidrosis/ (5040)
3 (perspir* or sweat*).ti,ab. (20466)
4 hyperhidrosis.ti,ab. (2855)
5 (excessive or idiopathic).ti,ab. (188917)
6 1 or 3 (29676)
7 5 and 6 (1297)
8 2 or 4 (5515)
9 7 or 8 (6434)
10 botox.ti,ab. (1835)
11 botulinum toxin/ (10244)
12 10 or 11 (11750)
13 9 and 12 (441)
14 limit 13 to "reviews (maximizes specificity)" (5)

Cochrane Library 2013 Issue 1 (systematic reviews and trials)

#1 MeSH descriptor: [Sweating] explode all trees
#2 MeSH descriptor: [Hyperhidrosis] explode all trees
#3 (perspir* or sweat*)
#4 hyperhidrosis
#5 excessive
#6 #1 or #3
#7 #5 and #6
#8 #2 or #4
#9 #7 or #8
#10 "botulinum toxin* or botox"
Trials

**Ovid MEDLINE(R) 1946 to January Week 4 2013**

1. Sweating/ (5365)
2. exp Hyperhidrosis/ (2707)
3. (perspir* or sweat*).ti,ab. (15734)
4. hyperhidrosis.ti,ab. (2181)
5. (excessive or idiopathic).ti,ab. (143388)
6. 1 or 3 (18132)
7. 5 and 6 (810)
8. 2 or 4 (3301)
9. 7 or 8 (3854)
10. exp Botulinum Toxins/ (10958)
11. botox.ti,ab. (1106)
12. 10 or 11 (11067)
13. 9 and 12 (484)
14. limit 13 to "therapy (maximizes specificity)" (36)

**Ovid Embase 1980 to 2013 Week 04**

1. Sweating/ (14862)
2. exp Hyperhidrosis/ (5040)
3. (perspir* or sweat*).ti,ab. (20466)
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11. botulinum toxin/ (10244)
12. 10 or 11 (11750)
13. 9 and 12 (441)
14. limit 13 to "therapy (maximizes specificity)" (30)
Appendix 2. Flow diagram of results from search strategy.

Titles and abstracts identified and screened $n = 143$

- Excluded $n = 129$
- Duplicates $n = 57$
- Not relevant/study design $n = 72$

Full copies retrieved and assessed for eligibility $n = 14$

- Excluded $n = 7$ (Study design)

Publications meeting inclusion criteria $n =$
- ERs = 1, SRs = 1, RCTs = 4,
- ongoing review = 1
Appendix 3. Oxford Centre for Evidence Based Medicine Levels of Evidence Table.

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1)</th>
<th>Step 2 (Level 2)</th>
<th>Step 3 (Level 3)</th>
<th>Step 4 (Level 4)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances</td>
<td>Systematic review of cross sectional studies with consistently applied reference standards and setting</td>
<td>Non-consensus studies, or studies without consistently applied reference standards</td>
<td>Case-series**</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate?</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and setting</td>
<td>Individual cross sectional studies with consistently applied reference standard and setting</td>
<td>Non-consensus studies, or studies without consistently applied reference standards</td>
<td>Case-control studies, or “poor or non-independent reference standard”**</td>
<td>N/A</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy?</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort studies</td>
<td>N/A</td>
</tr>
<tr>
<td>Does the intervention help? (treatment benefit)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>N/A</td>
</tr>
<tr>
<td>What are the COMMON harms? (treatment harms)</td>
<td>Systematic review of randomized trials, systematic review of historical and observational study with dramatic effect</td>
<td>Individual randomized trial or (prevalently) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm, (not long term harms the duration of follow-up must be sufficient)**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>N/A</td>
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<tr>
<td>What are the RARE harms? (treatment harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>N/A</td>
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<tr>
<td>Is this detection) test worthwhile? (screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>N/A</td>
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</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

* OCEBM Levels of Evidence Working Group • Andrew Henry, John Tjalma, Elie Akl, Chiara Guerriero, John Glasziou, Trish Greenhalgh, Karl Hemphill, Alessandro Liberati, Ivano Moschetti, Bob Phillips, Hazel Thornbury, Oliver Godlitt and Mary Hodgkinson
## Appendix 4. Summary of findings: Systematic reviews

<table>
<thead>
<tr>
<th>Citation</th>
<th>Number of studies</th>
<th>With or without meta-analysis</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome measures</th>
<th>Findings</th>
<th>Summary Finding</th>
<th>Quality</th>
<th>OCEBM Level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 Assessments: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence review) Naumann M et al.</td>
<td>Included: 5 trials. Axillary – 2 class I studies. Palmar – 2 Class II studies; 1 Class III study</td>
<td>Without m-a</td>
<td>Primary focal hyperhidrosis</td>
<td>Botulinum Toxin Type A injections of various preparations and brands</td>
<td>Placebo</td>
<td>Sweat production; hand muscle strength (palmar hyperhidrosis)</td>
<td>Quality of Life, Adverse events</td>
<td><strong>Axillary hyperhidrosis</strong></td>
<td>Effective, statistically significant BotTox for axillary hyperhidrosis <strong>Indeterminate or of limited effect</strong> BotTox for palmar hyperhidrosis</td>
<td>AMSTAR assessment – Medium (given its methodology) PRISMA assessment – 15 items not reported however since not a SR, many items are not relevant</td>
<td>A reasonable narrative summary of the research evidence having no quantitative summary of findings. No quality assessment of included studies done. Small no of included studies for hyperhidrosis Biases: drug company sponsored study, authors carry out BoTox injections, Some authors have financial interests in the manufacturer s of BoTox or received honoraria for speaking.</td>
</tr>
<tr>
<td>Citation</td>
<td>Number of studies</td>
<td>With or without meta-analysis</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome measures Primary</td>
<td>Outcome measure Secondary</td>
<td>Findings</td>
<td>Summary Finding</td>
<td>Quality</td>
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| 2004 Safety of botulinum toxin type A: a systematic review and meta-analysis. Naumann M et al. | Included: 36 trials in total; 3 relevant to hyperhidrosis (2 studies on axillary and 1 on palmar) | With meta | Dystonia/movement disorders; GI/urology; glandular (hyperhidrosis); pain/headache; spasticity; cerebral palsy; cosmetic | BOTOX (Allergan) preparation of botulinum toxin type A | Placebo or standard treatment | Adverse reactions and complications | No treatment related severe adverse events (AEs) (as defined by original investigators). Mild – moderate AEs (as defined by original investigators): significantly greater in the treated grp compared with control – 24.7% v 15.0%, p<0.001. Focal weakness: significantly greater frequency of reporting in the treatment group in patients with blepharospasm and cervical dystonia compared with controls -0.25, 95% CI 0.07-0.44. | Findings suggest that Botulinum Toxin type A is safe and well tolerated. | AMSTAR assessment – Medium - Low PRISMA assessment – 10 items not reported | Level 1 | None of the trials assessed long term safety (after 2 years). Study supported by Allergan Inc, Irvine, CA. No quality assessment of included studies performed to assess risk of bias; effect size may differ according to the methodologic quality of included trials with regard to...
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The 2 studies included for hyperhidrosis showed no difference between treatment and control.

Pain: no significant difference between treatment and control 0.01, 95% CI -0.02-0.03. The 1 included study for hyperhidrosis showed no difference between treatment and control.

Headache: not significantly different between treatment and control -0.09, 95% CI -0.22-0.05

Back, neck pain or soreness: not significantly different between the 2 grps 0.02, 95% CI -0.07-0.03

Ptosis: no significant difference between the 2 grps 0.10, 95% CI -0.02-0.22

‘Other’ AEs: No significant

randomisation, concealment of allocation, blinding & loss to follow-up)

No detailed characteristics of included studies reported which means it is not possible to assess whether the included studies are relevant to the review and therefore the validity & applicability of the results cannot be gauged.
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<th>Intervention</th>
<th>Comparator</th>
<th>Outcome measures Primary</th>
<th>Outcome measures Secondary</th>
<th>Findings</th>
<th>Summary Finding</th>
<th>Quality</th>
<th>OCEBM Level</th>
<th>Comments</th>
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<td>difference between the 2 grps.0.00 95% CI -0.04-0.05</td>
<td>Systemic AEs: no included studies reported the occurrence.</td>
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## Appendix 5. Summary of findings: Systematic reviews

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<tr>
<th>Citation / Reference</th>
<th>Type of study</th>
<th>No of participants</th>
<th>Population/patients/inclusion criteria</th>
<th>Setting</th>
<th>Interventions</th>
<th>Comparison</th>
<th>Outcomes: Benefit</th>
<th>Harms</th>
<th>Adverse effects</th>
<th>Cost-effectiveness</th>
<th>Effect estimates (95%CI) of outcome measures with comparison (control) risk</th>
<th>Summarized measures of effect</th>
<th>Quality of evidence (CEBM)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Naumann M. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis BMJ 2001;323:1-4</td>
<td>Randomized parallel group, double blind placebo controlled trial</td>
<td>320</td>
<td>Bilateral primary axillary hyperhidrosis.</td>
<td>European dermatology and neurology clinics</td>
<td>BoTox type A 50 U intradermal injections</td>
<td>Placebo</td>
<td>Incidence of responders in each treatment grp at wk 4 (≥ 50% reduction from baseline in axillary sweating as measured gravimetrically)</td>
<td>Percentage change from baseline and absolute sweat reduction.</td>
<td>Persistent responders at wk 16.</td>
<td>Size of sweat reduction area.</td>
<td>Global assessment of treatment satisfaction score.</td>
<td>Adverse events.</td>
<td>Responders at wk 4: 1.94% (227) v 36% (28). Difference in responder rates between treatment grps at all time points much greater than the 25% that was predefined as clinically important: wk 1:63% 95 CI 52%-74%. Wk 4: 55% CI 47%-69%. Wk 16: 61% CI 51%-72%. Absolute sweat reduction (mg): Reduced from baseline mean 215.8 (SD178.7) in treatment grp to53.7 (SD67.7) at wk 16 v from</td>
<td>Level 2</td>
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<td>Citation / Reference</td>
<td>Type of study</td>
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<td>Population/patients/inclusion criteria</td>
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<td>235.7 (SD213.8) to 190.5 (195.6) in placebo.</td>
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<td>BoTox.</td>
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<td>Persistent responders: Significantly higher percentage of patients in the botulinum toxin type A treated group were persistent treatment responders at the end of the study (77%; 182/235) compared with the placebo group (18%; 13/74) (P &lt; 0.001).</td>
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<td>Area of sweat production (cm²): from baseline mean 5.3 (SD7) to 0.2 (SD0.9) at wk 16 in treatment grp v from 6.0 (SD7) to 2.3 (SD5.5) in placebo.</td>
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<tr>
<td>Naumann MK et al.</td>
<td>RCT</td>
<td>320</td>
<td>Bilateral primary axillary hyperhidrosis</td>
<td>European dermatology and neurology clinics</td>
<td>Botulinum toxin type A (Botox, Allergan, Irvine, CA) 50 U per axilla by 10-15 intradermal injections – quality of life as assessed using</td>
<td>Placebo</td>
<td>Time spent treating hyperhidrosis</td>
<td>Changing clothing</td>
<td>Impact of hyperhidrosis on daily life</td>
<td>Impact on employment and productivity</td>
<td>Treating hyperhidrosis: At baseline, 151 of 242 (62.3%) patients in the BTX-A group and 40 of 78 (52%) patients in the placebo group reported spending only 15 min or less</td>
<td>Level 2</td>
<td>No report of blinding which is an important safeguard against bias. A drug company sponsored trial. Author performs BoTox.</td>
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Satisfaction score at 4 wks: significantly higher patient satisfaction reported in the treatment group than the placebo group (3.3 v 0.8, P < 0.001).

Adverse events: reported by 27 patients (11%) in the treatment group and four (5%) in the placebo group (P > 0.05).
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<th>Citation / Reference</th>
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<th>Harm</th>
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<tbody>
<tr>
<td>trial. Br J Derm</td>
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<td>Hyperhidrosis Impact Questionnaire (HHIQ) and Medical Outcomes Trust Short Form-12 Health Survey.</td>
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<td>Impact on general QOL</td>
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<td>per day treating their hyperhidrosis. Following treatment, this percentage was significantly greater in the BTX-A group than the placebo group at every follow-up visit (P ≤ 0.001). In the BTX-A group, the percentage of patients spending less than 15 min per day treating their hyperhidrosis increased to 82.5% at week 1, remained above 85% through week 12, and was 78.8% at week 16 post-treatment.</td>
<td>Changing clothing: Following treatment, the</td>
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percentage of patients changing clothing multiple times per day decreased in the BTX-A group and remained significantly lower than the percentage in the placebo group at all follow-up visits (P ≤ 0.001). For most of the follow-up period, fewer than 10% of patients in the BTX-A group had to change their clothing two or more times per day, significantly lower than the placebo group.

Impact on daily life: Following treatment, the limitations resulting from hyperhidrosis
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<td>were significantly less in the BTX-A group than in the placebo group at all follow-up visits (P ≤ 0.01). Employment and productivity: At baseline, less than one fifth of patients in either group considered themselves either somewhat satisfied or very satisfied with their ability to perform their current work activities. After treatment, the satisfaction rate in the BTX-A group increased markedly and was significantly higher than in the placebo</td>
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<tr>
<td>Lowe NJ et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52 wk randomized placebo controlled study of efficacy and safety, J Am</td>
<td>Double blind randomized placebo controlled trial</td>
<td>322</td>
<td>At least 18 yrs old with persistent bilateral primary axillary hyperhidrosis, A HDSS score of 3 or 4 and a baseline gravimetric measurement of spontaneous resting sweat production of at least 50 mg/axilla, measured over 5 mins at room temp.</td>
<td>Bot toxin type A.</td>
<td>BoNTA 75 U or BoNTA 50U or placebo</td>
<td>Primary: Proportion of treatment responders, defined as subjects who reported at least a 2-point improvement from baseline HDSS score 4 weeks after each of the first 2 treatment BoNTA treatment significantly reduced daily activity limitations at 4 weeks after injection. A 2-point improvement on the 4-point Hyperhidrosis Disease Severity Scale (HDSS) was</td>
<td>group at every follow-up visit (Ps ≤ 0.001). General QOL: There was a statistically significant improvement in QOL as measured by the SF-12 in both the PCS score and the MCS score in BTX-A-treated patients. Changes in the placebo group were not statistically significant.</td>
<td>Level 2</td>
<td>Method of randomization, sequence generation and concealment of the sequence from the investigators are not reported. All are important safeguards.</td>
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| Odderson IR. Long term quantitative benefits of botulinum toxin type A in the treatment of axillary hyperhidrosis. Derm Surg | Double blind placebo controlled study | 18 | Symptoms of hyperhidrosis | Patients recruited through advertisements and reports of the study in the media | 1 mil BoTox type A injection | Placebo | Sweating per surface area quantified monthly for 5 months. | The BoTox group had an average reduction in sweat production of 91.6% at 2 weeks (from 5.03 ml/min/m² to 0.42 ml/min/m², P<.001). | | | | | | Level 2 | There are more participants in the treatment grp (12) than the placebo grp (6). Baseline characteristics of the |}
<p>| Acad Derm 2007; 56:604-11 | | | | | | | sessions or who had a sustained response after their first treatment session and did not receive retreatment during the 52-week study. | | | | | | | Level 2 | | against bias. The study was funded by the drug manufacture r (Allergan). The main author owns stocks in Allergan as do some of the co-authors who are also Allergan employees. |</p>
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<tbody>
<tr>
<td>Heckmann M, Ceballos-Baumann AO et al Botulinum toxin A for axillary hyperhidrosis (excessive sweating). NEJM 2001, 344(7):488-493</td>
<td>Double-blinded placebo controlled RCT (within patient comparison)</td>
<td>158</td>
<td>Adults over age 18 years, male/female ratio, size of hyperhidrosis area, smoker/non-smoker, excessive axillary perspiration for more than one year, a rate of sweat production greater than 50mg per minute on at least two occasions (measured by gravimetric test), and failure of 10% or 20% solutions of topical aluminium chloride, applied daily before bed for four weeks to control sweating</td>
<td>Multicentre trial</td>
<td>Botulinum toxin type A, 100U, 200U</td>
<td>Placebo (saline) followed by 100U Botulinum toxin A</td>
<td>The study reported rate of sweat production as the primary outcome using a gravimetric test and also a questionnaire at week 28 on patient satisfaction after treatment. Temporary adverse effects in botA treated axillae included headache in 4 patients, muscle soreness of the At baseline the rate of sweat production was 192±136 mg/min. 2 weeks after the 1st injection, the mean rate of sweat production in boNTA treated axillae was 24±27mg/min compared to placebo (144±113mg/min, P&lt;0.001). In placebo axillae treated with 100U</td>
<td>5. Average reduction over 5 months was 86.2%. At the end of the study only 1 of 12 botox A treated patients had returned to baseline sweat production.</td>
<td>m</td>
<td>Level 2</td>
<td>Treatment with boNTA is effective, but need to consider limitations. The study was sponsored by Ipsen-Pharma (Germany) and supplied botA but did not design the study, did not collect or analyse or</td>
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<td>shoulder girdle in two patients, increased facial sweating in one, and axillary itching in one.</td>
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<td>boNT A after 2 weeks, the rate of sweat production was 32±39 mg/min, P&lt;0.001. At 24 weeks after injection of 100U boNT A in placebo arm, in 136 patients, the rate of sweat production was 65±64 mg/min, and 67±66 mg/min in axillae receiving 200U bot A. At 4 weeks, 118 patients rated tolerance of boNTA treatment as 'excellent', 25 rated treatment as 'good', and two patients rated treatment as 'fair'. 92 patients were completely satisfied with</td>
<td></td>
<td>boNT A after 2 weeks, the rate of sweat production was 32±39 mg/min, P&lt;0.001. At 24 weeks after injection of 100U boNT A in placebo arm, in 136 patients, the rate of sweat production was 65±64 mg/min, and 67±66 mg/min in axillae receiving 200U bot A. At 4 weeks, 118 patients rated tolerance of boNTA treatment as 'excellent', 25 rated treatment as 'good', and two patients rated treatment as 'fair'. 92 patients were completely satisfied with</td>
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<td>write up any part of the study. Lack of explanation of revealing code of allocation after two weeks of treatment. No explanation of missing patients at week 26 after treatment. No information on intention to treat.</td>
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<td>Schnider P et al. A randomized, double blind, placebo controlled trial of botulinum A toxin for severe axillary hyperhidrosis . Br J Derm 1999;</td>
<td>Double-blinded placebo controlled trial (within group comparison)</td>
<td>13</td>
<td>Severe axillary hyperhidrosis resistant to conventional treatment and socially handicapped by the condition.</td>
<td>Not stated</td>
<td>200 mouse units of botox A</td>
<td>placebo</td>
<td>Objective quantification of sweat production using digitised ninhydrin-stained sheets at 3,8 and 13 weeks.</td>
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<td>Three weeks after treatment, the mean difference in ninhydrin staining between botulinu</td>
<td>Level 2</td>
<td>A small within group comparison trial which does not report allocation concealment, intention to treat analysis or blinding. Also, the</td>
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<td>m-treated and placebo-treated axillae was - 34.5% (P &lt; 0.001), after 8 weeks - 36.9% (P &lt; 0.001) and after 13 weeks - 28.4% (P &lt; 0.001). Subjective rating of sweat production was evaluated on a visual analog scale (0, no sweating , to 100, most severe sweating ). Three weeks characteristics of the study population are not given therefore it is not possible to tell whether they were the same at baseline.</td>
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<td>after treatment the difference between the botulinum-treated and placebo-treated axillae was -56.5% (P &lt; 0.001), after 8 weeks -67.4% (P &lt; 0.001) and after 13 weeks -62.5% (P &lt; 0.001). No serious side-effects were observed.</td>
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Palmar hyperhidrosis
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<td>Schnider P et al. Double-blinded trial of Botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Brit J Derm 1997; 136:548-552</td>
<td>Double-blinded placebo controlled RCT (within patient comparison)</td>
<td>11</td>
<td>Patients resistant to any conventional treatments, socially handicapped by palmar hyperhidrosis. Adults of 18 years and over. Hyperhidrosis had been present since childhood</td>
<td>Single centre trial</td>
<td>Botulinum toxin type A, 120mU</td>
<td>Placebo (0.9% saline)</td>
<td>Objective measurement: ninhydrin sweat test on both palms before treatment and at 3, 8 and 13 weeks after boNTA injections, quantified by digital image analysis, amount of stained area. Subjective rating: intensity of sweat production using a VAS of 100 points for both left and right palm (0=no sweating, 100=most severe sweating)</td>
<td>At baseline no significant differences were found between boNTA treatment and placebo for both objective and subjective ratings (1%, P=0.91). Objective rating: at 3 weeks after initial treatment, the mean reduction in sweat production in boNTA treated palms was 26% (95%CI, 13-39%, P=0.002) and after 13 weeks 31% (95%CI 20-42%, P&lt;0.001). There were no significant changes in mean sweat production and varied from 0.2%-1.2%.</td>
<td>Level 2</td>
<td>The study shows that bot A has an effect in reducing sweat production over a 13-week period, however, the study group is very small, only containing 11 participants, which can influence results greatly. Most of the patients had hyperhidrosis from childhood, but there was one patient who had hyperhidrosis for 3 years due to major head trauma. Characteristics of participants have not</td>
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<td>Harms</td>
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<td>Cost-effectiveness</td>
<td>Effect estimates (95%CI) of outcome measures with comparison (control) risk</td>
<td>Summary measures of effect</td>
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| Lowe JL et al. Efficacy and safety of Botulinum toxin type A in the treatment of palmar hyperhidrosis | Double-blinded, Placebo-controlled RCT (within patient) | 19 | Patients aged between 18-80 years old with bilateral, symmetrical palmar hyperhidrosis, including the fingers. Key inclusion criteria included a gravimetric measurement of sweat production of at least 150 mg/5 min. | Single-centre | Botulinum toxin type A, 100U | Placebo (0.9% saline) | Gravimetric measurement: Mean sweat production | Minor iodine starch test: visual | Gravimetric measurement of sweat production: 198 mg/5 min mean difference from baseline and | Level 2 | Authors conclude that botNTA injections produce significant improvements in palmar hyperhidrosis.

Subjective rating: mean improvement after 3 weeks in boNTA treated palms was 38% (95% CI 17-59%, P=0.002), after 8 weeks 40% (95% CI 18-63%, P=0.002) and after 13 weeks 38% (95% CI 16-61%, P=0.002). In the placebo treated palm there was no significant subjective improvement at any time points.

Confidence intervals are large, bias of results.

There is no indication of where the study was carried out and although the authors say that the trial was double-blinded, there is no information about the process of allocation and randomization procedures, which could be potential biases.
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| hyperhidrosis: a double-blind, randomised, placebo-controlled study. Derm Surg 2002, 28:822-827 | comparison | least 40 mg/min, as well as an unsatisfactory response to previous treatment by local and/or systemic drug therapy. | | | | | improvement in sweat reduction | | | | at day 28 after injection, \( P=0.0027 \). BoNTA produced a Visual reduction in sweat production observed in iodine test compared to placebo. Physicians assessment: Day 0= 21%; day 28=37%. Difference of 16% of palms improving by at least 2 points from baseline Patient assessment: day 0= rating of 8/10; day 28= rating of 4/10, \( P<0.0001 \) for boNTA treated palm compared to placebo at day 28 Patient satisfaction: hyperhidrosis without concomitant decrease in grip or dexterity, or the occurrence of serious adverse events. The study looks at various levels of assessment to ascertain reduction of sweat production upon boNTA treatment. Authors did not report figures for each patient, which may come later on as the author's state that long-term crossover studies are being completed. Intention to treat method has not
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<td>17/17 patients</td>
<td>rated treatment as successful in BoNTA treated palm compared with 2/17 in the placebo-treated arm (P&lt;0.0001)</td>
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<td>17/17 patients rated treatment as successful in BoNTA treated palm compared with 2/17 in the placebo-treated arm (P&lt;0.0001)</td>
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<td>reported by authors, which may have questions about statistical power of the study. The study size is small, which can affect the overall effect of the intervention. Confidence intervals at 95% have not been included, and conclusion cannot be made from standard error values. 16/19 participants have completed 28 days after initial treatment, 3 dropouts were due to protocol violation.</td>
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<td>There was no information of where participants were recruited.</td>
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<td>Iodine starch tests would have been apparent to the physician, and possibly the patient, which could be potential bias.</td>
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<td>More information on data is required to make further assumptions</td>
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Reference List


(14) Stolman L. Hyperhidrosis: Medical and surgical treatment. ePlasty 2008 [cited 2013 Feb 18];8(e22)


(18) Committee for proprietary medicinal products summary information on referral opinion following arbitration pursuant to article 29 of council directive 2001/83/EC for Botox. European Medicines Agency 2003 [cited 2013 Feb 18];


