Interventions for hyperhidrosis in secondary care: a systematic review and value-of-information analysis

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Scientific summary

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Background

Hyperhidrosis is characterised by uncontrollable, excessive and unpredictable sweating that occurs at rest, regardless of temperature. Primary hyperhidrosis has no discernible cause. It most commonly involves the axillae, palms and soles, but may also involve the face, groin or any area of the body.

Primary hyperhidrosis is thought to affect approximately 1% of the UK population, with around 100 new patients being referred to an average NHS dermatology department each year. The symptoms of hyperhidrosis can significantly affect quality of life and can lead to social embarrassment, loneliness, anxiety and depression.

There is significant variation in the treatment for primary hyperhidrosis available in secondary care and current recommendations are not underpinned by robust evidence; there are many areas of uncertainty.

Objectives

The aim of this project was to establish the expected value of undertaking additional clinical studies to determine the most effective interventions for the management of refractory primary hyperhidrosis (excluding patients with social anxiety disorder) in secondary care.

The key objectives were:

1. to undertake an evidence synthesis by systematic review to estimate the clinical effectiveness and safety of treatments that would be available in secondary care and inform key clinical parameters for a decision model
2. to develop a decision model to estimate cost-effectiveness
3. using the decision model, to undertake a value-of-information (VOI) analysis to help inform the design of future clinical studies.

Methods of the clinical effectiveness review

A systematic review was conducted to inform the clinical effectiveness and safety of treatments that would be available for prescription by dermatologists and minor surgical treatments. The protocol included all treatments for hyperhidrosis prescribed in secondary care. However, screening and selecting the relevant literature revealed that endoscopic thoracic sympathectomy (ETS) could not be included in a comparative review as the position of ETS in the treatment pathway is uncontestable; ETS is considered only as an intervention of last resort because of its significant risks. Recent studies of ETS have focused on the details of the surgical procedure, addressing a question that is beyond the remit of the current project.

Fifteen databases (e.g. CENTRAL, PubMed and PsycINFO) were searched in January 2016. Clinical advisors were consulted for additional potentially relevant studies and reference lists of relevant systematic reviews were manually searched. Information on studies in progress and unpublished research was sought by searching conference proceedings and trial registers, in July 2016.

Studies assessing treatments for primary hyperhidrosis that would be available for prescription by dermatologists and minor surgical treatments were eligible for inclusion. For each intervention, randomised
controlled trials (RCTs), non-RCTs and large prospective case series were identified and the more robust study designs were included in the review. Outcomes of interest included disease severity, sweat rate, quality of life, patient satisfaction and adverse events.

Pairwise meta-analyses were conducted for comparisons between botulinum toxin (BTX) injections and placebo for axillary hyperhidrosis. The evidence for other comparisons was too limited or too heterogeneous to allow pooling; therefore, data were tabulated and synthesised narratively.

**Results of the clinical effectiveness review**

Fifty studies were included in the systematic review: 32 RCTs, 17 non-RCTs and one case series. Most studies were small, rated as having a high risk of bias and poorly reported. The interventions in the included studies were iontophoresis, BTX, anticholinergic medications, curettage and newer technologies that damage the sweat gland (e.g. laser, microwave).

There is moderate-quality evidence of a large statistically significant effect of subcutaneous BTX on symptoms of axillary hyperhidrosis in the short and medium term (up to 16 weeks) [pooled Hyperhidrosis Disease Severity Scale (HDSS) response at 4 weeks: risk ratio 3.30, 95% confidence interval 2.46 to 4.43]. Short-term evidence indicated that BTX may improve quality of life compared with placebo but is associated with adverse events, notably injection site pain. Evidence comparing the effectiveness of BTX injections to the axillae with curettage is very low quality and uncertain, although there is no evidence to suggest that curettage is more effective than BTX in the short to medium term and there is evidence to suggest that there is a higher incidence of adverse events with curettage. Trials are too short term to explore the potential curative nature of curettage compared with the retreatment needed with BTX.

There is very low-quality evidence suggesting that BTX injections had a small positive effect on palmar hyperhidrosis symptoms compared with placebo or no treatment, although there was a high incidence of adverse events with BTX.

There is insufficient evidence to draw conclusions on the effectiveness and safety of topical BTX for primary hyperhidrosis.

There were no studies assessing the clinical effectiveness of iontophoresis for axillary hyperhidrosis. There is very low-quality evidence suggesting a short-term beneficial effect of tap water iontophoresis on palmar hyperhidrosis compared with placebo and of dry-type iontophoresis compared with no treatment. Compared with tap water iontophoresis alone, the evidence for the effectiveness of combining anticholinergic therapy with iontophoresis is mixed and inconclusive. There is 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 effect duration is shorter than with BTX.

There were no studies assessing the clinical effectiveness of oral glycopyrrolate. There is very low-quality evidence regarding the effectiveness and safety of topical glycopyrrolate for axillary and facial hyperhidrosis. No evidence for other treatment sites was found.

There is low-quality evidence suggesting a short-term small benefit of other oral anticholinergics in hyperhidrosis symptoms compared with placebo. Both oxybutynin and methantheline bromide are associated with dry mouth symptoms. There were no studies assessing the clinical effectiveness of propantheline bromide for hyperhidrosis.

The limited evidence precludes any conclusions regarding the effectiveness and safety of curettage, laser epilation, fractionated microneedle radiofrequency, microwave or ultrasound.
Review of quality-of-life measures/tools

A narrative review was conducted to identify the tools that are commonly used to measure quality of life in studies of patients with hyperhidrosis. Study eligibility was not restricted to the interventions considered in the separate systematic review of effectiveness: all studies that reported measuring quality of life or described a quality-of-life measure/tool in the context of hyperhidrosis were included. Information on the tools and their use in hyperhidrosis was summarised in a narrative synthesis.

The review included 184 studies, many of which used two or more tools for measuring quality of life. Twenty-two individual tools were identified. In addition, 32 studies were identified that reported quality-of-life outcomes, but the method used to measure quality of life was not reported.

The Dermatology Life Quality Index (DLQI), the HDSS and the Hyperhidrosis Quality of Life Questionnaire (HQLQ) were used more often than any other tool for measuring quality of life in hyperhidrosis. The Hyperhidrosis Quality of Life Index (HidroQoL©) is the most recent tool to be designed and validated for measuring quality of life in patients with hyperhidrosis.

Development of a new cost-effectiveness model

The review of cost-effectiveness studies did not identify any modelling studies, so a de novo cost-effectiveness model was developed to formally assess the cost-effectiveness of treatments for primary hyperhidrosis and to estimate the VOI to aid decisions about further research. Cost-effectiveness analysis (CEA), expected value of perfect information (EVPI) and expected value of partial perfect information (EVPPI) analyses were conducted for the axillae body site only: insufficient evidence was available to warrant an analysis for any other body site. A NHS and Personal Social Services perspective was adopted for the analysis. The axillae CEA was a state-transition cohort model with a time horizon of 48 years. Quality-adjusted life-years (QALYs) and costs, discounted at a rate of 3.5%, were calculated for 64 different treatment sequences. The treatments in the sequences included: aluminium chloride, iontophoresis (sponge for axilla), medication, BTX, curettage and ETS. Technologies such as laser, microwave, ultrasound and fractionated microneedle radiofrequency were not included in the base-case model as they are not common practice in the UK. The model was based on treatment response defined as at least a two-point reduction on the HDSS.

The clinical evidence was based on a network meta-analysis conducted on the studies identified in the review of clinical effectiveness. When the response was reported as a continuous variable, a binary variable was derived. Withdrawal rates for iontophoresis sponge and medication were obtained from a survey of dermatologists conducted to inform the model parameters. EuroQol-5 Dimensions (EQ-5D) utility estimates were derived from a primary study of EQ-5D at different levels of response with a small sample size. Costs were mostly obtained from the national published sources.

Scenario, sensitivity and threshold analyses were conducted on the effectiveness of iontophoresis sponge, NHS payment of home iontophoresis sponge, the long-term effectiveness of medication, the price of medication, the probability of withdrawal due to adverse effects for BTX, the frequency of BTX injections, the disease severity of people having surgery and the likelihood of retrying different treatments.

Cost-effectiveness, expected value of perfect information and expected value of partial perfect information results

The base-case results indicated that iontophoresis, BTX, medication, curettage and ETS was the most cost-effective sequence, with an incremental cost-effectiveness ratio of £9304 per QALY (probability of 0.8). A total of 59 out of the 64 treatment sequences were either strictly dominated or dominated by extension.
The next most cost-effective sequences involved those with medication either before BTX in the sequence or not in the sequence at all. This reflects the uncertainty in the estimate of the effectiveness of medication versus placebo.

The following scenarios had an effect on the results:

- If the cost of medication increased from the cost of propantheline bromide to an average of the cost of propantheline bromide and glycopyrrolate bromide, then it would no longer be cost-effective to include medication in the treatment sequence at a willingness-to-pay threshold of £30,000 per QALY.
- If the effectiveness of medication declines over time, then it becomes significantly less cost-effective to include medication in a treatment sequence.
- If the iontophoresis response rate were only half the placebo response rate of 0.13, then iontophoresis would come after medication in the sequence; BTX would be first.
- If partial responders to non-surgical options as well as patients with no response at all had curettage instead of only those that had no response at all to previous treatments, then curettage would come after iontophoresis in the treatment sequence as it is relatively cost-effective compared with BTX and medication given the assumptions in the model.

The EVPI has been calculated based on the model assuming that the NHS pays for home iontophoresis and the iontophoresis device has a life expectancy of 10 years. This is the estimated difference between the expected value of the decision made with perfect information and the decision made with current information.

The population EVPPI results indicate that the value of further research on any model parameter is unlikely to be greater than the cost at a threshold of £20,000 per QALY. The exceptions are research on withdrawal rates due to adverse effects if the annual incidence of axillary hyperhidrosis is 2%, and on curettage compared with BTX effectiveness if the annual incidence of axillary hyperhidrosis is 2% and the odds ratio (OR) of response of iontophoresis compared with placebo is 1.

If the cost-effectiveness threshold is £30,000 per QALY and the annual incidence of axillary hyperhidrosis is 2%, then the value of further research may be greater than the cost for research on medication compared with placebo effectiveness. If the annual incidence is 2% and the OR of response of iontophoresis compared with placebo is 1, then research on BTX compared with medication effectiveness may be cost-effective.

**Patient and clinician perspective on research findings**

In order to elicit the opinions of hyperhidrosis patients and clinicians, an end-of-project workshop was held at Harrogate District Hospital with four patients and one dermatologist. Other clinicians provided advice during telephone meetings.

Patients and clinicians were unsurprised by the positive findings regarding BTX for axillary hyperhidrosis and did not consider that further research on iontophoresis for the axilla would be worthwhile. Despite the lack of trial evidence, they believed that iontophoresis was effective in some patients. Patients and clinicians agreed that a trial of BTX (plus anaesthetic) compared with iontophoresis for palmar hyperhidrosis would be useful.

Patients and clinicians were satisfied with the sequence of treatments identified as being cost-effective in the modelling exercise: iontophoresis, BTX, medication, curettage and ETS.

A trial comparing the different anticholinergic medications currently available for hyperhidrosis was not considered to be worthwhile. Although there was interest in the new energy-based ‘destructive’ technologies as potential cures for hyperhidrosis of the axilla, patients and clinicians agreed that better evidence was needed before a comparative trial against BTX was warranted.
All patient advisors agreed that the HidroQoL tool was superior to the other tools commonly used in hyperhidrosis research (HDSS, DLQI, HQLQ) for assessing quality of life. Patients considered that the HidroQoL tool should be the primary outcome in future studies and that measuring the actual amount of sweat produced should only be considered as a secondary outcome.

**Conclusions**

The evidence for the effectiveness and safety of second-line treatments for primary hyperhidrosis is limited overall and few firm conclusions can be drawn. However, there is moderate-quality evidence to support the use of BTX injections for axillary hyperhidrosis.

The cost-effectiveness analysis for axillary hyperhidrosis found that the treatment sequence of iontophoresis, BTX, medication, curettage and ETS was most cost-effective. Despite high levels of uncertainty, iontophoresis and BTX maintained their position as first and second treatment options in the majority of cost-effective sequences. The VOI analyses included relative effectiveness parameters for BTX, medication and curettage, and the results suggested that a trial on medication compared with placebo with a HDSS outcome measure may be of value if the cost-effectiveness threshold is £30,000 and the annual incidence of axillary hyperhidrosis is 2%. Given the level of uncertainty and its impact on the model, further research on the annual incidence of axillary hyperhidrosis may be warranted.

Based on clinical and patient opinion, and inferences from findings from the evidence, a well-conducted, adequately powered RCT of BTX (with anaesthesia), compared with iontophoresis, for palmar hyperhidrosis may be warranted. The new HidroQoL tool appears appropriate for capturing hyperhidrosis-related quality-of-life issues. BTX plus anaesthesia costs considerably more than iontophoresis and, therefore, cost-effectiveness would also need to be assessed.

There are ongoing studies of the new ‘destructive’ technologies: microwave, laser, fractionated micronneedle radiofrequency and ultrasound. If the results of this ongoing research are promising, then trials comparing these with BTX and with curettage for axillary hyperhidrosis may be warranted.

There are ongoing and recently completed trials of new oral and topical anticholinergic medication formulations; therefore, it is unlikely to be worthwhile undertaking further research of the anticholinergic medications currently available. There is little value in undertaking further studies of BTX compared with placebo for hyperhidrosis of the axilla or iontophoresis compared with placebo for hyperhidrosis of the hand.

**Study registration**

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