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Interventional Management of Hyperhidrosis in Secondary Care: A Systematic Review

Running head: Management of hyperhidrosis in secondary care: A systematic review

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What's already known about this topic?

- Hyperhidrosis is characterised by uncontrollable excessive sweating, which occurs at rest, regardless of temperature; symptoms can significantly affect quality of life.
- Hyperhidrosis with no discernible cause is known as primary hyperhidrosis.
- Despite the existence of a wide range of treatments for primary hyperhidrosis and a large number of clinical studies, there is uncertainty regarding optimal patient management and substantial variation in the availability of secondary care treatments in the UK.

What does this study add?

- This high-quality systematic review synthesises the large amount of research evidence for the effectiveness and safety of treatments for primary hyperhidrosis, which unfortunately is of limited quality and few firm conclusions can be drawn.
- There is moderate quality evidence to support the use of botulinum toxin injections for axillary hyperhidrosis.
- Recommendations for robust research are made, based on the results of the systematic

review, alongside clinical and patient advice.

Summary

Background

Hyperhidrosis is uncontrollable excessive sweating, which occurs at rest, regardless of temperature. The symptoms of hyperhidrosis can significantly affect quality of life.

Objectives

To undertake a systematic review of the clinical effectiveness and safety of treatments available in secondary care for the management of primary hyperhidrosis.

Methods

Fifteen databases (including trial registers) were searched to July 2016 to identify studies of secondary care treatments for primary hyperhidrosis. For each intervention randomised controlled trials (RCTs) were included, where available; where RCT evidence was lacking, non-randomised trials or large prospective case series were included. Outcomes of interest included disease severity, sweat rate, quality of life, patient satisfaction and adverse events. Trial quality was assessed using a modified version of the Cochrane Risk of Bias tool. Results were pooled in pair-wise meta-analyses where appropriate, otherwise a narrative synthesis was presented.

Results

Fifty studies were included in the review; 32 RCTs, 17 non-randomised trials and one case series. Studies varied in terms of population, intervention and methods of outcome assessment. Most studies were small, at high risk of bias and poorly reported. The interventions assessed were iontophoresis, botulinum toxin injections (BTX), anticholinergic medications, curettage and newer energy-based technologies that damage the sweat gland.

Conclusions

The evidence for the effectiveness and safety of 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 for axillary hyperhidrosis. A trial comparing BTX with iontophoresis for palmar hyperhidrosis is warranted.

Introduction

Hyperhidrosis is characterised by uncontrollable excessive and unpredictable sweating, which occurs at rest, regardless of temperature. Primary hyperhidrosis, which is the focus of this review, 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 at least 1% of the UK population.[1] The symptoms of hyperhidrosis can significantly affect quality of life, and can lead to social embarrassment, loneliness, anxiety and depression. It can impair work activities or studying in those handling pens, paper and electronic equipment. Functional problems may arise from skin maceration and soreness. Severely affected patients also may have secondary microbial infections. The unpredictable and uncontrollable nature of the condition can make it very distressing for sufferers.

In primary care, patients may initially be advised to make lifestyle changes such as restricting stimulant-containing foods, losing weight and avoiding clothing that can make sweating worse. First line treatment includes topical pharmacological agents: aluminium chloride has been shown to be effective for mild-to-moderate axillary hyperhidrosis and formaldehyde solution can be prescribed for plantar hyperhidrosis.[2,3] Unfortunately, skin irritation is very common with these antiperspirants and often forces discontinuation of the treatment.[4] Patients may be referred to a dermatologist if treatment fails or is not tolerated. However, current recommendations are not underpinned by robust evidence and there is significant variation in the availability of treatments for primary hyperhidrosis in secondary care in the UK. Further clinical trials may be required, in particular comparing the effectiveness of treatments prescribed by a dermatologist, but first a thorough review of the available evidence is warranted.

Objectives

To undertake a systematic review of the clinical effectiveness and safety of treatments available in secondary care for the management of patients with refractory primary hyperhidrosis.

Methods

A protocol for the systematic review was developed and registered on PROSPERO (number CRD42015027803). The review included studies of patients (adults and children) with primary hyperhidrosis. Studies of any treatment for hyperhidrosis offered in secondary care for prescription by dermatologists and minor surgical treatments were eligible for inclusion. Endoscopic thoracic sympathectomy was not included as it is not recommended by many practitioners: it is generally considered only as an intervention of last resort due to its significant risks and common adverse effects such as compensatory hyperhidrosis.[5]

For each intervention randomised controlled trials (RCTs) were included, where available. For interventions where RCT evidence was lacking, non-randomised controlled trials (non-RCTs) or large prospective case series were included. Recently published high quality systematic reviews were also considered if they were directly relevant. Outcomes of interest included disease severity, sweat rate, quality of life, patient satisfaction and adverse events.

Potentially relevant studies were identified through literature searching. Twelve databases were searched in January 2016 (including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials). No date or language limits were applied. The MEDLINE search strategy (which identified the greatest number of records) is presented in Supplementary Appendix 1. Clinical advisors were consulted for additional 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.

Two researchers (RW and J J-D) undertook the screening of titles and abstracts obtained through the search, although the library was split between the researchers, rather than each record being double screened. A sample of just over 10% of records was double screened in order to assess the level of agreement between the researchers; it was planned to undertake full double screening if the level of

agreement was poor, but this was not necessary as the level of agreement between researchers was 96.2%. Full manuscripts of potentially relevant studies were obtained and independently screened by two researchers (RW and J J-D), using pre-defined eligibility criteria. Disagreements were resolved through discussion or consultation with a third researcher. Relevant foreign language studies were translated and included.

Data were extracted directly into a standardised, piloted, spreadsheet developed in Microsoft Excel (RW, AL and J J-D). Data extracted included study design, sample size, participant characteristics (body site treated, age, sex, previous treatments, baseline disease severity), treatment characteristics (dose, frequency, duration), outcomes assessed (measurement tool and time point) and results. Data extraction was conducted by one researcher and checked for accuracy by a second. In cases of multiple publications of the same study, the publication with the largest sample or longest follow-up was treated as the main source. Where possible we extracted intention-to-treat (ITT) data. Where results data were missing or limited (e.g. only presented in graphical format, or conference abstracts), authors were contacted and, where relevant, manufacturer trials registers were consulted for further data. If the authors did not respond, data from graphs were extracted using Graph Grabber (Quintessa) software.

The quality of RCTs and non-RCTs was assessed using a modified version of the Cochrane Risk of Bias tool by one researcher and checked for accuracy by a second (RW, AL and J J-D).[6] An additional question relating to the similarity of treatment groups at baseline was added.[7] In addition, a question about 'within patient' study designs was added, owing to concerns about the validity of certain outcome measures in 'within patient' study designs, in which patients receive different interventions on different sides of the body (i.e. the left versus the right axilla). See Supplementary Appendix 2 for the results of the risk of bias assessment. Case series were not formally quality-assessed; their results were presented as supporting evidence. No systematic reviews were included in the review except as a source of relevant studies, so they were not quality assessed.

Results were pooled in pair-wise meta-analyses if at least two studies of the same intervention and comparator reported the same outcome and were considered sufficiently similar for analysis to be appropriate and feasible. Otherwise, results were summarised in a narrative synthesis. Where meta-analyses were performed, dichotomous outcomes were combined to estimate pooled risk ratios (RR) and continuous outcomes were combined to estimate pooled mean differences (MD) using random-effects DerSimonian-Laird meta-analyses.[8] Statistical heterogeneity was assessed using the I^2 statistic and visual inspection of forest plots. Studies using different units of analysis (i.e. axilla in half-side comparisons versus patients in between-patient comparisons) were pooled where deemed appropriate and reported in separate subgroups. For studies that included two separate intervention groups with two different doses and used one control group, data from each intervention group were entered separately to explore any dose response effect, and the number of participants in the control group was divided by two to reduce the risk of double counting data.[9] Although this approach may artificially reduce the power of the study in the meta-analysis and does not account for potential correlation between the two active treatment groups, a separate analysis combining the two arms showed no significant difference in results.

Meta-regressions and other subgroup analyses were considered inappropriate due to the small number of studies. All analyses were conducted using Review Manager 5.3.

Clinical and patient advisors contributed to the interpretation of the results.

Results

The electronic searches identified a total of 4057 records; the flow diagram of the study selection process is presented in Figure 1.

Supplementary Appendix 3 presents the 155 records that met the inclusion criteria for the systematic review. For each intervention for which there were RCTs or non-randomised comparative studies available, less robust studies were excluded, resulting in 93 small case series being excluded from the review. Five additional studies were excluded because they were systematic reviews that were not considered to be sufficiently good quality, up to date or directly relevant to be relied upon, resulting in 57 records (reporting 48 studies) identified for inclusion in the review.

An additional two studies were identified from the separate searches of conference proceedings and trial registers (flow diagram presented in Supplementary Appendix 4). Therefore, a total of 50 studies were included in the review: 32 RCTs, 17 non-RCTs and one case series.

Study characteristics

Studies varied in terms of country of origin (indicating climate and population differences), intervention and the methods of outcome assessment. Most studies were small (sample sizes ranged from 4 to 339, with most studies including fewer than 50 patients), at high risk of bias and poorly reported, see Supplementary Appendix 2 for further details. The interventions assessed were iontophoresis, botulinum toxin (BTX), anticholinergic medications, curettage and newer technologies that damage the sweat gland. The majority of studies only included adult patients and the majority of participants across the studies were female. Where reported, baseline disease severity was moderate to severe, with a Hyperhidrosis Disease Severity Scale (HDSS) score of 3-4 and/or a sweat rate of at least 50 mg/5 minutes. The site of hyperhidrosis differed between studies of different interventions. A summary of the study characteristics is presented in Table 1, with further details presented in Supplementary Appendix 5.

Clinical effectiveness

This section presents a summary of the results, presented by intervention. Further results of each study are presented in Supplementary Appendix 5.

Iontophoresis

Ten studies (4 RCTs, 5 non-RCTs, 1 case series) of iontophoresis were included.[10-19] All were at a high or unclear risk of bias. There were a number of differences in the iontophoresis interventions used across these studies with variations in the medium used (tap water, with aluminium chloride or an anticholinergic added, or a “dry type” device), the electric current used, and the frequency of iontophoresis sessions. No meta-analysis was possible owing to the differences between interventions and outcomes assessed.

Three very small studies (2 RCTs and 1 interrupted time series) with short follow-up times compared

tap water iontophoresis with placebo for palmar hyperhidrosis[10-12] and found a positive effect of iontophoresis as assessed by gravimetry or iodine starch test. This finding was supported by a larger case series.[13]

Of two small non-randomised comparisons of a hand-held "dry type" iontophoresis device compared with no treatment;[14,15] only one found a statistically significant reduction in sweating, assessed by gravimetry.[14]

Two studies compared iontophoresis alone with iontophoresis combined with anticholinergic therapy for palmoplantar hyperhidrosis; one RCT found no significant benefit with the addition of oral oxybutynin,[16] while a non-RCT reported that iontophoresis with topical glycopyrrolate resulted in a longer duration of effect.[17] The addition of anticholinergic therapy was associated with dry throat, mouth or eyes in some patients.

Two studies (1 RCT, 1 non-RCT)[18,19] compared iontophoresis with BTX injections for palmar hyperhidrosis. The RCT found a statistically and clinically significant difference in treatment response (HDSS) and patient reported symptoms between the two interventions favouring BTX at four weeks from baseline.[18] This result was supported by the non-RCT, but the difference in treatment benefit was no longer statistically significant at six or 12 months.[19] Patients receiving BTX were more likely to report mild to moderate pain associated with treatment.

Overall, there is very low quality but consistent evidence suggesting a short term beneficial effect of tap water iontophoresis in the treatment of palmar hyperhidrosis. There is inconsistent evidence regarding the beneficial effect of adding anticholinergic therapy to iontophoresis for palmoplantar hyperhidrosis. There is very low quality evidence suggesting that BTX is more effective than iontophoresis for palmar hyperhidrosis in the short term. No serious adverse events related to iontophoresis were reported.

Botulinum toxin (subcutaneous injection)

Twenty-three studies of BTX, delivered by subcutaneous injection, were included. There was some variation in the BTX used in these trials. Most studies used BTX type A, only two used type B. Where stated, the most common dosage of BTX-A was 50 U, although some studies used up to 250 U. The studies of BTX-B used 2500 U or 5000 U.

For axillary hyperhidrosis, BTX was compared with placebo in nine studies (8 RCTs,[20-27] 1 open label continuation study[28]), no treatment in three studies (non-RCTs[29-31]), and with curettage in four studies (1 RCT,[32] 3 non-RCTs[33-35]).

For the comparison with placebo, meta-analysis of some trials was possible for the following outcomes: patient-reported symptom improvement (HDSS reduction of at least 2 points RR: 3.30, 95% CI: 2.46 to 8.32; p<0.001, I^2=0%, 2 studies) (Fig. 2), sweat reduction (gravimetry) expressed as mean differences (MD at 16 weeks: -66.93, 95% CI: -82.76 to -51.10; p<0.001, I^2=0%, 3 studies) (Figs 3-4) or risk ratios (RR at 16 weeks: 2.87, 95% CI: 1.94 to 4.26; p<0.001, I^2=48%, 3 studies) (Figs 5-7), and quality of life (MD: -4.80, 95% CI: -5.67 to -3.94; p<0.001, I^2=3%, 2 studies) (Fig. 8). Overall, the meta-analyses showed a large and clinically significant effect of BTX for axillary hyperhidrosis; benefits were largely sustained at 16 weeks follow-up (Figs 4 and 6). The placebo controlled BTX trials that were not included in the meta-analyses also reported clinically relevant improvements in

sweating[26,27] and improvements in quality of life.[21,28,36] No serious or severe treatment related adverse events were reported; the most common treatment-related adverse events were injection-site pain and compensatory sweating.

The three non-RCTs comparing BTX with no treatment reported broadly similar results; significant reductions in sweating but injection-site pain associated with BTX injections.[29-31]

Results of the studies comparing BTX with curettage are described in the 'Curettage' section below.

For palmar hyperhidrosis, BTX was compared with placebo in three RCTs, which reported a small statistically significant reduction in sweating at three to thirteen weeks, measured by gravimetry[37] or sweat area,[38] but not by iodine starch test.[36] Patients' assessment of disease severity was statistically significantly improved in the BTX group in all three RCTs. One of the RCTs reported a high incidence of treatment related adverse events, including decreased grip strength, muscle weakness and dry mouth.[36] Two non-randomised studies compared BTX with no treatment.[30,39] Results were similar to the findings of the RCTs.

Overall, there is moderate quality evidence of a large statistically significant effect of BTX injections on symptoms of axillary hyperhidrosis in the short and medium term (up to 16 weeks) compared with placebo. Short term evidence indicated that BTX may improve quality of life compared with placebo. BTX is associated with mild adverse events, notably injection-site pain. Evidence comparing the effectiveness of BTX injections to the axillae with curettage is very low quality and uncertain. 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 adverse events were reported. As stated above, there is very low quality evidence suggesting that BTX is more effective than iontophoresis for palmar hyperhidrosis in the short term. There is insufficient evidence on the effect of BTX injections on quality of life in palmar hyperhidrosis.

Topical botulinum toxin

Only one very small placebo-controlled RCT (unclear risk of bias) evaluated the efficacy of topically applied BTX for axillary hyperhidrosis; there was a greater reduction in sweating with BTX than placebo.[40] Therefore there is insufficient evidence to conclude on the effectiveness and safety of topical BTX for primary hyperhidrosis.

Anticholinergics

Studies of three anticholinergics were identified: topical glycopyrrolate; oral oxybutynin and oral methantheline bromide. No meta-analysis was possible owing to the differences between interventions and outcomes assessed. Two small low-quality (high or unclear risk of bias) RCTs evaluated short term treatment with glycopyrrolate wipes against placebo, used for hyperhidrosis of the axilla[41] or the face.[42] Both studies found a significant treatment benefit in terms of sweating (gravimetry), but improvement in HDSS was seen only in patients receiving treatment for axillary hyperhidrosis.[41] There was limited and inconclusive evidence from one non-RCT[43] regarding the effectiveness (HDSS) and safety of glycopyrrolate spray compared with BTX injections for axillary hyperhidrosis. There were no studies assessing the clinical effectiveness of oral glycopyrrolate.

Three placebo-controlled RCTs evaluated the effectiveness and safety of oral oxybutynin for hyperhidrosis of the axilla and palm,[44] foot[45] and generalised hyperhidrosis,[46] and two placebo-controlled RCTs assessed oral methantheline bromide for axillary and palmar hyperhidrosis.[47,48] All

studies were at a high or unclear risk of bias and reported treatment benefits as well as a significantly higher incidence of dry mouth symptoms in patients receiving active therapy.

Overall, the evidence for anticholinergic medications was limited, but suggested short term benefits of topical glycopyrrolate, oral oxybutynin and oral methantheline bromide on hyperhidrosis symptoms. Oral oxybutynin and methantheline bromide were also associated with dry mouth adverse events.

Curettage

Nine studies (4 RCTs, 5 non-RCTs) evaluated curettage for axillary hyperhidrosis. All were at high risk of bias. No meta-analysis was possible owing to the differences between interventions and outcomes assessed.

Of four studies (1 RCT, 3 non-RCTs) that compared curettage with BTX in axillary hyperhidrosis,[32-35] only the small RCT[32] found a statistically significant difference in HDSS score (at three and six months follow-up) favouring BTX. The other studies found no significant difference between treatment groups in sweating, quality of life and satisfaction outcomes. However, where reported, the incidence of adverse events was higher with curettage than BTX.

Five studies (3 RCTs, 2 non-RCTs) compared suction curettage with other surgical interventions: radical skin excision; liposuction curettage, radical skin excision and a skin-sparing technique (Shelley radical skin excision); curettage with and without aggressive manual shaving; tumescent suction curettage and laser.[49-53] Overall, there is very low quality evidence regarding the relative effectiveness and safety of curettage compared with other minor surgical interventions for axillary hyperhidrosis. Compared with the more radical excision techniques, there is insufficient evidence to demonstrate a clinically significant difference in sweat reduction, patient satisfaction or safety.

Energy-based 'destructive' technologies

Three RCTs evaluated the efficacy and safety of laser epilation for axillary hyperhidrosis.[53-55] All were at high risk of bias and, as well as other study differences, the wavelength used varied between the studies. No meta-analysis was possible owing to the differences between interventions and outcomes assessed. One RCT compared laser with curettage (described in the 'Curettage' section above).[53] Two small RCTs compared laser epilation with no treatment; one found that sweating was visibly reduced on the laser-treated side compared with the untreated side at one month,[55] but the other study found no significant difference between treated and untreated sides in sweat reduction at 12 months.[54] Both studies reported no serious adverse events.

One non-randomised study (high risk of bias) compared the efficacy of fractionated microneedle radiofrequency with a sham control for axillary hyperhidrosis.[56] The study reported significantly better results in mean HDSS scores and sweating intensity at 21 weeks follow-up, with transient but not severe adverse events.

One RCT (high risk of bias) compared a microwave device with sham treatment for axillary hyperhidrosis.[57] The study found that microwave therapy was more effective than placebo at reducing patient reported disease severity, although there was no evidence of a significant difference in the proportion of patients achieving 50% sweat reduction at up to six months. Adverse events were generally transient and none were considered severe.

Two small RCTs (high risk of bias) compared micro-focused ultrasound with sham treatment for axillary hyperhidrosis, reported in a single publication.[58] The studies reported some benefit in terms of sweating and HDSS.

Overall, there is insufficient evidence regarding the safety and effectiveness of laser epilation, fractionated microneedle radiofrequency, microwave therapy or ultrasound therapy for axillary hyperhidrosis.

Discussion

The evidence for the effectiveness and safety of second line treatments for primary hyperhidrosis is limited overall. Most of the included studies were small, at high risk of bias and poorly reported; only one RCT was judged to have a low overall risk of bias. There was insufficient evidence to draw firm conclusions regarding the relative effectiveness and safety of most of the available treatments for primary hyperhidrosis in secondary care.

There is, however, moderate quality evidence of a large effect of BTX injections on symptoms of axillary hyperhidrosis in the short to medium term, although injections were associated with transient injection-site pain. Evidence for other interventions is of low or very low quality. Although the evidence for iontophoresis is very low quality, it is consistent, suggesting that there is a short term beneficial effect of tap water iontophoresis in the treatment of palmar hyperhidrosis; no serious adverse events were reported. There is very low-quality evidence suggesting short term benefits of topical glycopyrrolate, oral oxybutynin and oral methantheline bromide on hyperhidrosis symptoms. However, oral oxybutynin and methantheline bromide were associated with dry mouth adverse events. There were no studies assessing the clinical effectiveness of oral glycopyrrolate or propantheline bromide for hyperhidrosis despite being commonly used anticholinergic drugs in hyperhidrosis. There was insufficient evidence to demonstrate a clinically significant difference between curettage and other minor surgical interventions or BTX for axillary hyperhidrosis. Evidence was very limited regarding the newer energy based 'destructive' technologies.

Despite its large volume the poor quality of much of the available research evidence is a limitation of this review. The only comparison for which adequate data were available to undertake meta-analysis was that between BTX and placebo for axillary hyperhidrosis. It was not feasible to undertake network meta-analysis; therefore, the comparative clinical effectiveness of the available treatments could not be estimated. In addition, the substantial variation among the included studies limits the generalisability and reliability of the results.

Recommendations for further research

There is limited but promising evidence for the effectiveness of BTX for palmar hyperhidrosis and therefore, a well conducted, adequately powered, randomised controlled trial of BTX (with anaesthesia), compared with iontophoresis (as the current standard treatment for palmar hyperhidrosis in many dermatology units), for palmar hyperhidrosis may be warranted. This trial should evaluate patient relevant outcomes based on a validated scale such as the new HidroQoL© tool. The cost of BTX plus anaesthesia is considerably higher than iontophoresis; therefore, the relative cost-effectiveness of these treatments should also be assessed.

Conclusions

The evidence for the effectiveness and safety of 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. A trial comparing BTX injections with iontophoresis for palmar hyperhidrosis is warranted.

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Table 1. Basic study characteristics

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
Dahl, 1989[10]	RCT (half side comparison)	Denmark	11	18-44	27 %	Palm	Iontophoresis (tap water) (n=11)	Sham (n=11)	N/A	Unclear
Karakoc, 2004[11]	Interrupted time series	Turkey	15	15-26	47 %	Palm	Iontophoresis (tap water) (n=15)	Sham (n=15)	N/A	High
Stolman, 1987[12]	RCT (half side comparison)	USA	18	20-46	44 %	Palm	Iontophoresis (tap water) (n=18)	Sham (n=18)	N/A	Unclear
Karakoc, 2002[13]	Case series	Turkey	112	8-32	45 %	Palm	Iontophoresis (DC tap water) (n=112)	N/A	N/A	High
Choi,	Non-	South	23	13-	30	Palm	Iontophore	No	N/A	High

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
2013[15]	RCT (half side comparison)	Korea		64	%		sis (dry type) (n=23)	treatment (right palm; n=23)		
Na 2007[14]	Non-RCT (half side comparison)	South Korea	10	18-34	70 %	Palm	Iontophoresis (dry type) (n=10)	No treatment (contralateral palm; n=10)	N/A	High
Shimizu, 2003[16]	RCT	Japan	52	NR	44 %	Palm & feet	Iontophoresis (AC tap water) (n=24)	Iontophoresis (AC) + oxybutynin (n=19)	Iontophoresis (DC) (n=9)	Unclear
Dolianitis, 2004[17]	Non-RCT (half side comparison)	Australia	20	12-50	30 %	Palm (n=20), feet (n=1)	Iontophoresis (glycopyrrolate 0.05%) (n=20)	Iontophoresis (tap water) (n=20)	Iontophoresis (glycopyrrolate 0.05%) (n=20)	High
Rajagopal, 2014[18]	RCT (crossover)	India	60	10-43	65 %	Palm	Iontophoresis + topical aluminium chloride (20% lotion) (n=30)	BTX-A (100 U) (n=30)	N/A	High
Wachal, 2009[19]	Non-RCT	Poland	86	18-43	28 %	Palm	Iontophoresis (DC) (n=28)	BTX-A (50 U Botox) (n=22)	Sympathectomy (n=36)	High
Balzani, 2001[26]	RCT	Italy	4	23-65	0%	Axilla	BTX-A (250 U) (n=2)	Placebo (n=2)	N/A	Unclear
Baumann, 2005[24]	RCT	USA	20	NR	35 %	Axilla	BTX-B (2500 U) (n=15)	Placebo (n=5)	N/A	High
Heckmann, 2001[25]	RCT (half side comparison)	Germany	145	NR	52 %	Axilla	BTX-A (200 U) (n=145)	Placebo (n=145) +BTX-A (100U) two weeks later	N/A	Low
Lowe, 2007[20]	RCT	USA	322	18-69	55 %	Axilla	BTX-A (50 U Botox) (n=104) BTX-A (75 U Botox) (n=110)	Placebo (n=108)	N/A	Unclear/ High
Naumann, 2001[21] Naumann, 2002[59] and Lowe, 2002[60]	RCT	Germany, Belgium and UK	320	17-74	46 %	Axilla	BTX-A (50 U) (n=242)	Placebo (n=78)	N/A	Unclear
Naumann, 2003[28]	Open label extensio	Germany, Belgiu	207	17-74	NR	Axilla	BTX-A (50 U) (n=80) BTX-A (50	Placebo (n=4)	N/A	High

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
	n of Naumann 2001	m and UK					U, 2 treatments, spaced by at least 16 weeks) (n=93) BTX-A (50 U, 3 treatments, spaced by at least 16 weeks) (n=30)			
Odderson, 2002[23]	RCT	USA	18	16-50	61 %	Axilla	BTX-A (50 U) (n=12)	Placebo (n=6)	N/A	Unclear
Ohshima, 2013[22,61]	RCT	Japan	152	NR	24 %	Axilla	BTX-A (50 U) (n=78)	Placebo (n=74)	N/A	Unclear
Schnider, 1999[27]	RCT (half side comparison)	Austria	13	21-55	31 %	Axilla	BTX-A (200 U) (n=13)	Placebo (n=13)	N/A	Unclear
Heckmann 1999[29]	Non-RCT (half side comparison)	Germany	12	21-42	42 %	Axilla	BTX-A (250 U Dysport) (n=12)	No treatment (n=12) followed by BTX-A (250U) 14 days later	N/A	High
Naver, 2000[30]	Non-RCT (half side comparison)	Sweden	28	19-57	38 %	Axilla and/or palm	BTX-A (Botox, mean 104U (axilla), 56U (palm) once or twice), local anaesthesia (palmar HH only) (n=28; palmar n=19; axillary n=13)	No treatment (n=28)	N/A	High
Wakugawa 2001[31]	Non-RCT (half side comparison)	Japan	20	NR	NR	Axilla	BTX-A (50 U Dysport) one side only (n=7) BTX-A (50 U Dysport) both sides (n=13)	No treatment (n=7)	N/A	High
Ibrahim, 2013[32] and Ibrahim, 2013[62]	RCT (half side comparison)	USA	20	19-50	65 %	Axilla	Tumescent suction curettage (tumescent anaesthesia) (n=20)	BTX-A (50 U) (n=20)	N/A	High
Ottomann, 2007[33]	Non-RCT	Germany	88	17-39	16 %	Axilla	Suction curettage	BTX-A (50 U)	N/A	High

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
							(n=41)	(n=47)		
Rompel, 2001[34]	Non-RCT	Germany	113	NR	36 %	Axilla	Suction curettage (subcutaneous) (n=90)	BTX-A (40-50 U Botox or 200-250 U Dysport per axilla) (n=23)	N/A	High
Vakili, 2016[35]	Non-RCT	UK	98	16-56	26 %	Axilla	Micro Retro-dermal Axillary Curettage (mRAC) (n=23)	BTX-A (Botox) (n=75)	N/A	High
Baumann, 2005[36]	RCT	USA	20	20-60	50 %	Palm	BTX-B (5000 U) (n=15)	Placebo (n=5)	N/A	High
Lowe, 2002[37]	RCT (half side comparison)	USA	19	NR	53 %	Palm	BTX-A (100 U) (n=19)	Placebo (n=19)	N/A	Unclear
Schnider, 1997[38]	RCT (half side comparison)	Austria	11	23-54	64 %	Palm	BTX-A (120 U Dysport) (n=11)	Placebo (n=11)	N/A	Unclear
Yamashita, 2008[39]	Non-RCT (half side comparison)	Japan	27	NR	22 %	Palm	BTX-A (60 U Botox) (n=27)	No treatment (n=27)	N/A	High
Glogau, 2007[40]	RCT (half side comparison)	USA	12	NR	50 %	Axilla	Topical BTX-A (200 U Botox) (n=12)	Placebo (n=12)	N/A	Unclear
Mehrotra, 2015[41]	RCT	USA	38	17-68	42 %	Axilla	Glycopyrrolate wipes (4% once daily for 4 weeks) (n=12) Glycopyrrolate wipes (2% once daily for 4 weeks) (n=12)	Placebo (n=14)	N/A	High
Hyun, 2015[42]	RCT (half side comparison)	South Korea	39	20-66	77 %	Face	Glycopyrrolate wipes (2% 9 times over 10 days) (n=39)	Placebo (n=39)	N/A	Unclear /High
Baker, 2013[43]	Non-RCT	UK	40	20-41	20 %	Axilla	Glycopyrrolate (1% spray)	BTX-A (dose NR) (n=10)	No treatment (n=10)	High

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
							(n=10) Glycopyrrolate (2% spray) (n=10)			
Wolosker, 2012[44]	RCT	Brazil	50	18-50	27 %	Primarily axilla and palm	Oxybutynin (2.5 mg to 10 mg daily) (n=25)	Placebo (n=25)	N/A	Unclear
Costa, 2014[45] and Costa, 2015[63]	RCT	Brazil	32	NR	0%	Primarily feet	Oxybutynin (2.5 mg to 10 mg daily) (n=16)	Placebo (n=16)	N/A	Unclear
Schollhammer, 2015[46]	RCT	France	62	18-62	43 %	Generalised (83%), localised (17%)	Oxybutynin (2.5 mg to 7.5 mg daily) (n=32)	Placebo (n=30)	N/A	Unclear
Muller, 2013[48]	RCT	Germany	339	NR	NR	Axilla and/or palm	Methanthelinе bromide (150 mg daily) (n=171)	Placebo (n=168)	N/A	Unclear/ High
Hund, 2004[47]	RCT	Germany	42	18-54	25 %	Axilla and/or palm	Methanthelinе bromide (100 mg daily) (n=23)	Placebo (n=19)	N/A	High
Bechara, 2008a[49]	RCT	Germany	40	19-57	45 %	Axilla	Curettage (liposuction) (n=15)	Shelley (skin-sparing technique) (n=11)	Radical skin excision (modified Bretteville-Jensen technique with Y-plasty closure) (n=14)	High
Jemec, 1975[52]	Non-RCT	Denmark	41	NR	NR	Axilla	Curettage (liposuction) (n=20)	Radical excision (n=21)	N/A	High
Bechara, 2008b[51]	Non-RCT (half side comparison)	Germany	4	NR	NR	Axilla	Curettage (liposuction) (n=4)	Curettage (liposuction) + aggressive manual shaving (n=4)	N/A	High
Tronstad, 2014[50]	RCT (half side comparison)	Norway	22	20-44	18 %	Axilla	Curettage (n=22)	Tumescent suction curettage (n=22)	N/A	Unclear (gravimetry) High (DLQI)
Leclère, 2015[53]	RCT	France,	100	NR	NR	Axilla	Laser alone (924/975	Laser (924/975	Laser alone (975 nm)	High

Study	Design	Study location	Sample size	Age range	Male %	Body site	Intervention 1	Intervention 2	Intervention 3	Risk of bias
		Germany and Spain					nm simultaneous) once (n=25)	nm) +curettage once (n=25)	once (n=25) **Intervention 4:** Suction curettage alone once (n=25)	
Bechara 2012[54]	RCT (half side comparison)	Germany	21	24-66	24 %	Axilla	Long-pulsed laser (800-nm) 5 treatments at 4-week intervals (n=21)	No treatment (n=21)	N/A	High
Letada 2012[55]	RCT (half side comparison)	USA	6	NR	17 %	Axilla	Long-pulsed laser (1064 nm) 6 treatments at monthly intervals (n=6)	No treatment (n=6)	N/A	High
Fatemi Naeini, 2015[56] and Abtahi-Naeini, 2015[64]	Non-RCT (half side comparison)	Iran	25	NR	32 %	Axilla	Fractionated microneedle radiofrequency (1 MHz of radiofrequency current) 3 sessions at 3 week intervals (n=25)	Sham fractionated microneedle radiofrequency (n=25)	N/A	High
Glaser, 2012[57] and Kilmer, 2011[65]	RCT	USA	120	NR	43 %	Axilla	Microwave, 2 sessions (approximately) (n=81)	Sham microwave (n=39)	N/A	High
Nestor, 2014[58] and Nestor 2012[66] (study 1)	RCT (half side comparison)	USA	14	NR	21 %	Axilla	Micro-focused ultrasound (n=14)	Placebo (n=14)		High
Nestor, 2014[58] and Nestor 2012[66] (study 2)	RCT	USA	20	21-52	65 %	Axilla	Micro-focused ultrasound (n=12)	Placebo (n=8)		High

Figure 1: Flow diagram of the study selection process

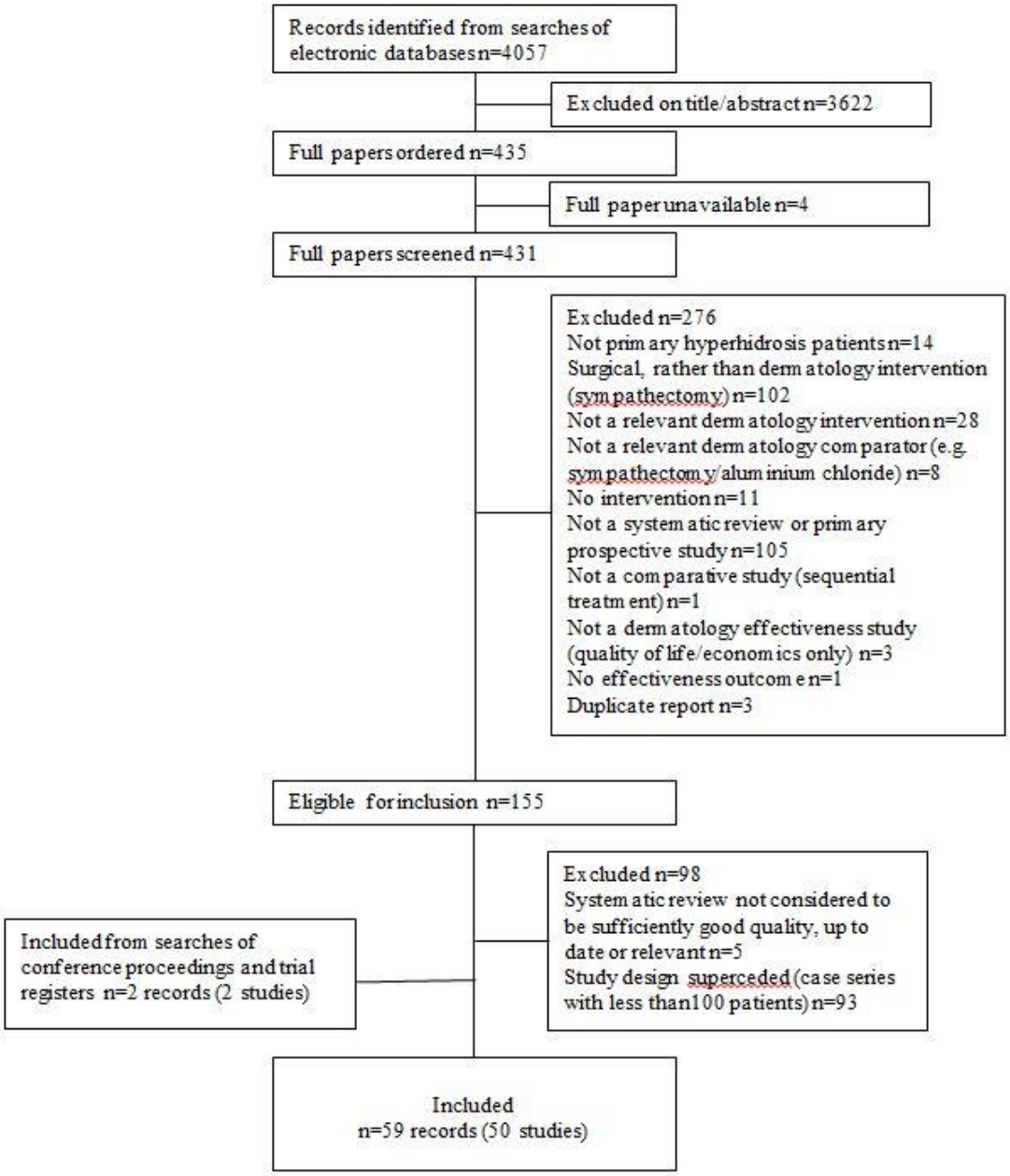
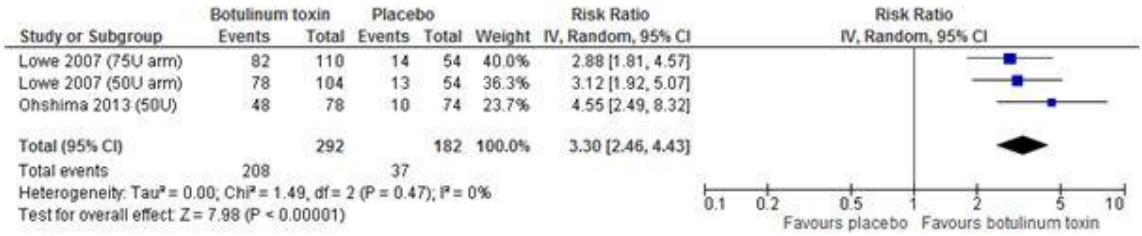
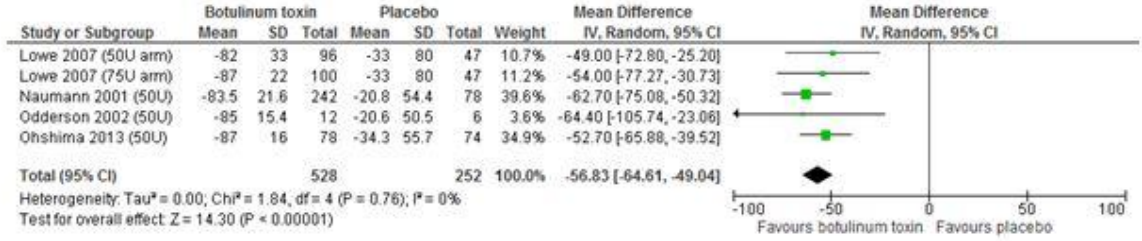


Figure 2: Botulinum toxin vs. placebo: Reduction of ≥2 pts in HDSS at 4 weeks*



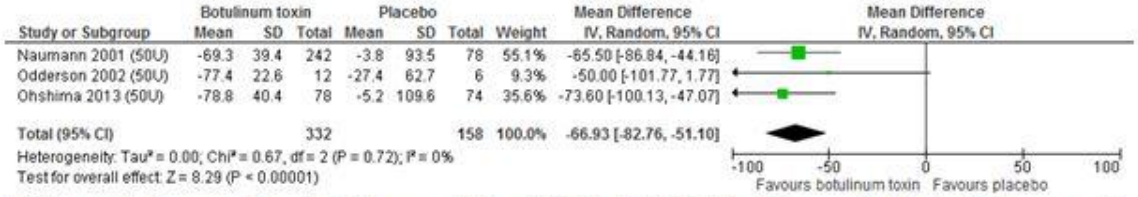
*In Lowe 2007, the total sample size of the placebo group (n=108) was divided by 2 to avoid double counting.

Figure 3: Botulinum toxin vs. placebo: Mean % change from baseline in sweating at 2-4 weeks*



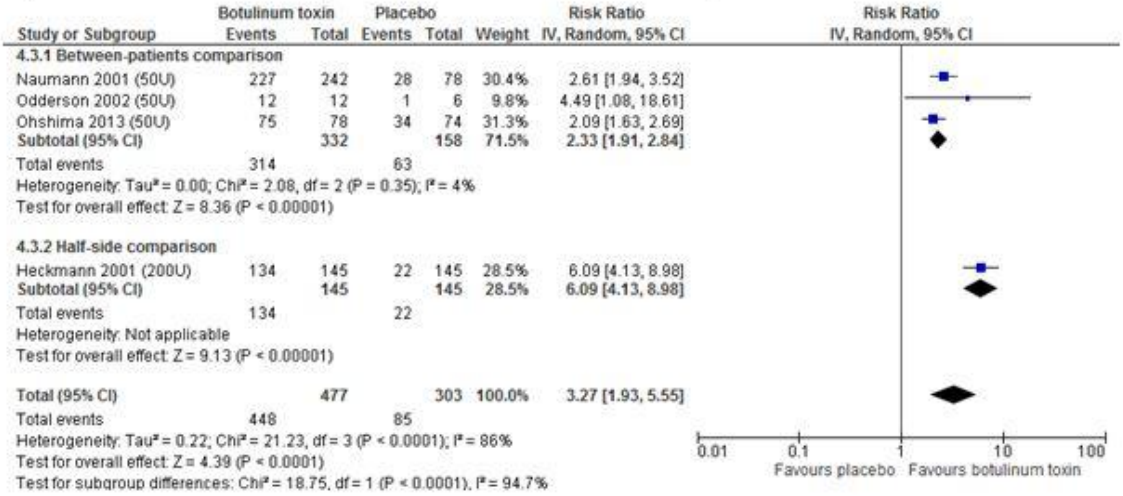
*Follow-up duration was 4 weeks for Lowe 2007, Naumann 2001 and Ohshima 2013. Median follow-up duration in Odderson 2002 was 2 weeks (range 1-8). Data for Odderson 2002 were extracted and calculated from figures.

Figure 4: Botulinum toxin vs. placebo: Mean % change from baseline in sweating at 16 weeks*



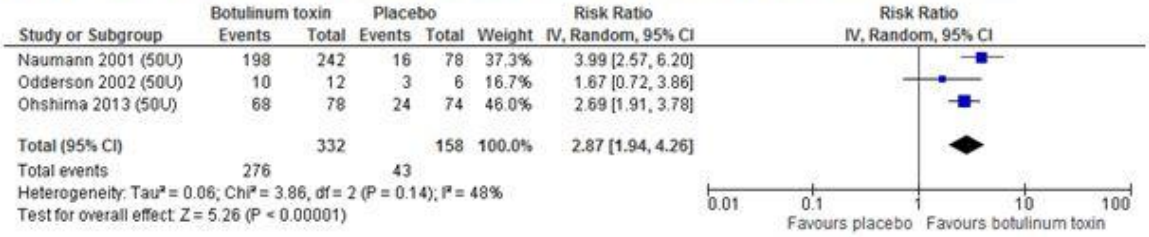
*Follow-up duration was 16 weeks for Naumann 2001 and Ohshima 2013. Median follow-up duration for Odderson was 16 weeks (range 10 to 20). Data for Odderson 2002 were extracted and calculated from figures.

Figure 5: Botulinum toxin vs. placebo: Reduction of ≥50% sweating from baseline at 2-4 weeks*



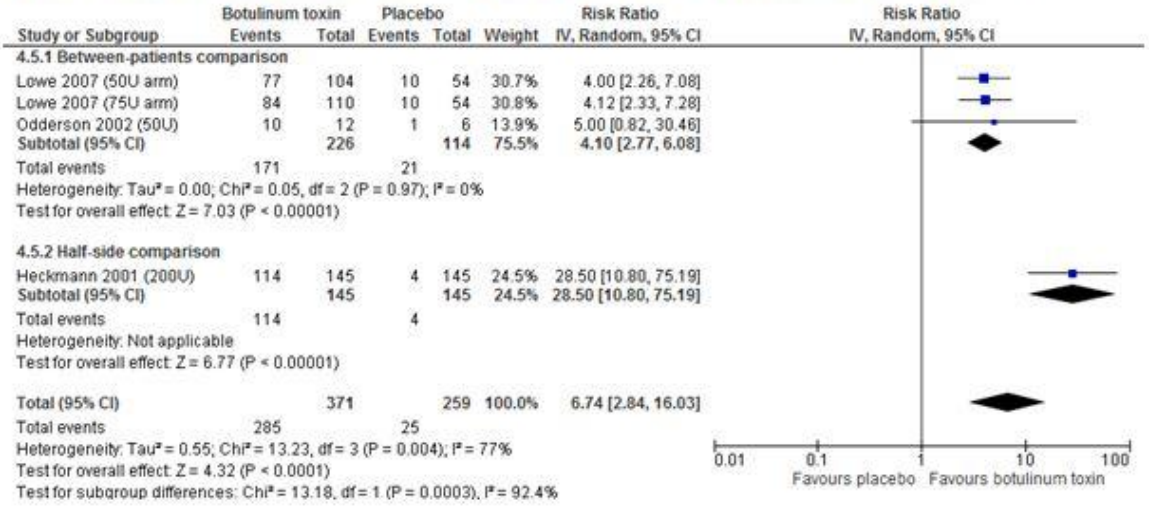
*Follow-up duration was 2 weeks for Heckmann 2001, and 4 weeks for Naumann 2001 and Ohshima 2013. Median follow-up duration in Odderson 2002 was 2 weeks (range 1-8). Data for Odderson 2002 were extracted from figures.

Figure 6: Botulinum toxin vs. placebo: Reduction of ≥50% sweating from baseline at 16 weeks*



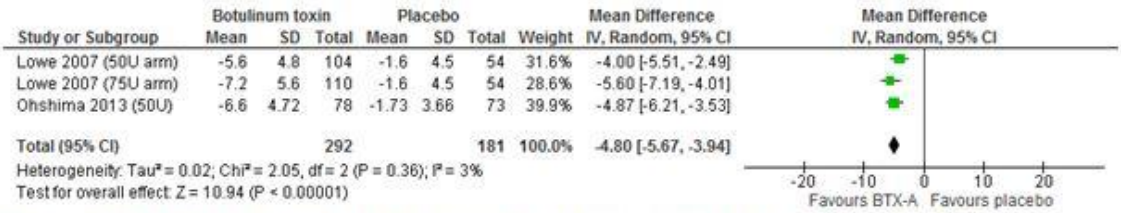
*Follow-up duration was 16 weeks for Naumann 2001 and Ohshima 2013. Median follow-up duration for Odderson was 16 weeks (range 10 to 21). Data for Odderson 2002 were extracted from figures.

Figure 7: Botulinum toxin vs. placebo: Reduction of ≥75% sweating from baseline at 2-4 weeks*



*Follow-up duration was 2 weeks for Heckmann 2001 and 4 weeks for Lowe 2007. Median follow-up duration in Odderson 2002 was 2 weeks (range 2-8). Data for Odderson 2002 were extracted from figures. In Lowe 2007, the total sample size of the placebo group (n=108) was divided by 2 to avoid double counting.

Figure 8: Botulinum toxin vs. placebo: Mean change from baseline in DLQI score at 4 weeks*



*In Lowe 2007, the total sample size of the placebo group (n=108) was divided by 2 to avoid double counting.