Clinical evidence for silk garments

Brief

Silk garments are included in the NHS England consultation document published in November 2018: "Items which should not routinely be prescribed in primary care: an update and a consultation on further guidance for CCGs". These items are classified as being of low clinical effectiveness, where there is a lack of robust evidence of clinical effectiveness or there are significant safety concerns. This evidence review has been prepared in response to concerns raised by the manufacturers of Dermasilk® regarding inclusion of silk garments in the NHS England consultation. This review aims to focus on the literature available and will assess the quality of this literature.

Summary of clinical evidence

- Silk garments are classified as medical devices. Currently, manufacturers need to ensure that their devices are safe and fit for their intended purpose to gain the CE mark; there is no requirement for clinical trials of efficacy
- Silk garments are primarily used in patients with atopic eczema although they have been used in a variety of other conditions including vulvar conditions, epidermolysis bullosa and burns. A range of garments are available including eye masks, socks, gloves, vests, pyjamas and body suits.
- The manufacturers of Dermasilk® provided a bibliography of 48 papers relating to the use of silk garments in a variety of clinical conditions.
- In addition to this, a literature search was undertaken by SPS of Medline, Embase, CINAHL, Cochrane Library and NHS Evidence. Search strategy is shown in Appendix 1. The search was limited to randomised controlled trials (RCTs), systematic reviews or reviews. It was not limited by clinical indication.
- Through this process we identified one systematic review published in 2013. We further included five RCTs of $\geq$ 30 patients, which were either not included in the systematic review (primarily due to different indications) or that were published subsequent to the systematic review.
- Trials of silk garments have generally included very small numbers of participants (range 11 to 300). Only one identified study has included more than 100 patients.
- It is widely recognised that treatment effect estimates are significantly larger in smaller trials, regardless of sample size[1]. Compared with trials of 1000 patients or more, treatment effects were, on average, 48% larger in trials with fewer than 50 patients (ratio of odds ratios 0.52, 0.41 to 0.66), 34% larger in trials with 50-99 patients (0.66, 0.56 to 0.79), 30% larger in trials with 100-199 patients (0.70, 0.61 to 0.80), 19% larger in trials with 200-499 patients (0.81, 0.73 to 0.88), and 10% larger in trials with 500-999 patients (0.90, 0.82 to 1.00).
- The GRADE handbook (*GRADE – the international standard for assessing clinical evidence*) suggests downgrading evidence for imprecision whenever sample sizes of less than 400 are used.
- Whilst we have included trials with small sample sizes in this review, clinical trials with such numbers of participants would never be an acceptable threshold for conventional medicines.
- We used the AMSTAR tool for scoring methodological quality of the systematic review. This scores a systematic review on a scale 0-11. We considered a score of 8-11 as a high quality systematic review; 4-7 moderate quality and 0-3 a low quality systematic review.
- Details and critique of these studies are reported below.

Place in national/ International guidance

- We have not identified any NICE or other UK guidance which recommends the use of silk garments for any clinical condition.
- NICE guidance on treatment of atopic eczema in children (2007) made no recommendations about the use of such garments in the management of eczema, though they included one of the largest studies in their review[2].

Evidence

Systematic reviews

Lopes et al[3]

A systematic review and meta-analysis of trials of functional textiles for atopic dermatitis. The review included 13 studies, six of which involved silk garments. Four studies included children whereas two included children and adults. Patient numbers ranged from 15 to 46. Only two studies of silk garments (tubular sleeves) were considered suitable for inclusion in a meta-analysis. From this the odds ratio of reduction of Eczema Area and

Severity Index (EASI) of atopic dermatitis symptoms in favour of silk was 1.74 (95% CI 2.19 to 1.30). The authors concluded that the quality of evidence for functional textiles for atopic eczema was low or very low.
The systematic review was considered moderate quality (AMSTAR score 7/11).

Published randomised controlled trials cited by Dermasilk® bibliography but not included in the systematic review:

D'Antuono et al (2011)[4]
A small (n=42), double-blind randomised controlled trial looking at the use of silk fabric (Dermasilk®) (treatment arm) compared to cotton briefs (control arm) in women (aged >18 years) with vulvar lichen sclerosus. The study looked at a range of subjective outcomes based on the signs and symptoms of vulvar lichen sclerosus.
The authors reported a lower rate of burning sensation in the treatment arm (9/21 patients) compared to the control arm (21/21 patients, p<0.0001) after six months treatment. Similarly, soreness was reported less often in the treatment arm (0/21 patients) than in the control arm (17/21 patients, p<0.0001) at six months. All other symptoms were numerically less frequent in the intervention arm than in the control arm, but p-values were not provided. A more mixed picture was presented for differences in rates of clinical signs at six months; only erythema was presented with a p-value (p<0.05) for a difference in rates between intervention (9/21 patients) versus control (19/21 patients). All patients in the treatment arm experienced either "complete response" or "good/partial response" in terms of symptoms and clinical signs, with none experiencing "poor response". Whereas 4/21 patients in the control arm had "poor response" for symptoms and 9/21 patients had poor response for clinical signs.
There are a number of methodological limitations of this study, which need to be considered. The study was not powered to provide assurance of statistical significance, and 17 different outcomes were compared for the two groups. It was not described how randomisation was carried out. Patient blinding will have been difficult to maintain due to the inherent differences between silk and cotton underwear. Adherence to use of this treatment underwear was not measured. The study relied on subjective outcomes, yet no information was provided on who was assessing the subjectivity (though logic suggests that patients will have reported the symptoms and a clinician will have been involved in assessing the signs). Use of subjective outcomes in trials where blinding may have been difficult to maintain presents a methodological limitation.
There was a large "placebo" response seen in this study, which may in part be due to patients in both control and intervention arms being directed to administer once daily "very potent" steroid cream and once daily moisturiser. Baseline severity was insufficiently described because data were not presented on prior use of steroid creams (which were noted as the standard of care used).

D'Antuono et al (2012)[5]
A double-blind, randomised controlled trial (n=96) comparing silk briefs (intervention) compared to cotton briefs (control) in adult women with recurrent vulvovaginal candidosis (at least 1 year history) and failure of fluconazole oral treatment. The study aimed to show a difference in signs and symptoms of recurrent vulvovaginal candidosis over a six month period.
The reduction in rate of recurrence between the treatment arm (11/48 without recurrence) and control arm (4/48 without recurrence) was an interesting outcome, but the study was not powered for this. Itching and burning symptoms were reduced more in the treatment arm than in the control arm at six months (6 patients vs. 28 patients reporting itching, p<0.0001; 1 patient vs. 8 patients reporting burning, p<0.01). Caution is advised when interpreting these patient-reported, subjective outcomes as blinding in this study will have been difficult to maintain thus introducing risk of bias. Erythema was lower in the treatment arm (6 patients) than the control arm (38 patients, p<0.0001) at six months. The change in severity of symptoms and signs was discussed in the paper, but results were not presented. Erythema severity was reported to have improved for more of the treatment arm (25/48 patients, 52%) vs. control arm (7/48 patients, 15%; p<0.0001) between three and six months. A higher proportion of the treatment arm did not experience a recurrence during the study (11/48 patients, 22.9%) compared to the control arm (4/48 patients, 8.3%; p=0.036). Although interesting findings, it should be noted that the study was not powered for these outcomes, so caution is needed when interpreting them.
The randomisation process was not described, and baseline data were not provided to allow comparison of the intervention and control arms. This study was not powered for any of the outcomes chosen. The outcomes were all subjective, with an unvalidated score used to compare severity of the symptoms measured. It was again not clear how blinding could be maintained in this study, as women were issued with either silk briefs or cotton briefs. As all women were concomitantly treated with oral weekly fluconazole, it is of concern that baseline data on extent of prior treatment with fluconazole was not provided. Lack of data on adherence to treatment means there is less certainty about where a failure in blinding may have contributed to the result.

D'Antuono et al (2013)[6]
A small (n=30) randomised controlled trial comparing silk briefs (treatment arm) to cotton briefs (control arm) to improve the signs and symptoms of recurrent vulvovaginal candidosis. Patients recruited to this study were adult

women (not menopausal) with a history of recurrent vulvovaginal candidosis (mean duration not stated). Unlike in D'Antuono *et al* (2011)[4] described above, women in this study were specifically instructed not to apply any topical creams or pessaries. Women recruited to this study had refused to take a course of fluconazole, though there were differing reasons for this, including having received a previous course or because they feared side effects (numbers in each group not provided). This adds a potential difference in initial disease severity that is not controlled through stratification.

The primary outcome considered was to evaluate impact on vulvovaginal symptoms and signs in recurrent vulvovaginal candidosis, with a secondary outcome looking at the impact of exacerbations of symptoms. Patients in the treatment arm were statistically significantly more likely to have an improvement in symptoms and signs compared to the control arm ($p<0.001$ for three out of three symptoms and three out of four signs). There was no difference in impact on the rarer symptom of excoriations/fissures. There was a statistically significantly lower overall rate of flares in the treatment arm compared to the control arm (24 episodes vs. 68 episodes, $p<0.001$). It is notable that only two women in the treatment arm and zero in the control arm were completely free from flares at 6 months.

As with the studies discussed above, there were a number of methodological limitations of this trial, which impact on confidence in the results. There is no power calculation, the sample size was small, and there is concern about the ability to maintain patient blinding. The primary outcome, improvement of signs and symptoms, relies in part on subjective patient response, hence the importance of maintaining blinding.

Fabbrocini et al. [Abstract][7]

An English abstract of an Italian-language paper was reviewed, but provided very little detail about either effectiveness of tolerability of the intervention. It is not possible to critically appraise this abstract alone, and therefore no comment can be made about its conclusions.

Other published randomised controlled trials identified by SPS:

Thomas et al 2017[8]

A pragmatic, randomised- controlled trial recruited 300 children aged 1-15 with moderate to severe eczema (the CLOTHES trial). Participants were randomised to standard care plus silk garments or standard care alone. The trial was funded by the National Institute for Health Research (NIHR) HTA programme. Two different brands of silk garments were used (DermaSilk® and DreamSkin®) and patients were instructed to wear them as often as possible during the day and at night. Given the design of the trial patients were not blinded to treatment although observers were. The primary outcome was eczema severity at 6 months, using the validated Eczema Area and Severity Index (EASI). A safety outcome was skin infections. The study was powered to show a 3 point difference in mean EASI scores between the groups. A minimally clinically important difference for EASI in adults receiving systemic therapy is 6 points.

Overall 282 patients were included in the outcome assessment. The garments were mostly worn at night (81% of nights vs 34% of days). The groups were generally well matched at baseline although the EASI was slightly higher in the intervention group. At 6 months mean EASI score had reduced from 9.2 to 5.4 in the intervention group and 8.4 to 5.4 in standard care group (ratio of geometric mean 0.95 (95%CI 0.85-1.07, p=0.43 NS). There were no differences between treatment group for any outcomes assessed by the observers or percentage of days on which topical steroids or calcineurin inhibitors were used. Skin infection occurred in 25% of the intervention group and 28% of the standard care group (p=0.66 NS). Two secondary measures (Patient Orientated Eczema Measure - POEM) and participant global assessment (PGA) showed statistically significant improvement in the silk group.

Limitations: The study was limited due to the lack of blinding of patients and did not reach the participant numbers according to the power calculation. It is also worth noting that, whilst the authors considered adherence was good, patients wore the clothing only on 34% of days. This may have impacted on the results although may also show the 'real-world' usage of such products.

References

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Written by Trent Medicines Information, Leicester and London Medicines Information Service.
Contact: medicines.info@uhl-tr.nhs.uk

February 2019.

Appendix: search strategy

Database	Search term	Results
EMBASE	((exp SILK/ OR (silk).af) AND (exp CLOTHING/ OR (clothing).af OR (garment).af)) AND (exp "CONTROLLED CLINICAL TRIAL"/ OR exp REVIEW/)	44
Medline	((exp SILK/ OR (silk).af) AND (exp CLOTHING/ OR (clothing).af OR (garment).af)) [Document type Meta-analysis OR Randomized Controlled Trial OR Review]	17
CINAHL	((silk).af AND (exp CLOTHING/ OR (clothing).af OR (garment).af)) [Publication types Meta Analysis OR Randomized Controlled Trial OR Systematic Review]	7
Cochrane Library via http://www.thecochranelibrary.com/view/0/index.html - 4/2/19	Search: Silk garments Silk clothing	 7 20
NICE Evidence – 04/02/19	Search: silk garments or clothing limited to systematic reviews	34